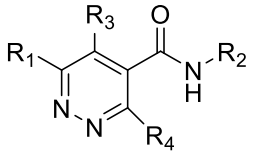
Claims

1. A compound of formula (I):

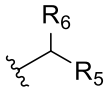


(I);

wherein:

R_1 is selected from the group consisting of aryl or heteroaryl, wherein the aryl or heteroaryl is substituted with one or more substituent groups selected from the group consisting of halogen, C_1-C_8 alkyl, C_1-C_8 alkoxyl, C_1-C_8 haloalkyl, C_3-C_{10} cycloalkyl, cyano, -O-$(CH_2)_p$-R_y, wherein p is an integer selected from 0, 1, 2, 3, and 4, and R_y is selected from C_3-C_{10} cycloalkyl and C_1-C_8 haloalkyl, -S(O)R', and -S(O_2)R', wherein each R' is independently selected from the group consisting of hydrogen, C_1-C_8 alkyl, C_1-C_8 haloalkyl, -NR_7R_8, where R_7 and R_8 are independently selected from C_1-C_8 alkyl and C_1-C_8 haloalkyl, and -O-CHR_{12}-R_{13}, wherein R_{12} is H or C_1-C_8 alkyl and R_{13} is C_3-C_8 cycloalkyl;

R_3 and R_4 are each independently selected from the group consisting of halogen, C_1-C_8 alkyl, C_1-C_8 alkoxyl, C_1-C_8 haloalkyl, C_1-C_8 haloalkoxyl, cyano, -S(O)R', and -S(O_2)R';

R_2 = 

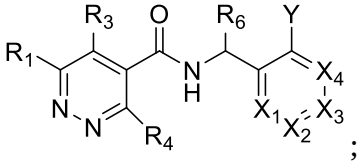
;

R_5 is selected from the group consisting of aryl or heteroaryl, wherein the aryl or heteroaryl is substituted with one or more substituent groups selected from the group consisting of halogen, C_1-C_8 alkyl, C_1-C_8 alkoxyl, C_1-C_8 haloalkyl, cyano, -O-$(CH_2)_p$-R_y, wherein p is an integer selected from 0, 1, 2, 3, and 4, and R_y is selected from C_3-C_{10} cycloalkyl and C_1-C_8 haloalkyl, -S(O)R', -S(O_2)R', -NR_7R_8, where R_7 and R_8 are independently selected from C_1-C_8 alkyl and C_1-C_8 haloalkyl, -NR_9R_{10}, where R_9 and R_{10} together form a saturated heterocyclic ring selected from the group consisting of piperidinyl, pyrrolidinyl, azetidinyl, morpholinyl, thiomorpholinyl, 1,4-oxazepanyl, 2-oxa-5-azabicyclo[2.2.1]heptanyl, and 2-oxa-6-azaspiro[3.3]heptan-6-yl, each of which can optionally substituted with deuterium, C_1-C_8 alkyl, or halogen;

R_6 is hydrogen or C_1-C_8 alkyl; or

a pharmaceutically acceptable salt thereof.

2. The compound of claim 1, wherein the compound of formula (I) has the following structure:



;

wherein:

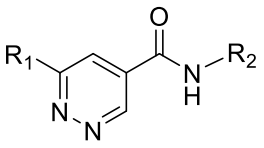
X_1, X_2, X_3, and X_4 are each independently -CR_x- or nitrogen;

if any of X_1, X_2, X_3, or X_4 is -CR_x-, then each R_x is independently selected from the group consisting of halogen, C_1-C_8 alkyl, and C_1-C_8 haloalkyl;

R_6 is hydrogen or C_1-C_8 alkyl; and

Y is selected from the group consisting of piperidinyl, pyrrolidinyl, azetidinyl, morpholinyl, azaspiro[3.3]heptanyl, 1,4-oxazepanyl, and azabicyclo[2.2.1]heptanyl, each of which can be substituted with one or more C_1-C_8 alkyl.

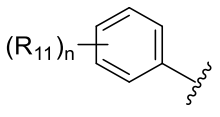
3. The compound of claim 1, wherein the compound of formula (I) has the following structure:

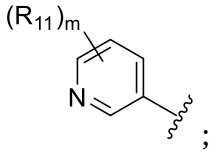


;

wherein:

R_1 is selected from the group consisting of:



; and


;

wherein:

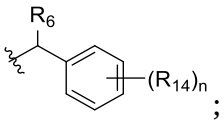
n is an integer selected from 0, 1, 2, 3, 4, and 5;

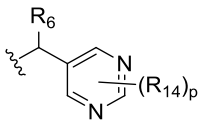
m is an integer selected from 0, 1, 2, 3, and 4;

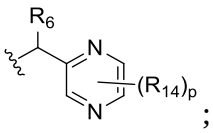
each R_{11} is independently selected from the group consisting of H, C_1-C_8 alkyl, halogen, cyano, C_1-C_8 alkoxyl, C_1-C_8 haloalkyl, -O-$(CH_2)_p$-R_y, wherein p is an integer selected from 0, 1, 2, 3, and 4, and R_y is selected from C_3-C_{10} cycloalkyl and C_1-C_8 haloalkyl, and -O-CHR_{12}-R_{13}, wherein R_{12} is H or C_1-C_8 alkyl and R_{13} is C_3-C_8 cycloalkyl;

R_2 is selected from the group consisting of:



;


;


; and


;

wherein:

n is an integer selected from 0, 1, 2, 3, 4, and 5;

m is an integer selected from 0, 1, 2, 3, and 4;

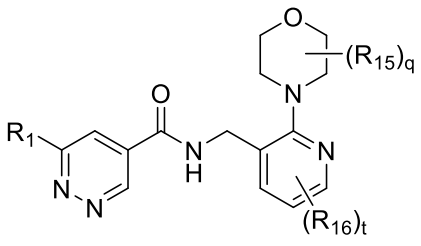
p is an integer selected from 0, 1, 2, and 3;

each R_6 is independently hydrogen or C_1-C_8 alkyl;

each R_{14} is independently selected from the group consisting of halogen, C_1-C_8 alkyl, C_1-C_8 alkoxyl, C_1-C_8 haloalkyl, cyano, -O-$(CH_2)_p$-R_y, wherein p is an integer selected from 0, 1, 2, 3, and 4, and R_y is selected from C_3-C_{10} cycloalkyl and C_1-C_8 haloalkyl, -S(O)R', -S(O_2)R', -NR_7R_8, where R_7 and R_8 are independently selected from C_1-C_8 alkyl and C_1-C_8 haloalkyl, -NR_9R_{10}, where R_9 and R_{10} together form a saturated heterocyclic ring selected from the group consisting of piperidinyl, pyrrolidinyl, azetidinyl, morpholinyl, thiomorpholinyl, 1,4-oxazepanyl, 2-oxa-5-azabicyclo[2.2.1]heptanyl, and 2-oxa-6-azaspiro[3.3]heptan-6-yl, each of which can optionally substituted with deuterium, C_1-C_8 alkyl, or halogen;

and pharmaceutically acceptable salts thereof.

4. The compound of claim 2, wherein the compound of formula (I) has the following structure:



;

wherein:

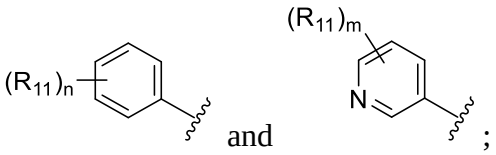
q is an integer selected from 0, 1, 2, 3, 4, 5, 6, 7, and 8;

t is an integer selected from 0, 1, 2, and 3;

each R_{15} is independently selected from deuterium, hydrogen, C_1-C_4 alkyl, and -CF_3;

each R_{16} is independently selected from hydrogen and halogen;

R_1 is selected from:



;

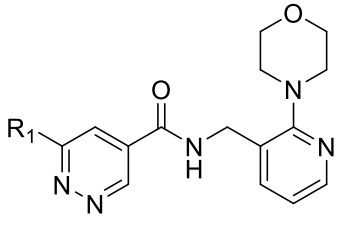
wherein:

n is an integer selected from 0, 1, 2, 3, 4, and 5;

m is an integer selected from 0, 1, 2, 3, and 4; and

each R_{11} is independently selected from the group consisting of H, C_1-C_8 alkyl, halogen, cyano, C_1-C_8 alkoxyl, -O-$(CH_2)_p$-R_y, wherein p is an integer selected from 0, 1, 2, 3, and 4, and R_y is selected from C_3-C_{10} cycloalkyl and C_1-C_8 haloalkyl, and -O-CHR_{12}-R_{13}, wherein R_{12} is H or C_1-C_8 alkyl and R_{13} is C_3-C_8 cycloalkyl.

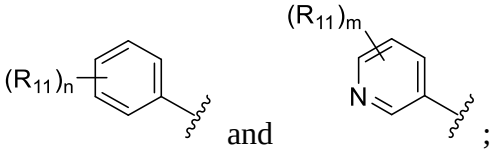
5. The compound of claim 4, wherein the compound of formula (I) has the following structure:



(I-A);

wherein:

R_1 is selected from:



;

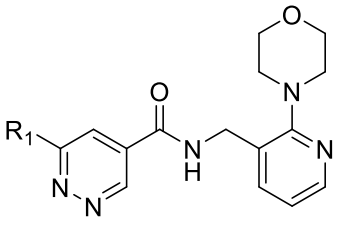
wherein:

n is an integer selected from 0, 1, 2, 3, 4, and 5;

m is an integer selected from 0, 1, 2, 3, and 4; and

each R_{11} is independently selected from the group consisting of C_1-C_8 alkyl, halogen, cyano, C_1-C_8 alkoxyl, -O-$(CH_2)_p$-R_y, wherein p is an integer selected from 0, 1, 2, 3, and 4, and R_y is selected from C_3-C_{10} cycloalkyl and C_1-C_8 haloalkyl, and -O-CHR_{12}-R_{13}, wherein R_{12} is H or C_1-C_8 alkyl and R_{13} is C_3-C_8 cycloalkyl.

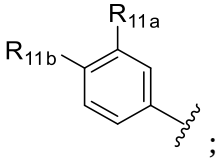
6. The compound of claim 4, wherein the compound of formula (I) has the following structure:



(I-D);

wherein:

R_1 is:



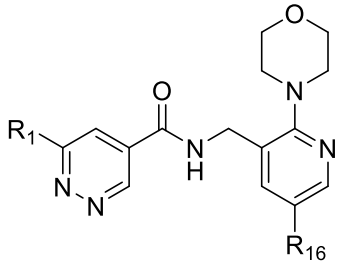
;

wherein:

R_{11a} is halogen or C_1-C_8 haloalkyl; and

R_{11b} is -O-CHR$_{12}$-R$_{13}$, wherein R_{12} is hydrogen or C_1-C_8 alkyl and R_{13} is C_3-C_8 cycloalkyl.

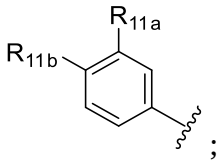
7. The compound of claim 4, wherein the compound of formula (I) has the following structure:



(I-F);

wherein:

R_1 is:



;

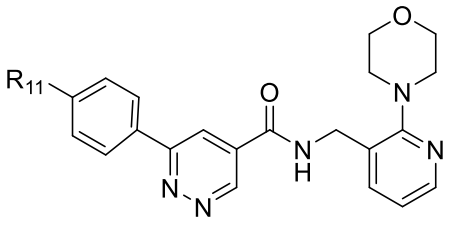
wherein:

R_{11a} is H;

R_{11b} is halogen or cyano; and

R_{16} is halogen.

8. The compound of claim 4, wherein the compound of formula (I) has the following structure:

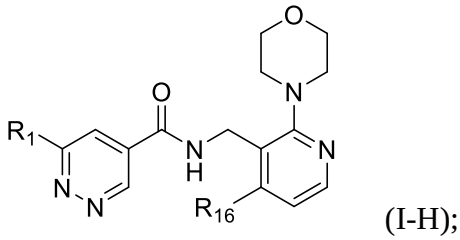


(I-G);

wherein:

R_{11} is selected from the group consisting of halogen, cyano, and -O-$(CH_2)_p$-R_y, wherein p is an integer selected from 0, 1, 2, 3, and 4, and R_y is C_1-C_8 haloalkyl.

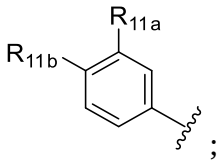
9. The compound of claim 4, wherein the compound of formula (I) has the following structure:



(I-H);

wherein:

R_1 is:



;

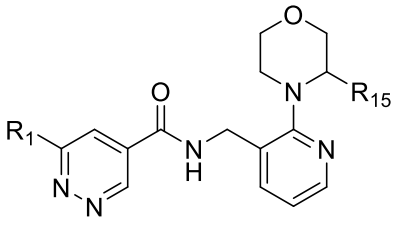
wherein:

R_{11a} is H;

R_{11b} is halogen or -O-$(CH_2)_p$-R_y, wherein p is an integer selected from 0, 1, 2, 3, and 4, and R_y is C_1-C_8 haloalkyl; and

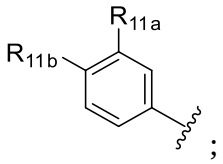
R_{16} is C_1-C_4 alkyl.

10. The compound of claim 4, wherein the compound of formula (I) has the following structure:


(I-I);

wherein:

R_1 is:


;

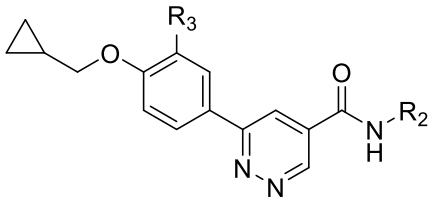
wherein:

R_{11a} is H;

R_{11b} is halogen or -O-$(CH_2)_p$-R_y, wherein p is an integer selected from 0, 1, 2, 3, and 4, and R_y is C_1-C_8 haloalkyl; and

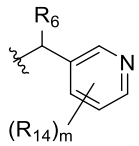
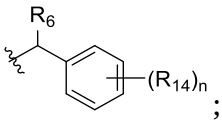
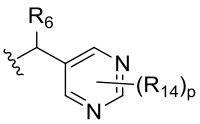
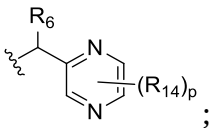
R_{15} is C_1-C_4 alkyl.

11. The compound of claim 1, wherein the compound of formula (I) has the following structure:


(I-B/E);

wherein:

R_2 is selected from the group consisting of:


;

;

; and

;

wherein:

m is an integer selected from 0, 1, 2, 3, and 4;

n is an integer selected from 0, 1, 2, 3, 4, and 5;

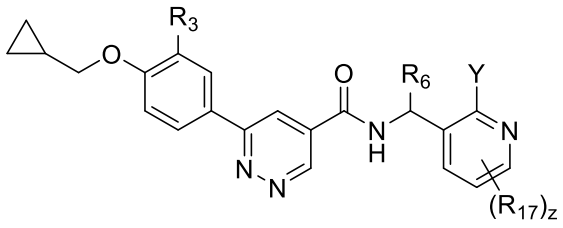
p is an integer selected from 0, 1, 2, and 3;

R_3 is hydrogen or halogen;

R_6 is hydrogen or halogen; and

each R_{14} is independently selected from the group consisting of halogen, C_1-C_8 alkyl, C_1-C_8 alkoxyl, C_1-C_8 haloalkyl, cyano, -O-$(CH_2)_p$-R_y, wherein p is an integer selected from 0, 1, 2, 3, and 4, and R_y is selected from C_3-C_{10} cycloalkyl and C_1-C_8 haloalkyl, -S(O)R', -S(O_2)R', -NR_7R_8, where R_7 and R_8 are independently selected from C_1-C_8 alkyl and C_1-C_8 haloalkyl, -NR_9R_{10}, where R_9 and R_{10} together form a saturated heterocyclic ring selected from the group consisting of piperidinyl, pyrrolidinyl, azetidinyl, morpholinyl, thiomorpholinyl, 1,4-oxazepan-4-yl, 2-oxa-5-azabicyclo[2.2.1]heptan-5-yl, and 2-oxa-6-azaspiro[3.3]heptan-6-yl, each of which can optionally substituted with deuterium, C_1-C_8 alkyl, or halogen.

12. The compound of claim 2, wherein the compound of formula (I) has the following structure:



(I-C);

wherein:

z is an integer selected from 0, 1, 2, and 3;

R_3 is hydrogen or halogen;

R_6 is hydrogen or C_1-C_4 alkyl;

Y is selected from the group consisting of C_1-C_4 alkyl, C_1-C_8 alkoxyl, and -S(=$O)_2$-R', wherein R' is C_1-C_4 alkyl;

R_{17} is halogen.

13. The compound of claim 1, wherein the compound of formula (I) is selected from the group consisting of:

6-[3-chloro-4-(cyclopropylmethoxy)phenyl]-N-[(2-morpholinophenyl)methyl]pyridazine-4-carboxamide;

6-(4-butoxy-3-chloro-phenyl)-N-[(2-morpholino-3-pyridyl)methyl]pyridazine-4-carboxamide;

6-(6-chloro-3-pyridyl)-N-[(2-morpholino-3-pyridyl)methyl]pyridazine-4-carboxamide;

6-(3-chlorophenyl)-N-[(2-morpholino-3-pyridyl)methyl]pyridazine-4-carboxamide;

6-(4-chloro-2-methyl-phenyl)-N-[(2-morpholino-3-pyridyl)methyl]pyridazine-4-carboxamide;

6-(4-isobutoxyphenyl)-N-[(2-morpholino-3-pyridyl)methyl]pyridazine-4-carboxamide;

N-[(2-morpholino-3-pyridyl)methyl]-6-[4-(trifluoromethoxy)phenyl]pyridazine-4-carboxamide;

N-[(2-morpholino-3-pyridyl)methyl]-6-[4-(2,2,2-trifluoroethoxy)phenyl]pyridazine-4-carboxamide;

6-[4-(cyclopropylmethoxy)phenyl]-N-[(2-morpholino-3-pyridyl)methyl]pyridazine-4-carboxamide;

6-(3-chloro-4-ethoxy-phenyl)-N-[(2-morpholino-3-pyridyl)methyl]pyridazine-4-carboxamide;

6-(3-chloro-4-propoxy-phenyl)-N-[(2-morpholino-3-pyridyl)methyl]pyridazine-4-carboxamide;

6-(3-chloro-4-isopropoxy-phenyl)-N-[(2-morpholino-3-pyridyl)methyl]pyridazine-4-carboxamide;

6-(4-ethoxy-3-fluoro-phenyl)-N-[(2-morpholino-3-pyridyl)methyl]pyridazine-4-carboxamide;

6-(3-fluoro-4-propoxy-phenyl)-N-[(2-morpholino-3-pyridyl)methyl]pyridazine-4-carboxamide;

6-(3-fluoro-4-isopropoxy-phenyl)-N-[(2-morpholino-3-pyridyl)methyl]pyridazine-4-carboxamide;

6-[4-(cyclopropoxy)phenyl]-N-[(2-morpholino-3-pyridyl)methyl]pyridazine-4-carboxamide;

6-[6-(cyclopropylmethoxy)-3-pyridyl]-N-[(2-morpholino-3-pyridyl)methyl]pyridazine-4-carboxamide;

6-(4-chlorophenyl)-N-[(2-morpholino-3-pyridyl)methyl]pyridazine-4-carboxamide;

6-[3-chloro-4-(cyclopropylmethoxy)phenyl]-N-[[2-(1-methylimino-1-oxo-1,4-thiazinan-4-yl)-3-pyridyl]methyl]pyridazine-4-carboxamide;

6-[3-chloro-4-(cyclopropylmethoxy)phenyl]-N-[[2-(2-oxa-6-azaspiro[3.3]heptan-6-yl)-3-pyridyl]methyl]pyridazine-4-carboxamide;

6-[3-chloro-4-(cyclopropylmethoxy)phenyl]-N-[[2-(2,2,2-trifluoroethoxy)-3-pyridyl]methyl]pyridazine-4-carboxamide;

6-[3-chloro-4-(cyclopropylmethoxy)phenyl]-N-[[2-(1,4-oxazepan-4-yl)-3-pyridyl]methyl]pyridazine-4-carboxamide;

6-[3-chloro-4-(cyclopropylmethoxy)phenyl]-N-[[2-(2-methylmorpholin-4-yl)-3-pyridyl]methyl]pyridazine-4-carboxamide;

6-[3-chloro-4-(cyclopropylmethoxy)phenyl]-N-[[2-(3-methylmorpholin-4-yl)-3-pyridyl]methyl]pyridazine-4-carboxamide;

6-[3-chloro-4-(cyclopropylmethoxy)phenyl]-N-[(6-methyl-2-morpholino-3-pyridyl)methyl]pyridazine-4-carboxamide;

6-[3-chloro-4-(cyclopropylmethoxy)phenyl]-N-[(4-methyl-2-morpholino-3-pyridyl)methyl]pyridazine-4-carboxamide;

6-[3-chloro-4-(cyclopropylmethoxy)phenyl]-N-[(5-methyl-2-morpholino-3-pyridyl)methyl]pyridazine-4-carboxamide;

6-[3-chloro-4-(cyclopropylmethoxy)phenyl]-N-[(2-morpholinophenyl)methyl]pyridazine-4-carboxamide;

6-[3-chloro-4-(cyclopropylmethoxy)phenyl]-N-[[2-(dimethylamino)-3-pyridyl]methyl]pyridazine-4-carboxamide;

6-[3-chloro-4-(cyclopropylmethoxy)phenyl]-N-[(2-pyrrolidin-1-yl-3-pyridyl)methyl]pyridazine-4-carboxamide;

6-[3-chloro-4-(cyclopropylmethoxy)phenyl]-N-[[2-(1-piperidyl)-3-pyridyl]methyl]pyridazine-4-carboxamide;

6-[3-chloro-4-(cyclopropylmethoxy)phenyl]-N-[(5-fluoro-2-morpholino-3-pyridyl)methyl]pyridazine-4-carboxamide;

6-[3-chloro-4-(cyclopropylmethoxy)phenyl]-N-[(4-morpholinopyrimidin-5-yl)methyl]pyridazine-4-carboxamide;

6-[3-chloro-4-(cyclopropylmethoxy)phenyl]-N-[(3-morpholinopyrazin-2-yl)methyl]pyridazine-4-carboxamide;

6-[3-chloro-4-(cyclopropylmethoxy)phenyl]-N-[[2-[(1S,4S)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl]-3-pyridyl]methyl]pyridazine-4-carboxamide;

6-(3-chloro-4-(cyclopropylmethoxy)phenyl)-N-(1-(2-methoxypyridin-3-yl)ethyl)pyridazine-4-carboxamide;

6-[3-chloro-4-(cyclobutylmethoxy)phenyl]-N-[(2-morpholino-3-pyridyl)methyl]pyridazine-4-carboxamide;

6-[3-chloro-4-(1-cyclopropylethoxy)phenyl]-N-[(2-morpholino-3-pyridyl)methyl]pyridazine-4-carboxamide;

6-[4-(cyclopropylmethoxy)-3-fluoro-phenyl]-N-[(2-morpholino-3-pyridyl)methyl]pyridazine-4-carboxamide;

6-[4-(cyclopropylmethoxy)-3-(trifluoromethyl)phenyl]-N-[(2-morpholino-3-pyridyl)methyl]pyridazine-4-carboxamide;

6-[4-(cyclopropylmethoxy)phenyl]-N-[(2-methoxy-3-pyridyl)methyl]pyridazine-4-carboxamide;

6-[4-(cyclopropylmethoxy)phenyl]-N-[(5-fluoro-2-morpholino-3-pyridyl)methyl]pyridazine-4-carboxamide;

6-[4-(cyclopropylmethoxy)phenyl]-N-[[2-(3-methylmorpholin-4-yl)-3-pyridyl]methyl]pyridazine-4-carboxamide;

6-[3-chloro-4-(cyclopropylmethoxy)phenyl]-N-[(2-methylsulfonylphenyl)methyl]pyridazine-4-carboxamide (LI-1693);

6-[3-chloro-4-(cyclopropylmethoxy)phenyl]-N-[(2-methoxyphenyl)methyl]pyridazine-4-carboxamide (LI-1694);

6-[3-chloro-4-(cyclopropylmethoxy)phenyl]-N-(o-tolylmethyl)pyridazine-4-carboxamide (LI-1699);

6-[3-chloro-4-(cyclopropylmethoxy)phenyl]-N-[[2-(2,2,3,3,5,5,6,6-octadeuteriomorpholin-4-yl)-3-pyridyl]methyl]pyridazine-4-carboxamide (LI-1701);

6-[3-chloro-4-(cyclopropylmethoxy)phenyl]-N-[[2-[2-(trifluoromethyl)morpholin-4-yl]-3-pyridyl]methyl]pyridazine-4-carboxamide (LI-1702);

6-[3-chloro-4-(cyclopropylmethoxy)phenyl]-N-[(5-fluoro-3-pyridyl)methyl]pyridazine-4-carboxamide (LI-1722);

6-[3-chloro-4-(cyclopropylmethoxy)phenyl]-N-[[2-(2-ethylmorpholin-4-yl)-3-pyridyl]methyl]pyridazine-4-carboxamide (LI-1723);

6-[3-chloro-4-(cyclopropylmethoxy)phenyl]-N-[(2-isopropoxy-3-pyridyl)methyl]pyridazine-4-carboxamide (LI-1724);

6-[4-(cyclopropylmethoxy)phenyl]-N-[(2-methoxy-3-pyridyl)methyl]pyridazine-4-carboxamide (LI-1646);

6-[4-(cyclopropylmethoxy)phenyl]-N-[(2-morpholinophenyl)methyl]pyridazine-4-carboxamide (LI-1685);

6-[4-(cyclopropylmethoxy)phenyl]-N-[[2-(2-oxa-6-azaspiro[3.3]heptan-6-yl)-3-pyridyl]methyl]pyridazine-4-carboxamide (LI-2126);

6-(4-cyanophenyl)-N-[(5-fluoro-2-morpholino-3-pyridyl)methyl]pyridazine-4-carboxamide (LI-1668);

6-(4-chlorophenyl)-N-[(5-fluoro-2-morpholino-3-pyridyl)methyl]pyridazine-4-carboxamide (LI-1669);

6-(4-chlorophenyl)-N-[(2-morpholinophenyl)methyl]pyridazine-4-carboxamide (LI-1673);

6-[4-(difluoromethoxy)phenyl]-N-[(2-morpholinophenyl)methyl]pyridazine-4-carboxamide (LI-1675);

6-[4-(trifluoromethoxy)phenyl]-N-[(2-morpholinophenyl)methyl]pyridazine-4-carboxamide (LI-1682);

6-(4-cyanophenyl)-N-[(2-morpholinophenyl)methyl]pyridazine-4-carboxamide (LI-1683);

6-[4-(trifluoromethoxy)phenyl]-N-[(4-methyl-2-morpholino-3-pyridyl)methyl]pyridazine-4-carboxamide (LI-1678);

6-(4-chlorophenyl)-N-[(4-methyl-2-morpholino-3-pyridyl)methyl]pyridazine-4-carboxamide (LI-1681);

6-[4-(trifluoromethoxy)phenyl]-N-[[2-(3-methylmorpholin-4-yl)-3-pyridyl]methyl]pyridazine-4-carboxamide (LI-1679); and

6-(4-chlorophenyl)-N-[[2-(3-methylmorpholin-4-yl)-3-pyridyl]methyl]pyridazine-4-carboxamide (LI-1680).

14. The compound of any of claims 1-13 for use in modulating a $Na_v1.8$ sodium ion channel, wherein a modulating-effective amount of the compound is to be administered to a subject in need thereof.

15. The compound of any of claims 1-13 for use in inhibiting $Na_v1.8$, wherein an inhibiting-effective amount of the compound is to be administered to a subject in need thereof.

16. The compound of any of claims 1-13 for use in the treatment and/or reduction of symptoms of a condition, disease, or disorder associated with an increased $Na_v1.8$ activity or expression, wherein a therapeutically effective amount of

the compound is to be administered to a subject in need of treatment thereof to treat and/or reduce the symptoms of the condition, disease, or disorder.

17. Use of the compound of any of claims 1-13 in the manufacture of a medicament for the treatment of a condition, disease, or disorder associated with an increased $Na_v1.8$ activity or expression in a subject afflicted with such a disorder.

18. The compound of claim 16 or the use of claim 17, wherein the condition, disease, or disorder associated with an increased $Na_v1.8$ activity or expression is selected from the group consisting of pain, respiratory diseases, neurological disorders, and psychiatric diseases, and combinations thereof.

19. The compound or the use of claim 18, wherein the pain is selected from the group consisting of neuropathic pain, inflammatory pain, visceral pain, cancer pain, chemotherapy pain, trauma pain, surgical pain, post-surgical pain, childbirth pain, labor pain, neurogenic bladder, ulcerative colitis, chronic pain, persistent pain, peripherally mediated pain, centrally mediated pain, chronic headache, migraine headache, sinus headache, tension headache, phantom limb pain, dental pain, peripheral nerve injury, and combinations thereof.

20. The compound or the use of claim 18, wherein the disease or condition is selected from the group consisting of HIV-treatment induced neuropathy, trigeminal neuralgia, post-herpetic neuralgia, eudynia, heat sensitivity, tosarcoidosis, irritable bowel syndrome, Crohns disease, multiple sclerosis (MS), amyotrophic lateral sclerosis (ALS), diabetic neuropathy, peripheral neuropathy, arthritis, rheumatoid arthritis, osteoarthritis, atherosclerosis, paroxysmal dystonia, myasthenia syndromes, myotonia, malignant hyperthermia, cystic fibrosis, pseudoaldosteronism, rhabdomyolysis, hypothyroidism, bipolar depression, anxiety, schizophrenia, sodium channel toxi related illnesses, familial erythromelalgia, primary erythromelalgia, familial rectal pain, cancer, epilepsy, partial and general tonic seizures, restless leg syndrome, arrhythmias, fibromyalgia, neuroprotection under ischaemic conditions cause by stroke or neural trauma, tach-arrhythmias, atrial fibrillation, ventricular fibrillation, and Pitt Hopkins Syndrome (PTHS).

21. The compound of claim 15, further comprising one or more additional therapeutic agents to be administered to the subject.

22. The compound of claim 21, wherein the one or more additional therapeutic agents is selected from the group consisting of acetaminophen, one or more NSAIDs, opioid analgesics, and combinations thereof.