

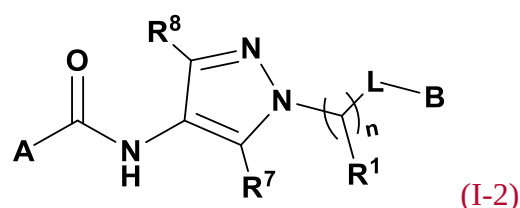
damage of continued ischemia, reperfusion itself is known to cause some additional damage, generally as a result of reactive oxygen species (ROS) (Murphy, E. and Steenbergen, C. 2008). The complex nature of cellular injury associated with ischemia or ischemia followed by reperfusion (I/R) has previously been shown to affect the levels and activities of numerous signaling pathways and transcription factors. One I/R-activated pathway that has been more recently studied involves the disruption of proteostasis. To protect against pathological ER stress induced by I/R, tissues activate endogenous adaptive stress-responsive signaling pathways, such as the unfolded protein response (UPR).

[16] Recent evidence highlights a protective role for the ATF6 arm of the UPR in mitigating adverse outcomes associated with ischemia/reperfusion (I/R) injury in multiple disease models (Kudo, T. et al. 2008; Oida, Y. et al. 2008; Prachasilchai, W. et al. 2009; Oida, Y. et al. 2010; Blackwood, E.A. et al. 2019 ; Yu, Z. et al. 2017; Bi, X. et al. 2018), suggesting ATF6 as a potential therapeutic target for intervening pharmacologically with activator compounds in diverse ischemia-related disorders (Plate, L. et al. 2016; Glembotski, C.C. et al 2019).

[17] 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, the modulation of the ATF6-mediated transcription may provide a therapeutic strategy for these and other diseases in which ATF6 activity is implicated.

BRIEF SUMMARY

[17a] In an aspect of the present disclosure, there is provided a compound of Formula (I-2):



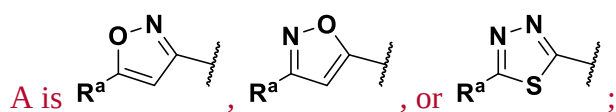
or a pharmaceutically acceptable salt thereof, wherein:

R¹ is H, C₁-C₆alkyl, C₃-C₈cycloalkyl, or C₁-C₆ haloalkyl;

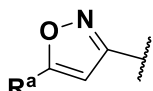
n is 0 or 1;

L is -CH₂- or is absent;

B is C₃-C₆cycloalkyl, 3-6 membered heterocyclyl, or 5-6 membered heteroaryl, wherein the C₃-C₆cycloalkyl and 5-6 membered heteroaryl are each independently optionally substituted with one or more groups selected from the group consisting of halo, CN, -OH, -NH₂, C₁-₆alkyl, C₁-₆alkoxy and C₁-C₆ haloalkyl;

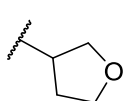
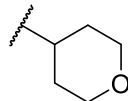
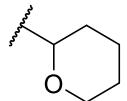
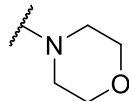


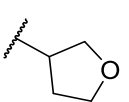
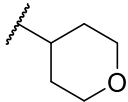
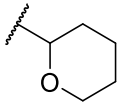
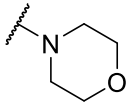
R^a is 5- or 6-membered heteroaryl optionally substituted with one to four halo;

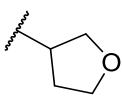
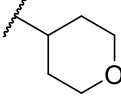
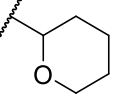
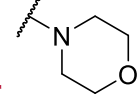
provided that, when A is , one of (i.)-(vii.) applies:

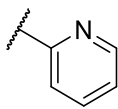
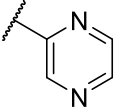
(i) B is C₃-C₆cycloalkyl, optionally substituted with one or more groups selected from the group consisting of halo, CN, -OH, -NH₂, C₁-₆alkyl, C₁-₆alkoxy and C₁-C₆ haloalkyl;

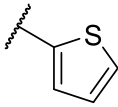
(ii) B is 3-6 membered heterocyclyl having one or more annular heteroatoms, wherein the 3-6 membered heterocyclyl is optionally substituted with one or more groups selected from the group consisting of halo, CN, -OH, -NH₂, C₁-₆alkoxy and C₁-C₆ haloalkyl, and wherein the one or more annular heteroatoms are nitrogen;

(iii) B is , ,  or , each of which is optionally substituted with one or more groups selected from the group consisting of halo, CN, -OH, -NH₂, C₁-₆alkyl, C₁-₆alkoxy and C₁-C₆ haloalkyl, n is 1, R¹ is CH₃, and L is absent;

(iv) B is , ,  or , each of which is substituted with one or more groups selected from the group consisting of halo, CN, -OH, -NH₂, C₁-₆alkyl, C₁-₆alkoxy and C₁-C₆ haloalkyl;

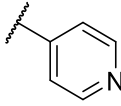
(v) B is , ,  or , each of which is optionally substituted with one or more groups selected from the group consisting of halo, CN, -

OH, -NH₂, C₁₋₆alkyl, C₁₋₆alkoxy and C_{1-C6} haloalkyl, and R^a is , ,

or , each of which optionally substituted with one to four halo;

(vi) B is 4-6 membered bridged heterocyclyl, optionally substituted with one or more groups selected from the group consisting of halo, CN, -OH, -NH₂, C₁₋₆alkyl, C₁₋₆alkoxy and C_{1-C6} haloalkyl;

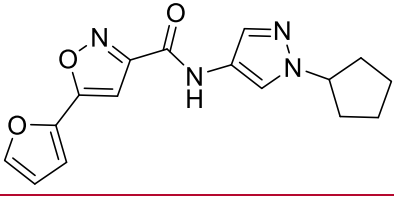
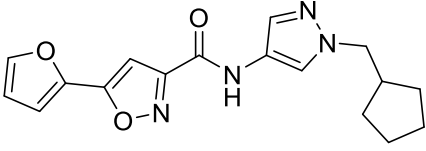
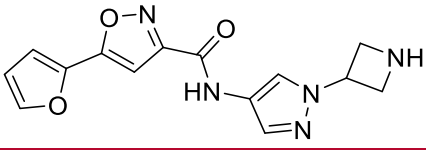
or

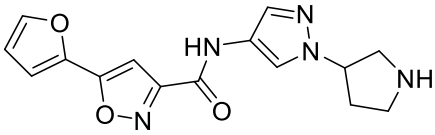
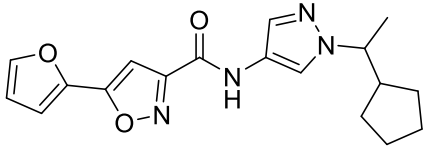
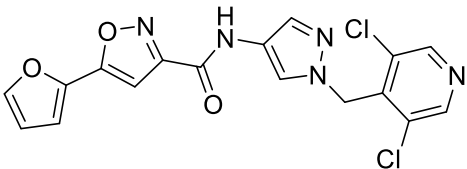
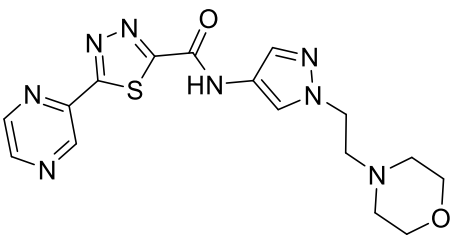
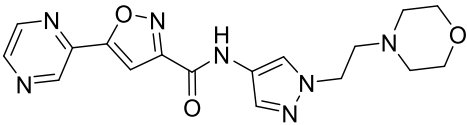
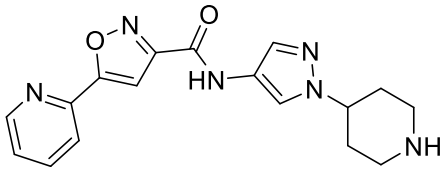
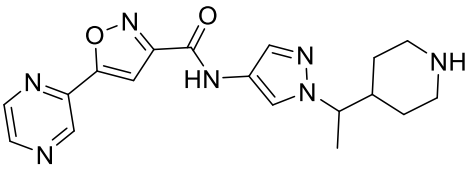
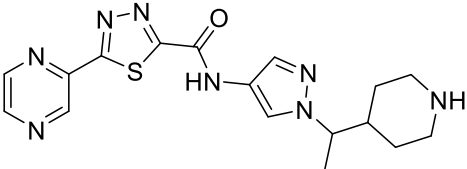
(vii) B is 5-membered heteroaryl or , each of which is optionally substituted with one or more groups selected from the group consisting of halo, CN, -OH, -NH₂, C₁₋₆alkyl, C₁₋₆alkoxy and C_{1-C6} haloalkyl;

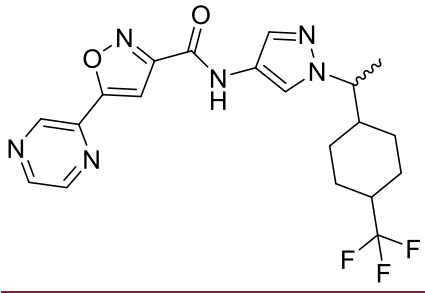
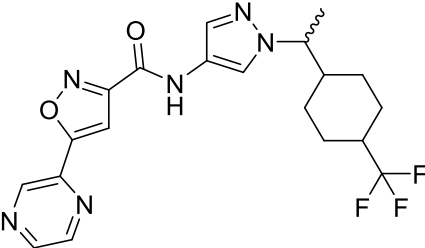
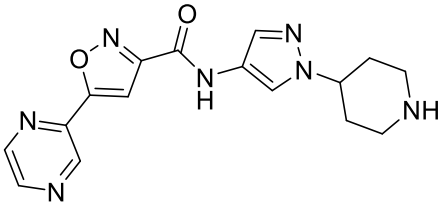
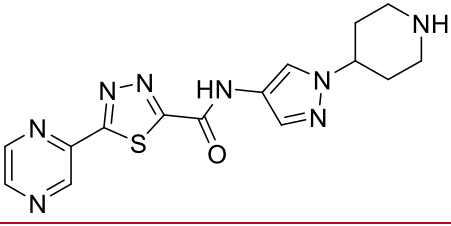
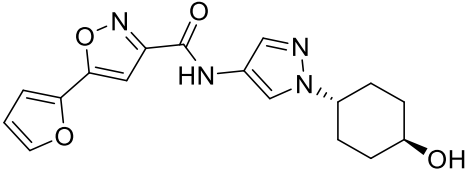
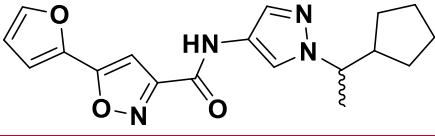
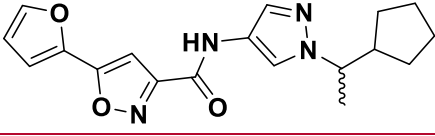
R⁷ is H, C₁₋₆alkyl or or C_{1-C6}haloalkyl; and

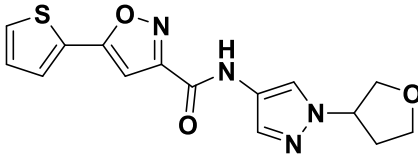
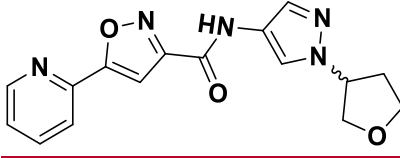
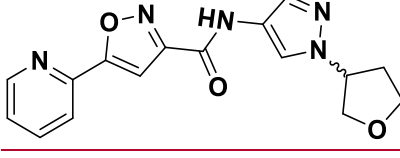
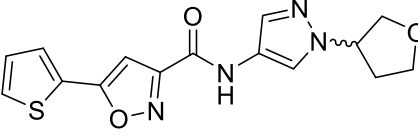
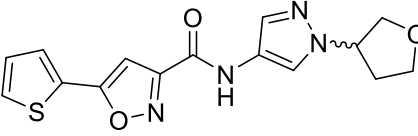
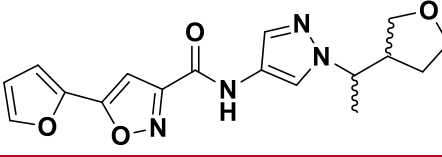
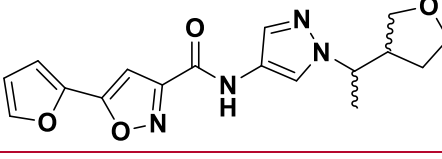
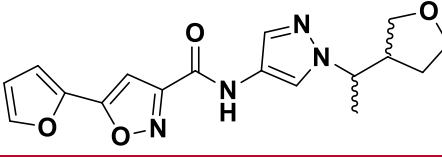
R⁸ is H or C₁₋₆alkyl.

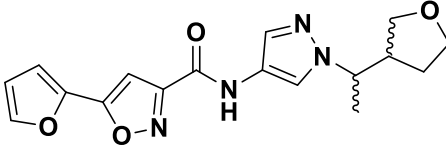
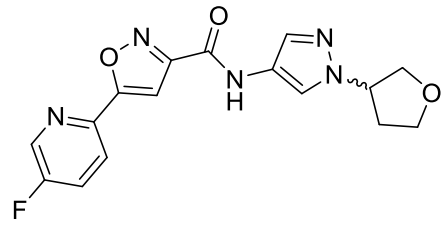
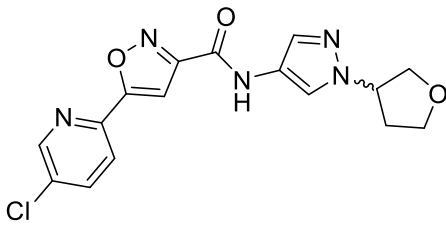
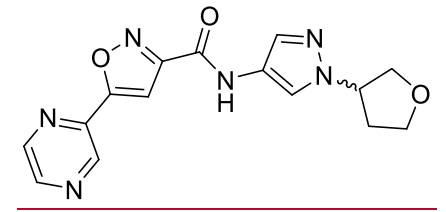
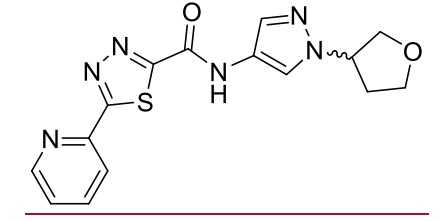
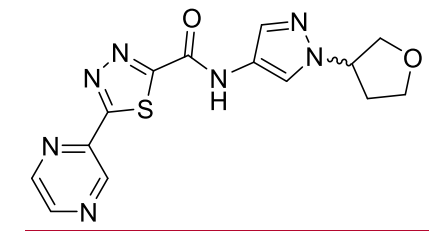
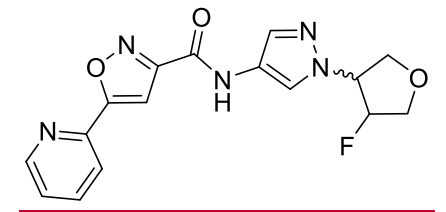
[17b] In another aspect of the present disclosure, there is provided a compound selected from the group consisting of:

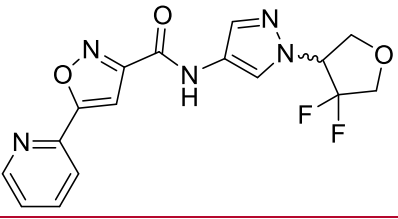
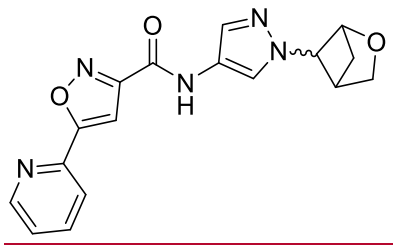
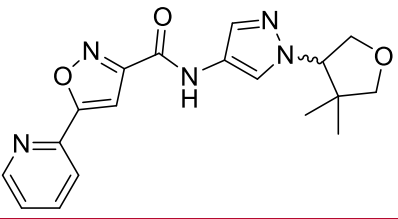
<u>3-1</u>	
<u>3-2</u>	
<u>3-3</u>	

<u>3-4</u>	
<u>3-5</u>	
<u>3-6</u>	
<u>3-7</u>	
<u>3-8</u>	
<u>3-9</u>	
<u>3-10</u>	
<u>3-11</u>	

<u>3-12</u>	
<u>3-13</u>	 <u>Isomer of compound 3-12</u>
<u>3-14</u>	
<u>3-15</u>	
<u>3-16</u>	
<u>3-17</u>	 <u>Isomer A of compound 3-5</u>
<u>3-18</u>	 <u>Isomer B of compound 3-5</u>

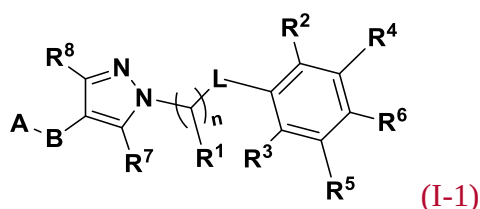
<u>3-19</u>	
<u>3-20</u>	
<u>3-21</u>	 <u>Isomer of compound 3-20</u>
<u>3-22</u>	 <u>Isomer A of compound 3-19</u>
<u>3-23</u>	 <u>Isomer B of compound 3-19</u>
<u>3-24</u>	
<u>3-25</u>	 <u>Isomer A of compound 3-24</u>
<u>3-26</u>	 <u>Isomer B of compound 3-24</u>

<u>3-27</u>	 <u>Isomer C of compound 3-24</u>
<u>3-28</u>	
<u>3-29</u>	
<u>3-30</u>	
<u>3-31</u>	
<u>3-32</u>	
<u>3-33</u>	

<u>3-34</u>	
<u>3-35</u>	
<u>3-36</u>	

or a pharmaceutically acceptable salt thereof.

[17c] In a further aspect of the present disclosure, there is provided a compound of formula (I-1):



or a pharmaceutically acceptable salt thereof, wherein:

R¹ is H, C₁-C₆alkyl, C₃-C₈cycloalkyl, or C₁-C₆ haloalkyl;

n is 0 or 1;

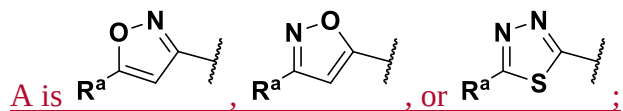
L is -CH₂- or is absent;

B is -CH₂CH₂-, -CH=CH-, or -C≡C-;

R², R³, R⁴, R⁵, and R⁶ are each independently H, halo, CN, -OH, -NH₂, C₁-6alkoxy, C₁-C₆alkyl, or C₁-C₆haloalkyl;

or R², R⁴, R⁵, and R⁶ are each independently H, halo, CN, -OH, -NH₂, C₁-6alkoxy, C₁-C₆alkyl, or C₁-C₆haloalkyl and R³ is taken together with R¹ and the atoms to which they are attached to form a 5- or 6-membered carbocyclic ring, wherein the 5- or 6-membered

carbocyclic ring is unsubstituted or substituted with one to three groups selected from the group consisting of halo, CN, -OH, C₁-C₆alkyl, and C₁-C₆haloalkyl;

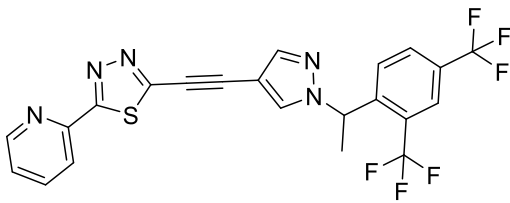
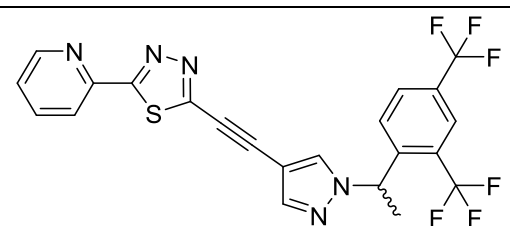
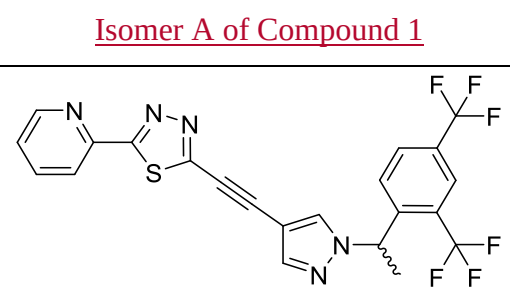
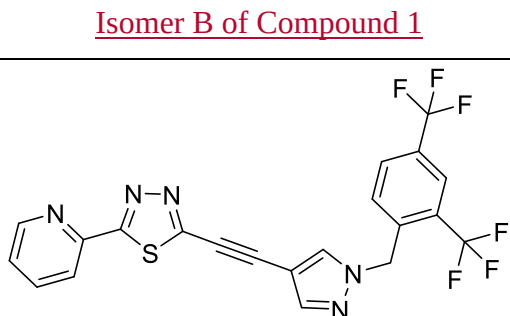


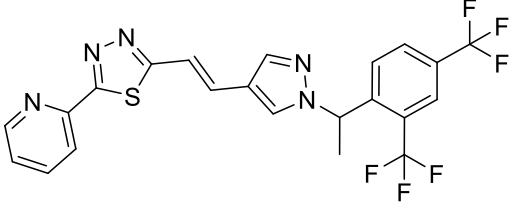
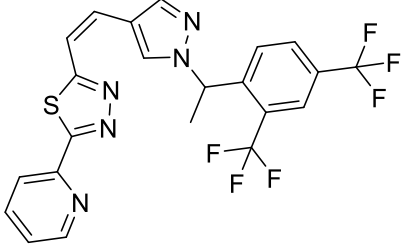
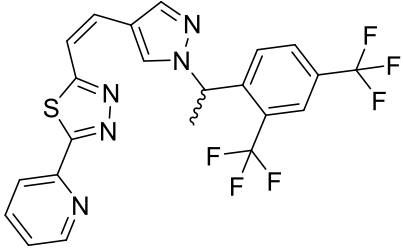
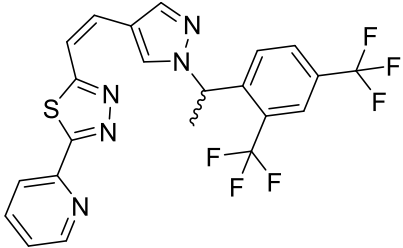
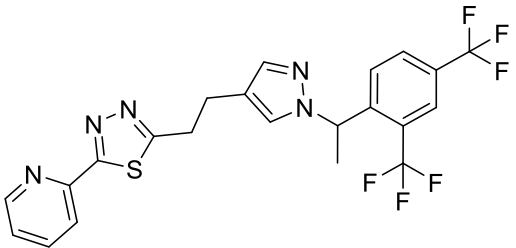
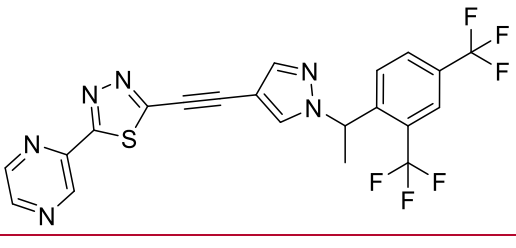
R^a is 5- or 6-membered heteroaryl, wherein the 5- or 6-membered heteroaryl is unsubstituted or substituted with one to four groups selected from the group consisting of OH, halo, C₁-C₆alkyl and C₁-C₆alkoxy,

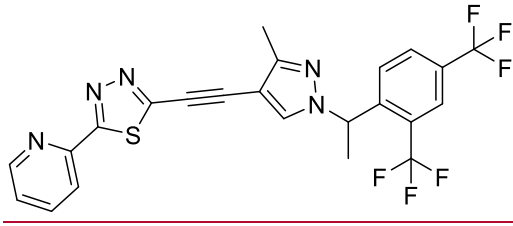
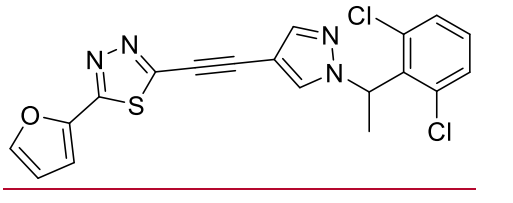
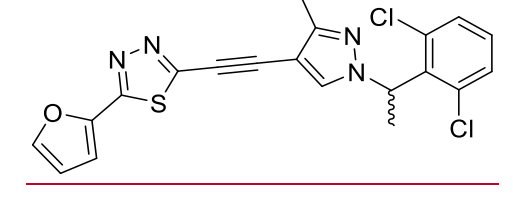
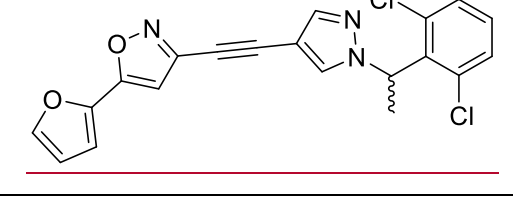
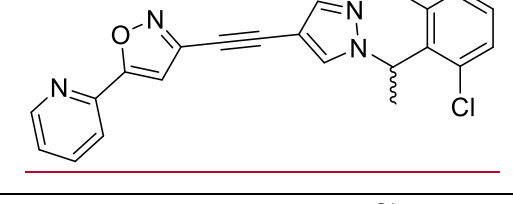
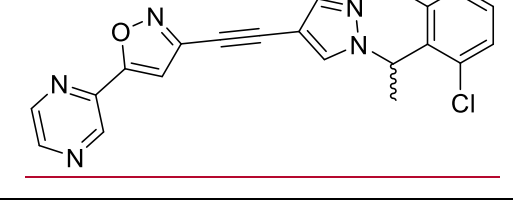
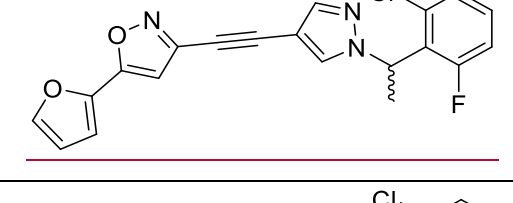
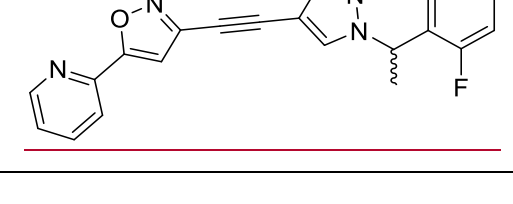
R⁷ is H, C₁-C₆alkyl or or C₁-C₆haloalkyl; and

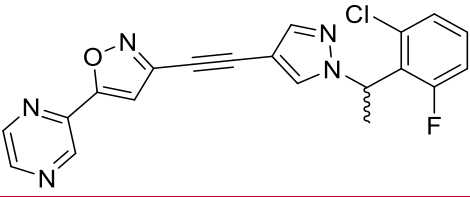
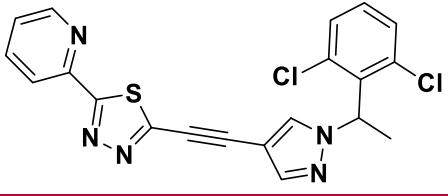
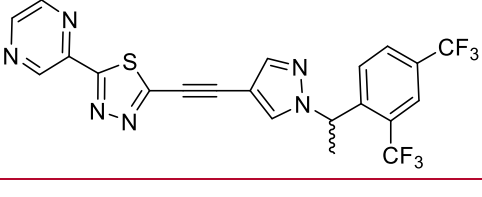
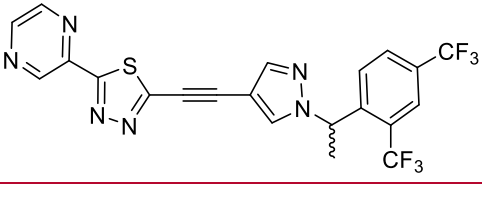
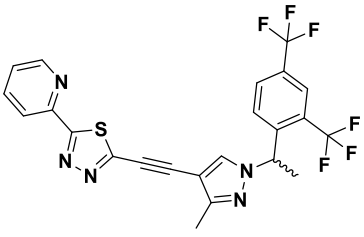
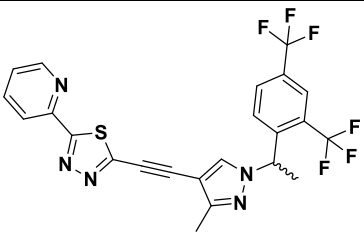
R⁸ is H or C₁-C₆alkyl.

[17d] In another aspect of the present disclosure, there is provided a compound selected from the group consisting of:

<u>2-1</u>	
<u>2-2</u>	 <u>Isomer A of Compound 1</u>
<u>2-3</u>	 <u>Isomer B of Compound 1</u>
<u>2-4</u>	

<u>2-5</u>	
<u>2-6</u>	
<u>2-7</u>	 <u>Isomer A of Compound 6</u>
<u>2-8</u>	 <u>Isomer B of Compound 6</u>
<u>2-9</u>	
<u>2-10</u>	

<u>2-11</u>	
<u>2-12</u>	
<u>2-13</u>	
<u>2-14</u>	
<u>2-15</u>	
<u>2-16</u>	
<u>2-17</u>	
<u>2-18</u>	

<u>2-19</u>	
<u>2-20</u>	
<u>2-21</u>	 <u>Isomer A of compound 2-10</u>
<u>2-22</u>	 <u>Isomer B of compound 2-10</u>
<u>2-23</u>	 <u>Isomer A of compound 2-11</u>
<u>2-24</u>	 <u>Isomer B of compound 2-11</u>

or a pharmaceutically acceptable salt thereof.

[17e] In a further aspect of the present disclosure, there is provided a pharmaceutical composition comprising a compound disclosed herein, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

[17f] In another aspect of the present disclosure, there is provided a use of a compound disclosed herein, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition disclosed herein, in the manufacture of a medicament for preventing and/or treating a disease or disorder mediated by activating transcription factor 6 (ATF6).

[17g] In a further aspect of the present disclosure, there is provided a use of a compound disclosed herein, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition disclosed herein, in the manufacture of a medicament for treating a disease or disorder characterized by activation of ATF6 in an individual in need thereof.

[17h] In another aspect of the present disclosure, there is provided a use of a compound disclosed herein, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition disclosed herein, in the manufacture of a medicament for treating cancer in an individual in need thereof.

[17i] In a further aspect of the present disclosure, there is provided a use of a compound disclosed herein, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition disclosed herein, in the manufacture of a medicament for treating a disease or disorder associated with angiogenesis in an individual in need thereof.

[17j] In another aspect of the present disclosure, there is provided a use of a compound disclosed herein, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition disclosed herein, in the manufacture of a medicament for treating a metabolic disorder in an individual in need thereof.

[17k] In a further aspect of the present disclosure, there is provided a use of a compound disclosed herein, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition disclosed herein, in the manufacture of a medicament for modulating ATF6 in an individual.

[17l] In another aspect of the present disclosure, there is provided a use of a compound disclosed herein, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition disclosed herein, or a metabolite of the foregoing, in the manufacture of a medicament for modulating ATF6 in a cell.

[17m] In a further aspect of the present disclosure, there is provided a use of a compound disclosed herein, or a pharmaceutically acceptable salt thereof, or a pharmaceutical

composition disclosed herein, in the manufacture of a medicament for activating ATF6 in an individual.

[17n] In another aspect of the present disclosure, there is provided a use of a compound disclosed herein, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition disclosed herein, or a metabolite of the foregoing, in the manufacture of a medicament for activating ATF6 in a cell.

[17o] In a further aspect of the present disclosure, there is provided a use of a compound disclosed herein, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition disclosed herein, in the manufacture of a medicament for inhibiting ATF6 in an individual.

[17p] In another aspect of the present disclosure, there is provided a use of a compound disclosed herein, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition disclosed herein, or a metabolite of the foregoing, in the manufacture of a medicament for inhibiting ATF6 in a cell.

[17q] In a further aspect of the present disclosure, there is provided a compound disclosed herein, or a pharmaceutically acceptable salt thereof, for use in therapy.

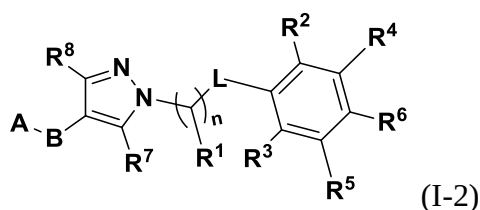
[17r] In another aspect of the present disclosure, there is provided a compound disclosed herein, or a pharmaceutically acceptable salt thereof, for use in treating a disease or disorder mediated by activating transcription factor 6 (ATF6) in an individual in need thereof.

[17s] In a further aspect of the present disclosure, there is provided a compound disclosed herein, or a pharmaceutically acceptable salt thereof, for use in treating a disease or disorder characterized by activation of ATF6 in an individual in need thereof.

[17t] In another aspect of the present disclosure, there is provided a compound disclosed herein, or a pharmaceutically acceptable salt thereof, for use in treating a disease or disorder associated with angiogenesis in an individual in need thereof.

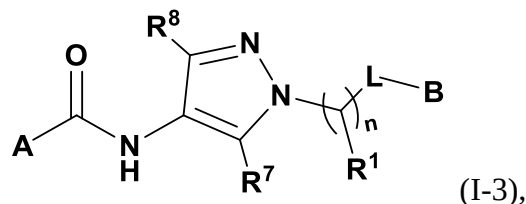
[17u] In a further aspect of the present disclosure, there is provided a compound disclosed herein, or a pharmaceutically acceptable salt thereof, for use in treating a metabolic disorder in an individual in need thereof.

[18] In one ~~aspect~~example, provided is a compound of the formula (I-1):



or a pharmaceutically acceptable salt thereof, wherein A, B, R¹, n, L, R², R³, R⁴, R⁵, R⁶, R⁷, and R⁸ are as detailed herein.

[19] In one [aspectexample](#), provided is a compound of the Formula (I-2):



or a pharmaceutically acceptable salt thereof, wherein A, B, L, n, R¹, R⁷, and R⁸ are as defined herein.

[20] In another [aspectexample](#), 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 (I) or a pharmaceutically acceptable salt thereof or a pharmaceutical composition comprising the compound. In some [embodimentexamples](#), the disease or disorder mediated by activating transcription factor 6 (ATF6) is viral infection, cancer, a neurodegenerative disease, or a vascular disease. In certain [embodimentexamples](#), 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 [embodimentexamples](#), the disease or disorder characterized by activating transcription factor 6 (ATF6) is cancer. In some [embodimentexamples](#), ATF6 is ATF6 α .

[21] In another [aspectexample](#), 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 (I) or a pharmaceutically acceptable salt thereof or a pharmaceutical composition comprising the compound. In some [embodimentexamples](#), the disease or disorder characterized by activation of ATF6 is viral infection, cancer, a neurodegenerative disease, or a vascular disease. In certain [embodimentexamples](#), 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 [embodimentexamples](#), the disease or disorder

characterized by activating transcription factor 6 (ATF6) is cancer. In some [embodimentexamples](#), ATF6 is ATF6 α .

[22] In another [aspectexample](#), 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 (I-1)/(I-2) or a pharmaceutically acceptable salt thereof or a pharmaceutical composition comprising the compound.

[23] In some [embodimentexamples](#), 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 [embodimentexamples](#), one or more cancer cells in the individual are dormant cancer cells.

[24] In some [embodimentexamples](#), the individual has had a prior treatment. In some [embodimentexamples](#), the cancer is resistant or refractory to the prior treatment. In some [embodimentexamples](#), 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.

[25] In some [embodimentexamples](#), the method further comprises administering radiation. In some [embodimentexamples](#), the method further comprises administering a second anticancer agent. In some [embodimentexamples](#), the second anticancer agent targets an immune checkpoint protein.

[26] In another [aspectexample](#), 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 (I-1)/(I-2) or a pharmaceutically acceptable salt thereof or a pharmaceutical composition comprising the compound. In some [embodimentexamples](#), the method further comprises administering a second anti-angiogenesis agent.

[27] In some [embodimentexamples](#) 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 [embodimentexamples](#), the second agent inhibits the IRE1/XBP1 pathway.

[28] In another [aspectexample](#), provided is a method of modulating (activating or inhibiting) ATF6 in an individual comprising administering to the individual a compound of formula (I-1)/(I-2) or a pharmaceutically acceptable salt thereof or a pharmaceutical composition comprising the compound.

[29] In another [aspectexample](#), provided is a method of modulating (activating or inhibiting) ATF6 in a cell comprising delivering to the cell a compound of formula (I-1)/(I-2) or a pharmaceutically acceptable salt thereof or a pharmaceutical composition comprising the compound.

[30] Also provided are pharmaceutical compositions comprising: (A) a compound detailed herein, such as a compound of formula (I-1)/(I-2) or a pharmaceutically acceptable salt thereof, or a compound of formula (I-1)/(I-2) or a pharmaceutically acceptable salt thereof; and (B) a pharmaceutically acceptable carrier or excipient. 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 [embodimentexamples](#), the disease or disorder is cancer, a neurodegenerative disease, or a vascular disease. In certain [embodimentexamples](#), 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.

DETAILED DESCRIPTION

Definitions

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

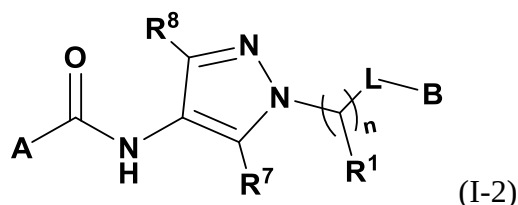
[32] Reference to “about” a value or parameter herein includes (and describes) embodiments that are directed to that value or parameter per se. For example, description referring to “about X” includes description of “X”.

[33] “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.*, C₁-C₁₀ means one to ten carbon atoms). Particular alkyl groups are those having 1 to 20 carbon atoms (a “C₁-C₂₀ alkyl”), having 1 to

CLAIMS

What is claimed is:

1. A compound of Formula (I-2):



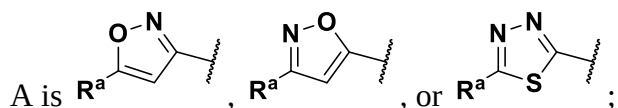
or a pharmaceutically acceptable salt thereof, wherein:

R^1 is H, C_1 - C_6 alkyl, C_3 - C_8 cycloalkyl, or C_1 - C_6 haloalkyl;

n is 0 or 1;

L is $-CH_2-$ or is absent;

B is C_3 - C_6 cycloalkyl, 3-6 membered heterocyclyl, or 5-6 membered heteroaryl, wherein the C_3 - C_6 cycloalkyl and 5-6 membered heteroaryl are each independently optionally substituted with one or more groups selected from the group consisting of halo, CN, $-OH$, $-NH_2$, C_1 - C_6 alkyl, C_1 - C_6 alkoxy and C_1 - C_6 haloalkyl;



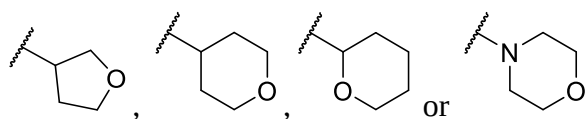
R^a is 5- or 6-membered heteroaryl optionally substituted with one to four halo;

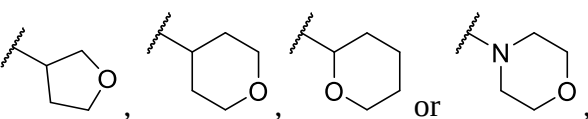
provided that, when A is , one of (i.)-(vii.) applies:

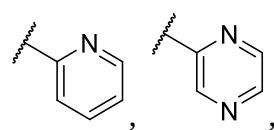
- (i) B is C_3 - C_6 cycloalkyl, optionally substituted with one or more groups selected from the group consisting of halo, CN, $-OH$, $-NH_2$, C_1 - C_6 alkyl, C_1 - C_6 alkoxy and C_1 - C_6 haloalkyl;
- (ii) B is 3-6 membered heterocyclyl having one or more annular heteroatoms, wherein the 3-6 membered heterocyclyl is optionally substituted with one or more groups selected from the group consisting of halo, CN, $-OH$, $-NH_2$, C_1 - C_6 alkoxy and C_1 - C_6 haloalkyl, and wherein the one or more annular heteroatoms are nitrogen;

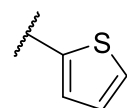
(iii) B is , each of which is optionally substituted with one or more groups selected from the group consisting of halo, CN, -

OH, -NH₂, C₁₋₆alkyl, C₁₋₆alkoxy and C₁₋₆ haloalkyl, n is 1, R¹ is CH₃, and L is absent;

(iv) B is , each of which is substituted with one or more groups selected from the group consisting of halo, CN, -OH, -NH₂, C₁₋₆alkyl, C₁₋₆alkoxy and C₁₋₆ haloalkyl;

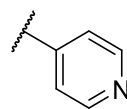
(v) B is , each of which is optionally substituted with one or more groups selected from the group consisting of halo, CN, -

OH, -NH₂, C₁₋₆alkyl, C₁₋₆alkoxy and C₁₋₆ haloalkyl, and R^a is ,

or , each of which optionally substituted with one to four halo;

(vi) B is 4-6 membered bridged heterocyclyl, optionally substituted with one or more groups selected from the group consisting of halo, CN, -OH, -NH₂, C₁₋₆alkyl, C₁₋₆alkoxy and C₁₋₆ haloalkyl;

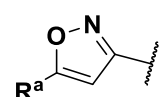
or

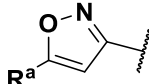
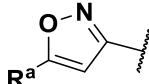
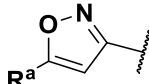
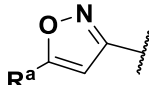
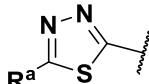
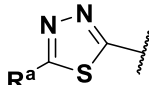
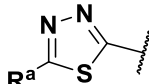
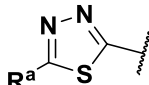
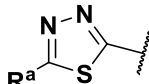
(vii) B is 5-membered heteroaryl or , each of which is optionally substituted with one or more groups selected from the group consisting of halo, CN, -OH, -NH₂, C₁₋₆alkyl, C₁₋₆alkoxy and C₁₋₆ haloalkyl;

R⁷ is H, C₁₋₆alkyl or or C₁₋₆haloalkyl; and

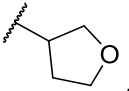
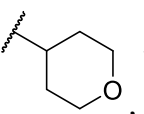
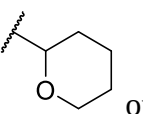
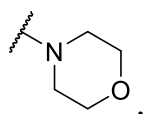
R⁸ is H or C₁₋₆alkyl.

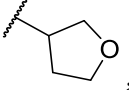
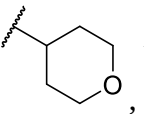
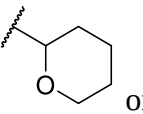
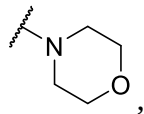
2. The compound of claim 1, wherein the 5- or 6-membered heteroaryl of R^a is selected from the group consisting of 2-furyl, 2-pyridinyl, 2-pyrimidinyl, 4-pyrimidinyl, and 2-pyrazinyl.

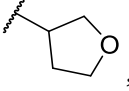
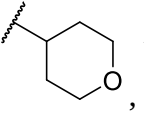
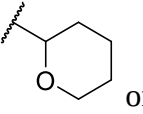
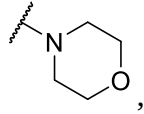
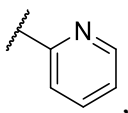
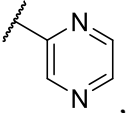
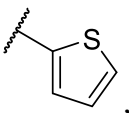
3. The compound of claim 1 or 2, wherein A is  and R^a is 2-furyl.

4. The compound of claim 1 or 2, wherein A is  and R^a is 2-pyridinyl.
5. The compound of claim 1 or 2, wherein A is  and R^a is 2-pyrimidinyl.
6. The compound of claim 1 or 2, wherein A is  and R^a is 4-pyrimidinyl.
7. The compound of claim 1 or 2, wherein A is  and R^a is 2-pyrazinyl.
8. The compound of claim 1 or 2, wherein A is  and R^a is 2-furyl.
9. The compound of claim 1 or 2, wherein A is  and R^a is 2-pyridinyl.
10. The compound of claim 1 or 2, wherein A is  and R^a is 2-pyrimidinyl.
11. The compound of claim 1 or 2, wherein A is  and R^a is 4-pyrimidinyl.
12. The compound of claim 1 or 2, wherein A is  and R^a is 2-pyrazinyl.
13. The compound of any one of claims 1-12, wherein B is C₃-C₆cycloalkyl, optionally substituted with one or more groups selected from the group consisting of halo, CN, -OH, -NH₂, C₁₋₆alkyl, C₁₋₆alkoxy and C₁-C₆ haloalkyl.

14. The compound of any one of claims 1-12, wherein B is 3-6 membered heterocyclyl having one or more annular heteroatoms, wherein the 3-6 membered heterocyclyl is optionally substituted with one or more groups selected from the group consisting of halo, CN, -OH, -NH₂, C₁-6alkoxy and C₁-C₆ haloalkyl, and wherein the one or more annular heteroatoms are nitrogen.

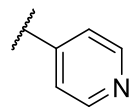
15. The compound of any one of claims 1-12, wherein B is , , , or , each of which is optionally substituted with one or more groups selected from the group consisting of halo, CN, -OH, -NH₂, C₁-6alkyl, C₁-6alkoxy and C₁-C₆ haloalkyl, n is 1, R¹ is CH₃, and L is absent.

16. The compound of any one of claims 1-12, wherein B is , , , or , each of which is substituted with one or more groups selected from the group consisting of halo, CN, -OH, -NH₂, C₁-6alkyl, C₁-6alkoxy and C₁-C₆ haloalkyl.

17. The compound of any one of claims 1-12, wherein B is , , , or , each of which is optionally substituted with one or more groups selected from the group consisting of halo, CN, -OH, -NH₂, C₁-6alkyl, C₁-6alkoxy and C₁-C₆ haloalkyl, and R^a is , , or , each of which optionally substituted with one to four halo.

18. The compound of any one of claims 1-12, wherein B is 4-6 membered bridged heterocyclyl, optionally substituted with one or more groups selected from the group consisting of halo, CN, -OH, -NH₂, C₁₋₆alkyl, C₁₋₆alkoxy and C₁₋₆ haloalkyl.

19. The compound of any one of claims 1-12, wherein B is 5-membered heteroaryl or



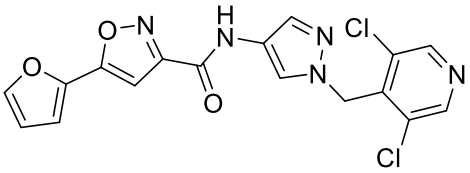
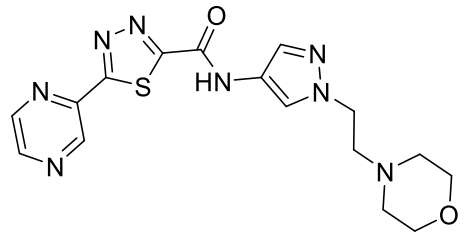
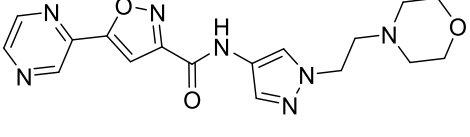
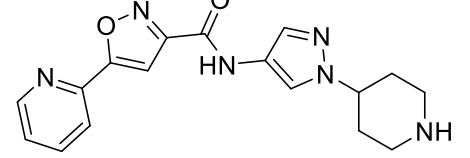
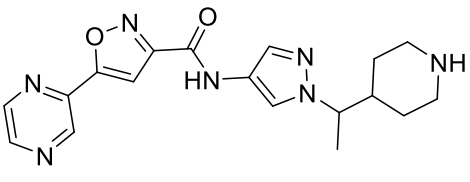
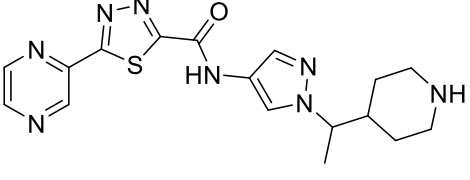
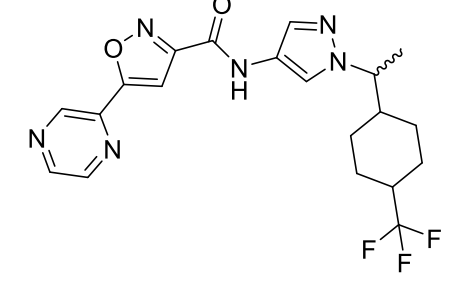
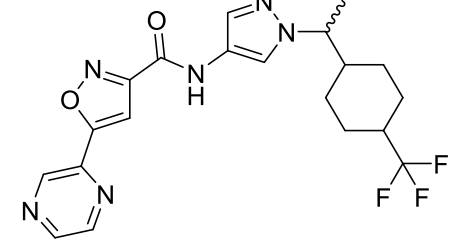
, each of which is optionally substituted with one or more groups selected from the group consisting of halo, CN, -OH, -NH₂, C₁₋₆alkyl, C₁₋₆alkoxy and C₁₋₆ haloalkyl.

20. The compound of any one of claims 1-19, wherein n is 0 and L is absent.

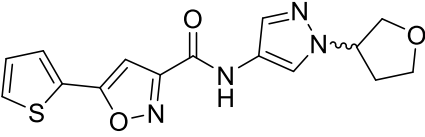
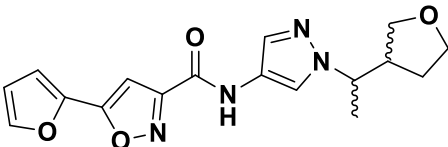
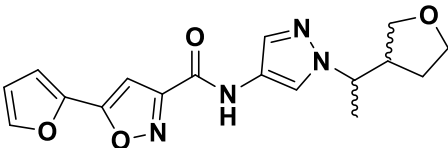
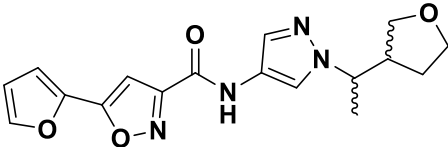
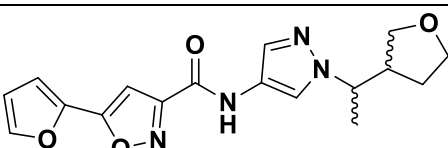
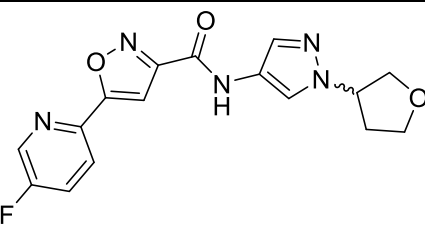
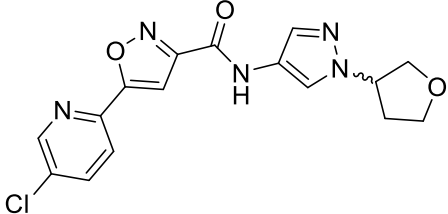
21. The compound of any one of claims 1-19, wherein n is 1, R¹ is CH₃, and L is absent.

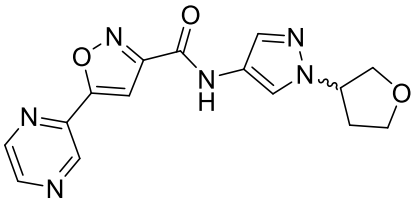
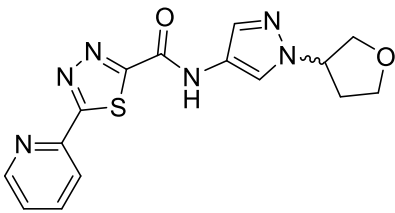
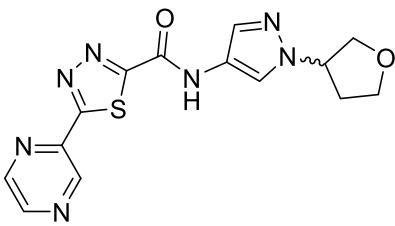
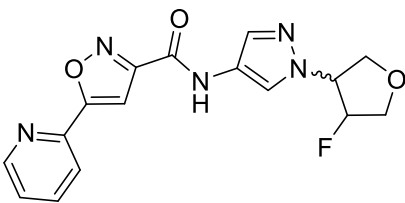
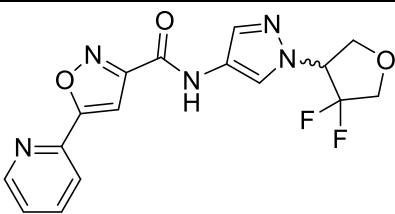
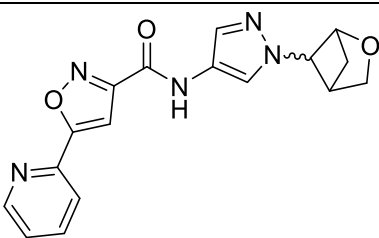
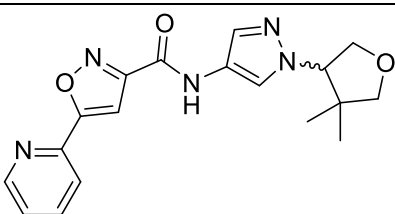
22. A compound selected from the group consisting of:

3-1	
3-2	
3-3	
3-4	
3-5	

3-6	
3-7	
3-8	
3-9	
3-10	
3-11	
3-12	
3-13	 Isomer of compound 3-12

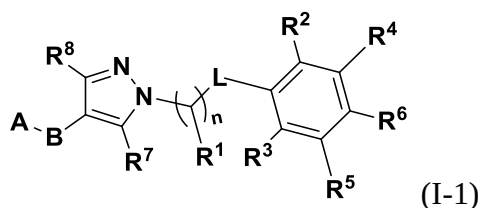
3-14	
3-15	
3-16	
3-17	 Isomer A of compound 3-5
3-18	 Isomer B of compound 3-5
3-19	
3-20	
3-21	 Isomer of compound 3-20
3-22	

	Isomer A of compound 3-19
3-23	
	Isomer B of compound 3-19
3-24	
3-25	
	Isomer A of compound 3-24
3-26	
	Isomer B of compound 3-24
3-27	
	Isomer C of compound 3-24
3-28	
3-29	

3-30	
3-31	
3-32	
3-33	
3-34	
3-35	
3-36	

or a pharmaceutically acceptable salt thereof.

23. A compound of formula (I-1):



or a pharmaceutically acceptable salt thereof, wherein:

R^1 is H, C_1 - C_6 alkyl, C_3 - C_8 cycloalkyl, or C_1 - C_6 haloalkyl;

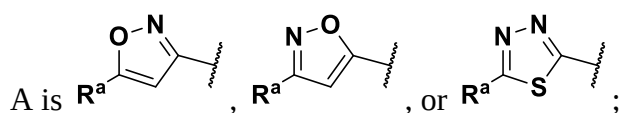
n is 0 or 1;

L is $-CH_2-$ or is absent;

B is $-CH_2CH_2-$, $-CH=CH-$, or $-C\equiv C-$;

R^2 , R^3 , R^4 , R^5 , and R^6 are each independently H, halo, CN, $-OH$, $-NH_2$, C_1 - C_6 alkoxy, C_1 - C_6 alkyl, or C_1 - C_6 haloalkyl;

or R^2 , R^4 , R^5 , and R^6 are each independently H, halo, CN, $-OH$, $-NH_2$, C_1 - C_6 alkoxy, C_1 - C_6 alkyl, or C_1 - C_6 haloalkyl and R^3 is taken together with R^1 and the atoms to which they are attached to form a 5- or 6-membered carbocyclic ring, wherein the 5- or 6-membered carbocyclic ring is unsubstituted or substituted with one to three groups selected from the group consisting of halo, CN, $-OH$, C_1 - C_6 alkyl, and C_1 - C_6 haloalkyl;



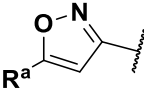
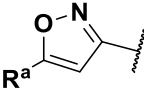
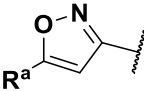
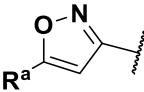
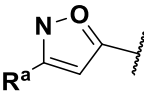
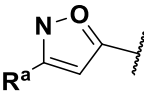
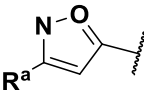
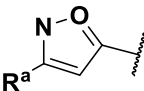
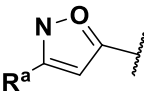
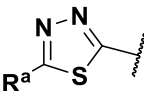
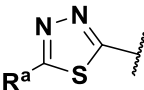
R^a is 5- or 6-membered heteroaryl, wherein the 5- or 6-membered heteroaryl is unsubstituted or substituted with one to four groups selected from the group consisting of OH, halo, C_1 - C_6 alkyl and C_1 - C_6 alkoxy,

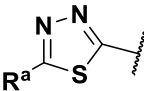
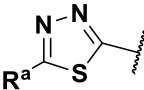
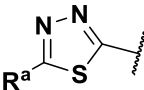
R^7 is H, C_1 - C_6 alkyl or C_1 - C_6 haloalkyl; and

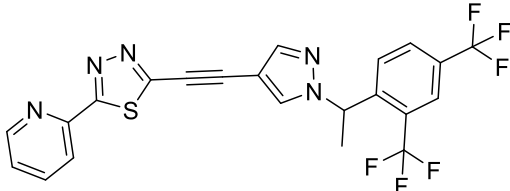
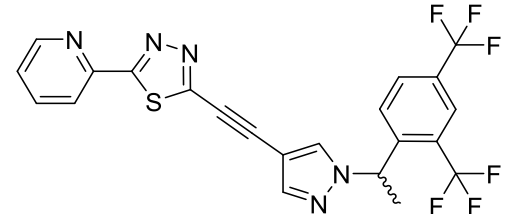
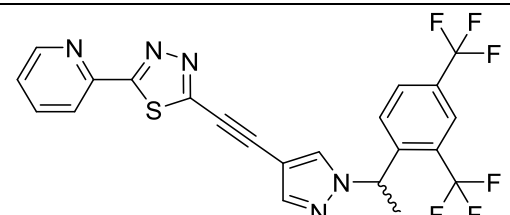
R^8 is H or C_1 - C_6 alkyl.

24. The compound of claim 23, wherein the 5- or 6-membered heteroaryl of R^a is selected from the group consisting of 2-furyl, 2-pyridinyl, 2-pyrimidinyl, 4-pyrimidinyl, and 2-pyrazinyl.

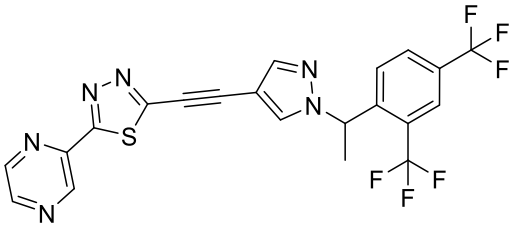
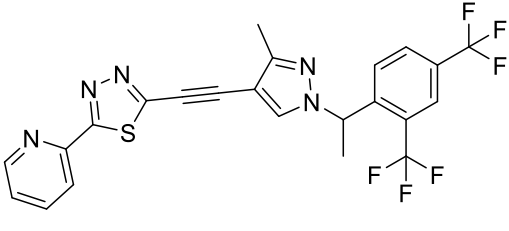
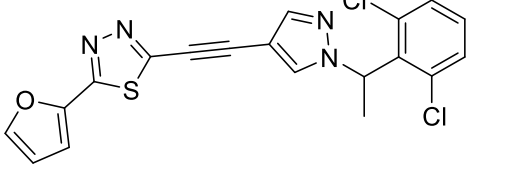
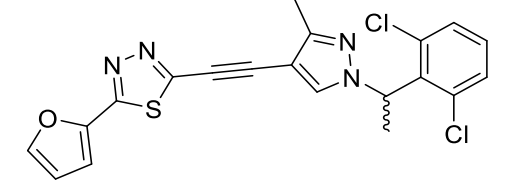
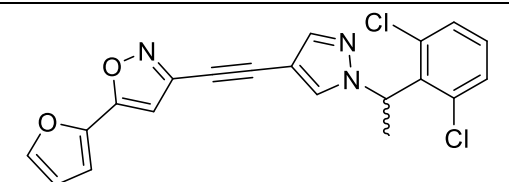
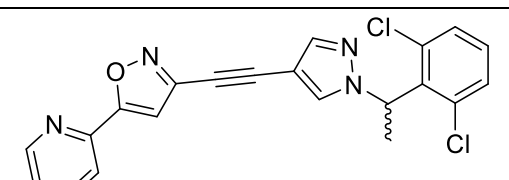
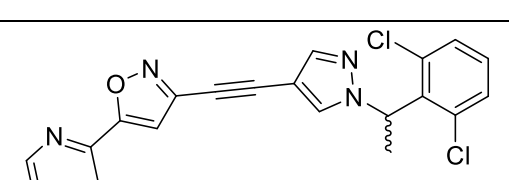
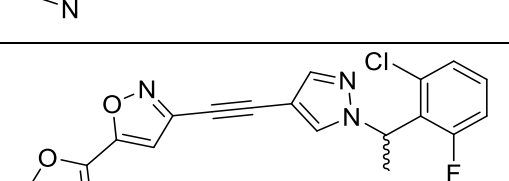
25. The compound of claim 23 or 24, wherein A is and R^a is 2-furyl.

26. The compound of claim 23 or 24, wherein A is  and R^a is 2-pyridinyl.
27. The compound of claim 23 or 24, wherein A is  and R^a is 2-pyrimidinyl.
28. The compound of claim 23 or 24, wherein A is  and R^a is 4-pyrimidinyl.
29. The compound of claim 23 or 24, wherein A is  and R^a is 2-pyrazinyl.
30. The compound of claim 23 or 24, wherein A is  and R^a is 2-furyl.
31. The compound of claim 23 or 24, wherein A is  and R^a is 2-pyridinyl.
32. The compound of claim 23 or 24, wherein A is  and R^a is 2-pyrimidinyl.
33. The compound of claim 23 or 24, wherein A is  and R^a is 4-pyrimidinyl.
34. The compound of claim 23 or 24, wherein A is  and R^a is 2-pyrazinyl.
35. The compound of claim 23 or 24, wherein A is  and R^a is 2-furyl.
36. The compound of claim 23 or 24, wherein A is  and R^a is 2-pyridinyl.

37. The compound of claim 23 or 24, wherein A is  and R^a is 2-pyrimidinyl.
38. The compound of claim 23 or 24, wherein A is  and R^a is 4-pyrimidinyl.
39. The compound of claim 23 or 24, wherein A is  and R^a is 2-pyrazinyl.
40. The compound of any one of claims 23-39, wherein n is 1, R¹ is H and L is absent.
41. The compound of any one of claims 23-40, wherein R⁷ and R⁸ are H.
42. The compound of any one of claims 23-41, wherein B is -CH=CH-, or -C≡C-.
43. A compound selected from the group consisting of:

2-1	
2-2	 Isomer A of Compound 1
2-3	

	Isomer B of Compound 1
2-4	
2-5	
2-6	
2-7	
	Isomer A of Compound 6
2-8	
	Isomer B of Compound 6
2-9	

2-10	
2-11	
2-12	
2-13	
2-14	
2-15	
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2-17	

2-18	
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2-21	
2-22	
2-23	
2-24	

or a pharmaceutically acceptable salt thereof.

44. A pharmaceutical composition comprising a compound of any one of claims 1-43, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

45. Use of a compound of any one of claims 1-43, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of claim 44, in the manufacture of a medicament for ~~A method of preventing and/or~~ treating a disease or disorder mediated by activating transcription factor 6 (ATF6) ~~in an individual in need thereof, comprising administering to the individual a therapeutically effective amount of a compound of any one of claims 1-43, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of claim 44.~~

46. Use of a compound of any one of claims 1-43, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of claim 44, in the manufacture of a medicament for ~~A method of~~ treating a disease or disorder characterized by activation of ATF6 in an individual in need thereof, ~~comprising administering to the individual a therapeutically effective amount of a compound of any one of claims 1-43, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of claim 44.~~

47. The ~~method~~use of claims 45 or 46, wherein ATF6 is ATF6 α .

48. The ~~method~~use of any one of claims 45-47, wherein the disease or disorder is cancer, a neurodegenerative disease, or a vascular disease.

49. The ~~method~~use of any one of claims 45-47, wherein the disease or disorder is a viral infection, hereditary cerebellar atrophy and ataxia, or Alzheimer's disease, type 2 diabetes mellitus, diabetic nephropathy, myocardial atrophy, heart failure, atherosclerosis, ischemia, ischemic heart disease, or cerebral ischemia.

50. Use of a compound of any one of claims 1-43, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of claim 44, in the manufacture of a medicament for ~~A method of~~ treating cancer in an individual in need thereof, ~~comprising administering to the~~

~~individual a therapeutically effective amount of a compound of any one of claims 1-43, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of claim 44.~~

51. Use of a compound of any one of claims 1-43, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of claim 44, in the manufacture of a medicament for
~~A method of~~ treating a disease or disorder associated with angiogenesis in an individual in need thereof, ~~comprising administering to the individual a therapeutically effective amount of a compound of any one of claims 1-43, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of claim 44.~~

52. Use of a compound of any one of claims 1-43, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of claim 44, in the manufacture of a medicament for
~~A method of~~ treating a metabolic disorder in an individual in need thereof, ~~comprising administering to the individual a therapeutically effective amount of a compound of any one of claims 1-43, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of claim 44.~~

53. Use of a compound of any one of claims 1-43, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of claim 44, in the manufacture of a medicament for
~~A method of~~ modulating ATF6 in an individual ~~comprising administering to the individual a compound of any one of claims 1-43, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of claim 44.~~

54. Use of a compound of any one of claims 1-43, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of claim 44, or a metabolite of the foregoing, in the manufacture of a medicament for
~~A method of~~ modulating ATF6 in a cell ~~comprising administering or delivering to the cell a compound of any one of claims 1-43, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of claim 44, or a metabolite of the foregoing.~~

55. Use of a compound of any one of claims 1-43, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of claim 44, in the manufacture of a medicament for
~~A method of~~ activating ATF6 in an individual ~~comprising administering to the individual a~~

~~compound of any one of claims 1-43, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of claim 44.~~

56. Use of a compound of any one of claims 1-43, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of claim 44, or a metabolite of the foregoing, in the manufacture of a medicament for ~~A method of~~ activating ATF6 in a cell ~~comprising administering or delivering to the cell a compound of any one of claims 1-43, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of claim 44, or a metabolite of the foregoing.~~

57. Use of a compound of any one of claims 1-43, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of claim 44, in the manufacture of a medicament for ~~A method of~~ inhibiting ATF6 in an individual ~~comprising administering to the individual a compound of any one of claims 1-43, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of claim 44.~~

58. Use of a compound of any one of claims 1-43, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of claim 44, or a metabolite of the foregoing, in the manufacture of a medicament for ~~A method of~~ inhibiting ATF6 in a cell ~~comprising administering or delivering to the cell a compound of any one of claims 1-43, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of claim 44, or a metabolite of the foregoing.~~

59. ~~Use of a compound of any one of claims 1-43, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of claim 44, in the manufacture of a medicament for the prevention and/or treatment of a disorder or disease mediated by ATF6.~~

~~60~~59. A compound according to any one of claims 1 to 43, or a pharmaceutically acceptable salt thereof, for use in therapy.

~~61~~60. A compound according to any one of claims 1 to 43, or a pharmaceutically acceptable salt thereof, for use in ~~a method of~~ treating a disease or disorder mediated by activating transcription factor 6 (ATF6) in an individual in need thereof.

6261. A compound according to any one of claims 1 to 43, or a pharmaceutically acceptable salt thereof, for use in ~~a method of~~ treating a disease or disorder characterized by activation of ATF6 in an individual in need thereof.

6362. A compound, or a pharmaceutically acceptable salt thereof, for use according to claim 61-60 or 6261, wherein ATF6 is ATF6 α .

6463. A compound, or a pharmaceutically acceptable salt thereof, for use according to any one of claims 61-60 to 6362, wherein the disease or disorder is cancer, a neurodegenerative disease, or a vascular disease.

6564. A compound, or a pharmaceutically acceptable salt thereof, for use according to any one of claims 61-60 to 6362, wherein the disease or disorder is a viral infection, hereditary cerebellar atrophy and ataxia, or Alzheimer's disease, type 2 diabetes mellitus, diabetic nephropathy, myocardial atrophy, heart failure, atherosclerosis, ischemia, ischemic heart disease, or cerebral ischemia.

6665. A compound according to any one of claims 1 to 43, or a pharmaceutically acceptable salt thereof, for use in ~~a method of~~ treating a disease or disorder associated with angiogenesis in an individual in need thereof.

6766. A compound according to any one of claims 1 to 43, or a pharmaceutically acceptable salt thereof, for use in ~~a method of~~ treating a metabolic disorder in an individual in need thereof.