

PYRIDAZINE COMPOUNDS FOR INHIBITING Nav1.8

CROSS-REFERENCE TO RELATED APPLICATIONS

This application claims the benefit of U.S. Provisional Application No.
5 62/695,510, filed July 9, 2018, which is incorporated herein by reference in its entirety.

BACKGROUND

The modern pharmacopoeia has a variety of treatments for acute and chronic
10 pain, such as steroidal and nonsteroidal anti-inflammatory drugs (NSAIDs), amine reuptake inhibitors, and opioids (*Pain Medicine*). All have liabilities, and extensive efforts have been undertaken to develop novel approaches for pain management (Yekkirala et al., 2017), especially given the recent epidemic of opioid abuse (Skolnick, 2018). Voltage-gated sodium channels (Navs), (Catterall 2012), are logical
15 targets for pain management given their prominent role in neuronal conduction in sensory neurons (Ruiz et al., 2015).

Overall there are nine known subtypes of the main pore-forming α subunit. The Nav1.1, Nav1.2, and Nav1.3 subtypes are primarily expressed in the central nervous system (CNS), while Nav1.4 and Nav1.5 are abundant in skeletal and cardiac
20 muscle. Nav1.6 has been shown to be expressed in both the peripheral nervous system (PNS) and CNS, whereas Nav1.7, Nav1.8, and Nav1.9 are usually thought to be restricted to the PNS (Yu and Catterall, 2003). Non-selective sodium channel inhibitors are available as antiarrhythmic, anticonvulsant, and local anesthetics, but none are appropriate for general treatment of chronic pain (Eijkelkamp, et al., 2012).
25 The Nav family of channels is highly homologous, and obtaining selective drug-like ligands is a significant challenge (Bagal, et al., 2014). Identification of selective inhibitors (Jukic, et al., 2014), or activators (Deuis, et al., 2017), of specific isoforms, however, has potential in numerous disorders.

Both the Nav1.7 and Nav1.8 isoforms have attracted considerable attention as
30 targets for the treatment of pain due to their presence on nociceptors in the PNS (Jukic, et al., 2014). Robust effort has been directed toward Nav1.7 (Vetter, et al., 2017), given the extensive human genetic validation of this channel (Bennett and Woods, 2014), and the discovery of a selective class of inhibitors (McCormack et al., 2013). Human clinical trials of several selective Nav1.7 inhibitors, however, have

been disappointing (Donnell et al., 2018; Zakrzewska et al., 2017), suggesting Nav1.8 as an alternate target (Han et al., 2016).

The pore-forming α subunit of the Nav1.8 sodium channel is encoded by the SCN10A gene and primarily (although not exclusively) expressed in dorsal root ganglion (DRG) neurons and in trigeminal and nodose ganglion neurons (Akopian et al., 1996; Shields et al., 2012). These neurons mediate most of the inward sodium currents during the depolarization phase of neuronal action potentials that are critical for transmission of action potentials and repetitive firing (Akopian et al., 1999). Rodent scn10a gene knockout and knockdown studies indicate the involvement of Nav1.8 in inflammatory and neuropathic pain (Dong et al., 2007). Heterozygous gain-of-function mutations in SCN10A cause aberrant firing of DRG neurons and have been linked to painful small-fiber neuropathies in humans, which further links Nav1.8 to nociceptive neuron function (Faber et al., 2012).

Opportunities also exist for Nav1.8 inhibitors beyond treatment of pain. Mounting evidence indicates that Nav1.8 is expressed in brain (Lu et al., 2015) and is involved in the pathogenesis of multiple sclerosis (MS). Several reports have shown that Nav1.8 is expressed ectopically in mice with experimental autoimmune encephalomyelitis (EAE) (Black et al., 2000) and cerebellar Purkinje neurons of patients with MS (Damarjian et al., 2004). Ectopic expression of Nav1.8 causes abnormal firing patterns in the cerebellar Purkinje cells and motor coordination deficits in the absence of obvious signs of ataxia in mice models (Shields et al., 2012).

Importantly, treatment with Nav1.8 blocker **1** (FIG. 1, prior art) reverses cerebellar deficits in a mouse model of MS, thereby establishing a potential novel approach toward treating MS (Shields et al., 2015). Data from an *ex vivo* cortical development model of transcription factor 4 (TCF4) disruption on cortical neuronal physiology demonstrates *in vivo* evidence that TCF4 normally represses expression of the SCN10A gene in the CNS. In an *ex vivo* cell model and in two independent rodent models of a genetic form of autism called Pitt Hopkins Syndrome (PTHS) that is defined by TCF4 haploinsufficiency (Sweatt, 2013), TCF4 deficiency was shown to produce aberrant electrophysiological phenotypes characterized by a significant reduction in action potential output and these phenotypes were associated with increased expression of SCN10A (Nav1.8) (Rannals et al., 2016). Furthermore, it has been shown in these PTHS models that Nav1.8 inhibitors, such as **2** and **5** (FIG. 1, prior art), can rapidly reverse some of the excitability phenotypes. These results

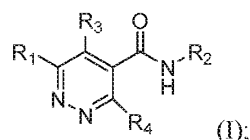
suggest that the ectopic expression in the brain of the normally peripherally-restricted sodium channel Nav1.8 may drive some of the symptoms of PTHS and that inhibitors of Nav1.8 will have therapeutic value for patients with PTHS.

The Nav1.8 channel also is expressed in structures relating to the back,
 5 (Bucknill et al., 2002), and tooth pulp (Renton et al., 2005), and there is evidence for a role of the Nav1.8 channel in causalgia (Shembalkar et al., 2001) and inflammatory bowel conditions (Beyak and Vanner 2005).

Nav1.8 is significantly different from most other members of the family of voltage gated ion channels in that it is “resistant” to inhibition by the classical sodium
 10 channel inhibitor tetrodotoxin, which inhibits most other members of the family (Cestele and Catterall, 2000). Nav1.8 inhibitors, such as **1** (Bagal et al., 2015), **5**, (Kort et al., 2008), and **6** (Zhang et al., 2010) (FIG. 1, prior art), are known in the literature. Efficacy in a variety of pain models was examined with effects seen in both inflammatory and neuropathic pain rodent models (Jarvis et al., 2007; Payne et
 15 al., 2015). These compounds, and ones like them, suffer from a variety of drawbacks, including selectivity versus other ion channels and poor pharmacokinetics.

SUMMARY

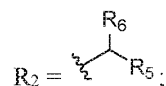
In some aspects, the presently disclosed subject matter provides a compound
 20 of formula (I):



wherein:

R₁ 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
 25 group consisting of halogen, C₁-C₈ alkyl, C₁-C₈ alkoxy, C₁-C₈ haloalkyl, C₃-C₁₀ cycloalkyl, cyano, -O-(CH₂)_p-R_y, wherein p is an integer selected from 0, 1, 2, 3, and 4, and R_y is selected from C₃-C₁₀ cycloalkyl and C₁-C₈ haloalkyl, -S(O)R', and -S(O₂)R', wherein each R' is independently selected from the group consisting of hydrogen, C₁-C₈ alkyl, C₁-C₈ haloalkyl, -NR₇R₈, where R₇ and R₈ are independently
 30 selected from C₁-C₈ alkyl and C₁-C₈ haloalkyl, and -O-CHR₁₂-R₁₃, wherein R₁₂ is H or C₁-C₈ alkyl and R₁₃ is C₃-C₈ cycloalkyl;

R₃ and R₄ are each independently selected from the group consisting of halogen, C₁-C₈ alkyl, C₁-C₈ alkoxy, C₁-C₈ haloalkyl, C₁-C₈ haloalkoxy, cyano, -S(O)R', and -S(O₂)R';



- 5 R₅ 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, C₁-C₈ alkyl, C₁-C₈ alkoxy, C₁-C₈ haloalkyl, cyano, -O-(CH₂)_p-R_y, wherein p is an integer selected from 0, 1, 2, 3, and 4, and R_y is selected from C₃-C₁₀ cycloalkyl and C₁-C₈ haloalkyl, -S(O)R', -S(O₂)R', -NR₇R₈, where R₇ and R₈ are independently selected from C₁-C₈ alkyl and C₁-C₈ haloalkyl, -NR₉R₁₀,
10 where R₉ and R₁₀ together form a saturated heterocyclic ring selected from the group consisting of piperidinyl, pyrrolidinyl, azetidiny, 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, C₁-C₈ alkyl, or halogen;
- 15 R₆ is hydrogen or C₁-C₈ alkyl; or
a pharmaceutically acceptable salt thereof.

In other aspects, the presently disclosed subject matter provides a method for modulating a Na_v1.8 sodium ion channel, the method comprising administering to a subject in need thereof, a modulating-effective amount of a compound of formula (I)
20 to the subject.

In other aspects, the presently disclosed subject matter provides a method for inhibiting Na_v1.8, the method comprising administering to a subject in need thereof, an inhibiting-effective amount of a compound of formula (I) to the subject.

In yet other aspects, the presently disclosed subject matter provides a method
25 for treating a condition, disease, or disorder associated with an increased Na_v1.8 activity or expression, the method comprising administering to a subject in need of treatment thereof a therapeutically effective amount of a compound of formula (I) to the subject.

In certain aspects, the condition, disease, or disorder associated with an
30 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.

Certain aspects of the presently disclosed subject matter having been stated hereinabove, which are addressed in whole or in part by the presently disclosed subject matter, other aspects will become evident as the description proceeds when taken in connection with the accompanying Examples as best described herein below.

5

BRIEF DESCRIPTION OF THE FIGURE

Having thus described the presently disclosed subject matter in general terms, reference will now be made to the accompanying Figure, which are not necessarily drawn to scale, and wherein:

10 FIG. 1 is representative of preclinical and clinical Nav1.8 inhibitors known in the art (prior art).

DETAILED DESCRIPTION

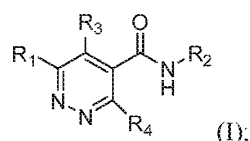
The presently disclosed subject matter now will be described more fully
15 hereinafter. The presently disclosed subject matter may be embodied in many different forms and should not be construed as limited to the embodiments set forth herein; rather, these embodiments are provided so that this disclosure will satisfy applicable legal requirements. Indeed, many modifications and other embodiments of the presently disclosed subject matter set forth herein will come to mind to one skilled
20 in the art to which the presently disclosed subject matter pertains having the benefit of the teachings presented in the foregoing descriptions. Therefore, it is to be understood that the presently disclosed subject matter is not to be limited to the specific embodiments disclosed and that modifications and other embodiments are intended to be included within the scope of the appended claims.

25 I. PYRIDAZINE COMPOUNDS FOR INHIBITING Nav1.8

The presently disclosed subject matter provides sodium channel inhibitors and their use for treating a condition, disease, or disorder associated with an increased Nav1.8 activity or expression.

A. Representative Compounds of Formula (I)

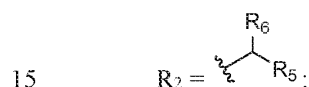
30 In some embodiments, the presently disclosed subject matter provides a compound of formula (I):



wherein:

R₁ 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, C₁-C₈ alkyl, C₁-C₈ alkoxy, C₁-C₈ haloalkyl, C₃-C₁₀ cycloalkyl, cyano, -O-(CH₂)_p-R_y, wherein p is an integer selected from 0, 1, 2, 3, and 4, and R_y is selected from C₃-C₁₀ cycloalkyl and C₁-C₈ haloalkyl, -S(O)R', and -S(O₂)R', wherein each R' is independently selected from the group consisting of hydrogen, C₁-C₈ alkyl, C₁-C₈ haloalkyl, -NR₇R₈, where R₇ and R₈ are independently selected from C₁-C₈ alkyl and C₁-C₈ haloalkyl, and -O-CHR₁₂-R₁₃, wherein R₁₂ is H or C₁-C₈ alkyl and R₁₃ is C₃-C₈ cycloalkyl;

R₃ and R₄ are each independently selected from the group consisting of halogen, C₁-C₈ alkyl, C₁-C₈ alkoxy, C₁-C₈ haloalkyl, C₁-C₈ haloalkoxy, cyano, -S(O)R', and -S(O₂)R';

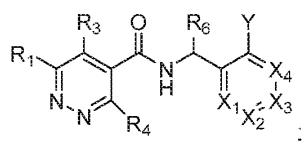


R₅ is selected from the group consisting of aryl or heteroaryl, wherein the aryl or heteroaryl is substituted with one or more substituent groups selected from the group consisting of halogen, C₁-C₈ alkyl, C₁-C₈ alkoxy, C₁-C₈ haloalkyl, cyano, -O-(CH₂)_p-R_y, wherein p is an integer selected from 0, 1, 2, 3, and 4, and R_y is selected from C₃-C₁₀ cycloalkyl and C₁-C₈ haloalkyl, -S(O)R', -S(O₂)R', -NR₇R₈, where R₇ and R₈ are independently selected from C₁-C₈ alkyl and C₁-C₈ haloalkyl, -NR₉R₁₀, where R₉ and R₁₀ together form a saturated heterocyclic ring selected from the group consisting of piperidinyl, pyrrolidinyl, azetidyl, 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, C₁-C₈ alkyl, or halogen;

R₆ is hydrogen or C₁-C₈ alkyl; or

a pharmaceutically acceptable salt thereof.

In certain embodiments, the compound of formula (I) has the following structure:



wherein:

X₁, X₂, X₃, and X₄ are each independently -CR_x- or nitrogen;

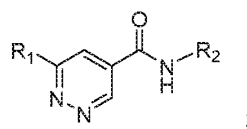
if any of X₁, X₂, X₃, or X₄ is -CR_x-, then each R_x is independently selected

5 from the group consisting of halogen, C₁-C₈ alkyl, and C₁-C₈ haloalkyl;

R₆ is hydrogen or C₁-C₈ alkyl; and

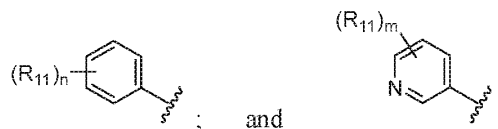
Y is selected from the group consisting of piperidinyl, pyrrolidinyl, azetidinyl, morpholinyl, azaspiro[3.3]heptanyl, 1,4-oxazepanyl, and azabicyclo[2.2.1]heptanyl, each of which can be substituted with one or more C₁-C₈ alkyl.

10 In more certain embodiments, the compound of formula (I) has the following structure:



wherein:

R₁ is selected from the group consisting of:



15

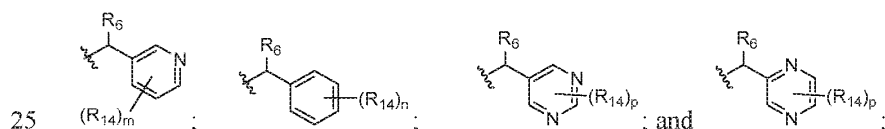
wherein:

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;

20 each R₁₁ is independently selected from the group consisting of H, C₁-C₈ alkyl, halogen, cyano, C₁-C₈ alkoxy, C₁-C₈ haloalkyl, -O-(CH₂)_p-R_y, wherein p is an integer selected from 0, 1, 2, 3, and 4, and R_y is selected from C₃-C₁₀ cycloalkyl and C₁-C₈ haloalkyl, and -O-CHR₁₂-R₁₃, wherein R₁₂ is H or C₁-C₈ alkyl and R₁₃ is C₃-C₈ cycloalkyl;

R₂ is selected from the group consisting of:



25

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;

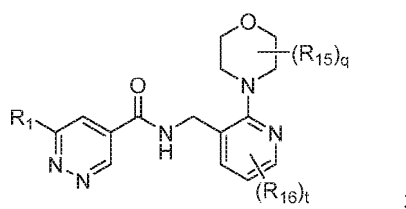
p is an integer selected from 0, 1, 2, and 3;

5 each R_6 is independently hydrogen or C₁-C₈ alkyl;

each R_{14} is independently selected from the group consisting of halogen, C₁-C₈ alkyl, C₁-C₈ alkoxy, C₁-C₈ haloalkyl, cyano, -O-(CH₂)_p-R_y, wherein p is an integer selected from 0, 1, 2, 3, and 4, and R_y is selected from C₃-C₁₀ cycloalkyl and C₁-C₈ haloalkyl, -S(O)R', -S(O₂)R', -NR₇R₈, where R₇ and R₈ are independently selected
10 from C₁-C₈ alkyl and C₁-C₈ haloalkyl, -NR₉R₁₀, where R₉ and R₁₀ together form a saturated heterocyclic ring selected from the group consisting of piperidinyl, pyrrolidinyl, azetidiny, 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, C₁-C₈ alkyl, or halogen;

15 and pharmaceutically acceptable salts thereof.

In some embodiments, the compound of formula (I) has the following structure:



wherein:

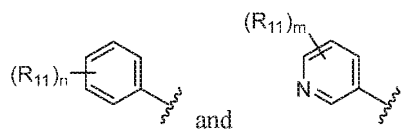
20 q is an integer selected from 0, 1, 2, 3, 4, 5, 6, 7, and 8;

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

each R_{15} is independently selected from deuterium, hydrogen, C₁-C₄ alkyl, and -CF₃;

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

25 R_1 is selected from:



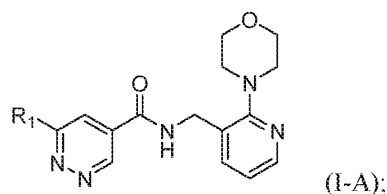
wherein:

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

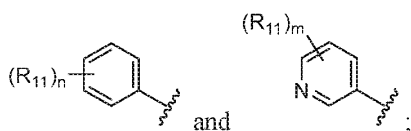
each R_{11} is independently selected from the group consisting of H, C₁-C₈ alkyl, halogen, cyano, C₁-C₈ alkoxy, -O-(CH₂)_p-R_y, wherein p is an integer selected from 0, 1, 2, 3, and 4, and R_y is selected from C₃-C₁₀ cycloalkyl and C₁-C₈ haloalkyl, and -O-CHR₁₂-R₁₃, wherein R₁₂ is H or C₁-C₈ alkyl and R₁₃ is C₃-C₈ cycloalkyl.

In certain embodiments, the compound of formula (I) has the following structure:



wherein:

10 R_1 is selected from:



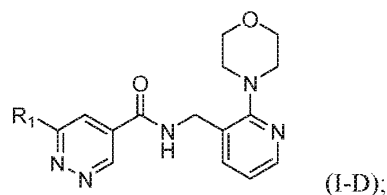
wherein:

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

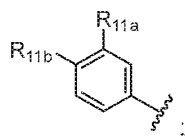
15 each R_{11} is independently selected from the group consisting of C₁-C₈ alkyl, halogen, cyano, C₁-C₈ alkoxy, -O-(CH₂)_p-R_y, wherein p is an integer selected from 0, 1, 2, 3, and 4, and R_y is selected from C₃-C₁₀ cycloalkyl and C₁-C₈ haloalkyl, and -O-CHR₁₂-R₁₃, wherein R₁₂ is H or C₁-C₈ alkyl and R₁₃ is C₃-C₈ cycloalkyl.

20 In certain embodiments, the compound of formula (I) has the following structure:



wherein:

R_1 is:



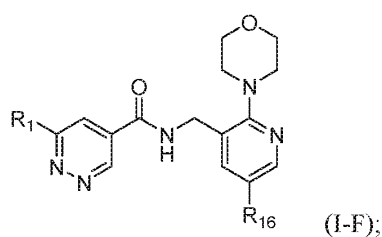
wherein:

R_{11a} is halogen or C₁-C₈ haloalkyl; and

R_{11b} is -O-CHR₁₂-R₁₃, wherein R₁₂ is hydrogen or C₁-C₈ alkyl and R₁₃ is C₃-C₈

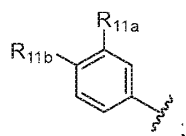
5 cycloalkyl.

In certain embodiments, the compound of formula (I) has the following structure:



wherein:

10 R₁ is:



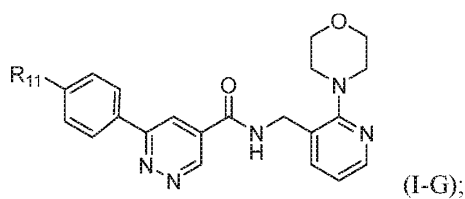
wherein:

R_{11a} is H;

R_{11b} is halogen or cyano; and

15 R₁₆ is halogen.

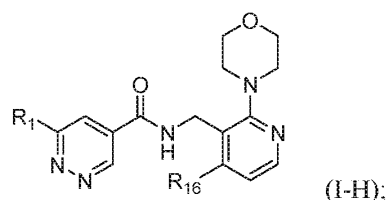
In certain embodiments, the compound of formula (I) has the following structure:



wherein:

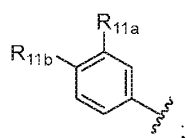
R_{11} is selected from the group consisting of halogen, cyano, and $-O-(CH_2)_p-R_y$, wherein p is an integer selected from 0, 1, 2, 3, and 4, and R_y is C_1 - C_8 haloalkyl.

In certain embodiments, the compound of formula (I) has the following
5 structure:



wherein:

R_1 is:



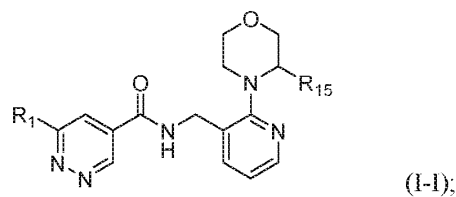
10 wherein:

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

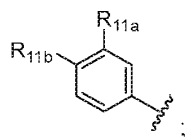
R_{16} is C_1 - C_4 alkyl.

15 In certain embodiments, the compound of formula (I) has the following structure:



wherein:

20 R_1 is:



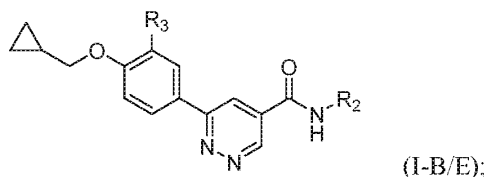
wherein:

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

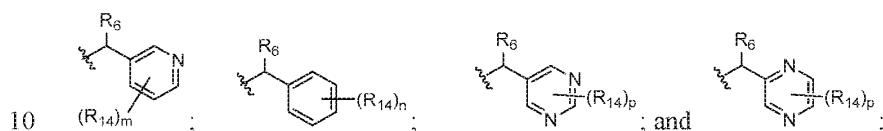
R_{15} is C_1 - C_4 alkyl.

5 In certain embodiments, the compound of formula (I) has the following structure:



wherein:

R_2 is selected from the group consisting of:



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;

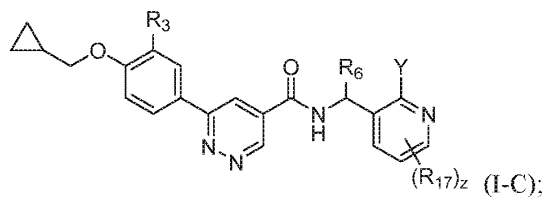
p is an integer selected from 0, 1, 2, and 3;

15 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 alkoxy, 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, azetidiny, 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
25 can optionally substituted with deuterium, C_1 - C_8 alkyl, or halogen.

In certain embodiments, the compound of formula (I) has the following structure:



wherein:

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

R₃ is hydrogen or halogen;

5 R₆ is hydrogen or C₁-C₄ alkyl;

Y is selected from the group consisting of C₁-C₄ alkyl, C₁-C₈ alkoxy, and -S(=O)₂-R', wherein R' is C₁-C₄ alkyl;

R₁₇ is halogen.

In particular embodiments, 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;

15 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;

20 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;

25 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;

30 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;
- 5 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;
- 10 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;
- 15 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-
- 20 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;
- 25 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;
- 30 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;
- 5 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;
- 10 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;
- 15 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;
- 20 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;
- 25 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;
- 30 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);
- 5 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);
- 10 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);
- 15 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);
- 20 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);
- 25 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);
- 30 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);

5 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).

10 *B. Methods for Treating a Condition, Disease, or Disorder Associated with an Increased NAV1.8 Activity or Expression*

In some embodiments, the presently disclosed subject matter provides a method for modulating a Nav1.8 sodium ion channel, the method comprising administering to a subject in need thereof, a modulating-effective amount of a compound of formula (I) to the subject.

15 In other embodiments, the presently disclosed subject matter provides a method for inhibiting Nav1.8, the method comprising administering to a subject in need thereof, an inhibiting-effective amount of a compound of formula (I) to the subject.

20 As used herein, the term “inhibit,” and grammatical derivations thereof, refers to the ability of a presently disclosed compound, e.g., a presently disclosed compound of formula (I), to block, partially block, interfere, decrease, or reduce the activity or expression of Nav1.8 in a subject. Thus, one of ordinary skill in the art would appreciate that the term “inhibit” encompasses a complete and/or partial decrease in the function of the channel, e.g., a decrease by at least 10%, in some embodiments, a decrease by at least 20%, 30%, 50%, 75%, 95%, 98%, and up to and including 100%.

25 In particular embodiments, the presently disclosed subject matter provides a method for treating a condition, disease, or disorder associated with an increased Nav1.8 activity or expression. In more particular embodiments, the condition, disease, or disorder associated with an increased Nav1.8 activity or expression is selected from the group consisting of pain, especially inflammatory, visceral, and neuropathic pain, neurological disorders, especially multiple sclerosis, autism, especially Pitt Hopkins Syndrome, and psychiatric diseases, and combinations thereof, wherein the method comprises administering to the subject in need thereof a therapeutically effective amount of a compound of formula I, or a pharmaceutically acceptable salt thereof.

In particular embodiments, the disease or condition 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, 5 peripherally mediated pain, centrally mediated pain, chronic headache, migraine headache, sinus headache, tension headache, phantom limb pain, dental pain, peripheral nerve injury or a combination thereof.

In other embodiments, the disease or condition is selected from the group consisting of pain associated with HIV, HIV treatment induced neuropathy, trigeminal 10 neuralgia, post-herpetic neuralgia, eudynia, heat sensitivity, tosaroidosis, irritable bowel syndrome, Crohn's disease, pain associated with 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, 15 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 20 fibrillation and ventricular fibrillation.

In some embodiments, the disease or condition is Pitt Hopkins Syndrome (PTHS).

The presently disclosed subject matter also includes use of a compound of formula (I) in the manufacture of a medicament for treating a condition, disease, or 25 disorder associated with an increased Nav1.8 activity or expression in a subject afflicted with such a disorder.

The "subject" treated by the presently disclosed methods in their many embodiments is desirably a human subject, although it is to be understood that the methods described herein are effective with respect to all vertebrate species, which 30 are intended to be included in the term "subject." Accordingly, a "subject" can include a human subject for medical purposes, such as for the treatment of an existing condition or disease or the prophylactic treatment for preventing the onset of a condition or disease, or an animal subject for medical, veterinary purposes, or developmental purposes. Suitable animal subjects include mammals including, but

not limited to, primates, e.g., humans, monkeys, apes, and the like; bovines, e.g., cattle, oxen, and the like; ovines, e.g., sheep and the like; caprines, e.g., goats and the like; porcines, e.g., pigs, hogs, and the like; equines, e.g., horses, donkeys, zebras, and the like; felines, including wild and domestic cats; canines, including dogs;

5 lagomorphs, including rabbits, hares, and the like; and rodents, including mice, rats, and the like. An animal may be a transgenic animal. In some embodiments, the subject is a human including, but not limited to, fetal, neonatal, infant, juvenile, and adult subjects. Further, a “subject” can include a patient afflicted with or suspected of being afflicted with a condition or disease. Thus, the terms “subject” and “patient”

10 are used interchangeably herein. The term “subject” also refers to an organism, tissue, cell, or collection of cells from a subject.

In general, the “effective amount” of an active agent or drug delivery device refers to the amount necessary to elicit the desired biological response. As will be appreciated by those of ordinary skill in this art, the effective amount of an agent or

15 device may vary depending on such factors as the desired biological endpoint, the agent to be delivered, the makeup of the pharmaceutical composition, the target tissue, and the like.

The term “combination” is used in its broadest sense and means that a subject is administered at least two agents, more particularly a compound of formula (I) and

20 at least one analgesic; and, optionally, one or more analgesic agents. More particularly, the term “in combination” refers to the concomitant administration of two (or more) active agents for the treatment of a, e.g., single disease state. As used herein, the active agents may be combined and administered in a single dosage form, may be administered as separate dosage forms at the same time, or may be

25 administered as separate dosage forms that are administered alternately or sequentially on the same or separate days. In one embodiment of the presently disclosed subject matter, the active agents are combined and administered in a single dosage form. In another embodiment, the active agents are administered in separate dosage forms (e.g., wherein it is desirable to vary the amount of one but not the

30 other). The single dosage form may include additional active agents for the treatment of the disease state.

Further, the compounds of formula (I) described herein can be administered alone or in combination with adjuvants that enhance stability of the compounds of formula (I), alone or in combination with one or more analgesic agents, facilitate

administration of pharmaceutical compositions containing them in certain embodiments, provide increased dissolution or dispersion, increase inhibitory activity, provide adjunct therapy, and the like, including other active ingredients.

Advantageously, such combination therapies utilize lower dosages of the conventional therapeutics, thus avoiding possible toxicity and adverse side effects incurred when those agents are used as monotherapies.

The timing of administration of a compound of formula (I) and at least one additional therapeutic agent can be varied so long as the beneficial effects of the combination of these agents are achieved. Accordingly, the phrase “in combination with” refers to the administration of a compound of formula (I) and at least one additional therapeutic agent either simultaneously, sequentially, or a combination thereof. Therefore, a subject administered a combination of a compound of formula (I) and at least one additional therapeutic agent can receive compound of formula (I) and at least one additional therapeutic agent at the same time (i.e., simultaneously) or at different times (i.e., sequentially, in either order, on the same day or on different days), so long as the effect of the combination of both agents is achieved in the subject.

When administered sequentially, the agents can be administered within 1, 5, 10, 30, 60, 120, 180, 240 minutes or longer of one another. In other embodiments, agents administered sequentially, can be administered within 1, 5, 10, 15, 20 or more days of one another. Where the compound of formula (I) and at least one additional therapeutic agent are administered simultaneously, they can be administered to the subject as separate pharmaceutical compositions, each comprising either a compound of formula (I) or at least one additional therapeutic agent, or they can be administered to a subject as a single pharmaceutical composition comprising both agents.

When administered in combination, the effective concentration of each of the agents to elicit a particular biological response may be less than the effective concentration of each agent when administered alone, thereby allowing a reduction in the dose of one or more of the agents relative to the dose that would be needed if the agent was administered as a single agent. The effects of multiple agents may, but need not be, additive or synergistic. The agents may be administered multiple times.

In some embodiments, when administered in combination, the two or more agents can have a synergistic effect. As used herein, the terms “synergy,” “synergistic,” “synergistically” and derivations thereof, such as in a “synergistic

effect” or a “synergistic combination” or a “synergistic composition” refer to circumstances under which the biological activity of a combination of a compound of formula (I) and at least one additional therapeutic agent is greater than the sum of the biological activities of the respective agents when administered individually.

- 5 Synergy can be expressed in terms of a “Synergy Index (SI),” which generally can be determined by the method described by F. C. Kull et al., Applied Microbiology 9, 538 (1961), from the ratio determined by:

$$Q_a/Q_A + Q_b/Q_B = \text{Synergy Index (SI)}$$

wherein:

- 10 Q_A is the concentration of a component A, acting alone, which produced an end point in relation to component A;
 Q_a is the concentration of component A, in a mixture, which produced an end point;
 Q_B is the concentration of a component B, acting alone, which produced an
15 end point in relation to component B; and
 Q_b is the concentration of component B, in a mixture, which produced an end point.

- Generally, when the sum of Q_a/Q_A and Q_b/Q_B is greater than one, antagonism is indicated. When the sum is equal to one, additivity is indicated. When the sum is
20 less than one, synergism is demonstrated. The lower the SI, the greater the synergy shown by that particular mixture. Thus, a “synergistic combination” has an activity higher than what can be expected based on the observed activities of the individual components when used alone. Further, a “synergistically effective amount” of a component refers to the amount of the component necessary to elicit a synergistic
25 effect in, for example, another therapeutic agent present in the composition.

More particularly, in some embodiments, the presently disclosed methods include co-administering to the subject a compound of formula (I) and/or a pharmaceutically acceptable salt thereof with one or more compounds selected from the group consisting of one or more:

- 30 nonsteroidal anti-inflammatory drugs (NSAIDs), including, but not limited to, aspirin, diclofenac, diflusal, etodolac, fenbufen, fenoprofen, flufenisal, flurbiprofen, ibuprofen, indomethacin, ketoprofen, ketorolac, meclofenamic acid, mefenamic acid, meloxicam, nabumetone, naproxen, nimesulide, nitroflurbiprofen, olsalazine,

oxaprozin, phenylbutazone, piroxicam, sulfasalazine, sulindac, tolmetin, and zomepirac;

- opioid analgesics, including, but not limited to, morphine, heroin, hydromorphone, oxycodone, levorphanol, levallorphan, methadone, meperidine, 5 fentanyl, cocaine, codeine, dihydrocodeine, oxycodone, hydrocodone, propoxyphene, nalmefene, nalorphine, naloxone, naltrexone, buprenorphine, butorphanol, nalbuphine, and pentazocine;

- barbiturates, including, but not limited to, amobarbital, aprobarbital, butabarbital, butabital, mephobarbital, metharbital, methohexital, pentobarbital, 10 phenobarbital, secobarbital, talbutal, thiamylal, and thiopental;

benzodiazepines, including, but not limited to, chlordiazepoxide, clorazepate, diazepam, flurazepam, lorazepam, oxazepam, temazepam, and triazolam;

histamine H₁ antagonists, including, but not limited to, diphenhydramine, pyrilamine, promethazine, chlorpheniramine, and chlorcyclizine;

- 15 sedatives, including, but not limited to, glutethimide, meprobamate, methaqualone, and dichloralphenazone;

a skeletal muscle relaxant, including, but not limited to, baclofen, carisoprodol, chlorzoxazone, cyclobenzaprine, methocarbamol, and orphenadine;

- an NMDA receptor antagonist, including, but not limited to, 20 dextromethorphan ((+)-3-hydroxy-N-methylmorphinan) or its metabolite dextrorphan ((+)-3-hydroxy-N-methylmorphinan), ketamine, memantine, pyrroloquinoline quinone, cis-4-(phosphonomethyl)-2-piperidinecarboxylic acid, bupidine, EN-3231 (MorphiDex[®]), a combination formulation of morphine and dextromethorphan), topiramate, neramexane or perzinfotel including an NR2B antagonist, e.g. ifenprodil, 25 traxoprodil, and (-)-(R)-6-{2-[4-(3-fluorophenyl)-4-hydroxy-1-piperidinyl]-1-hydroxyethyl-3,4-dihydro-2(1H)-quinolinone;

transient receptor potential ion channel antagonists;

- α-adrenergics, including, but not limited to, doxazosin, tamsulosin, clonidine, guanfacine, dexmetatomidine, modafinil, and 4-amino-6,7-dimethoxy-2-(5-methane- 30 sulfonamido-1, 2,3,4-tetrahydroisoquinol-2-yl)-5-(2-pyridyl) quinazoline;

tricyclic antidepressants, including, but not limited to, desipramine, imipramine, amitriptyline, and nortriptyline;

anticonvulsants, including, but not limited to, carbamazepine (Tegretol[®]), lamotrigine, topiramate, lacosamide (Vimpat[®]), and valproate;

- tachykinin antagonists, particularly an NK-3, NK-2 or NK-1 antagonist, including, but not limited to, (alphaR,9R)-7-[3,5-bis(trifluoromethyl)benzyl]-8,9,10,11-tetrahydro-9-methyl-5-(4-methylphenyl)-7H-[1,4]diazocino[2,1-g][1,7]-naphthyridine-6-13-di-one (TAK-637), 5-[[[(2R,3S)-2-[(1R)-1-[3,5-bis(trifluoromethyl)phenyl]ethoxy-3-(4-fluorophenyl)-4-morpholinyl]-methyl]-1,2-dihydro-3H-1,2,4-triazol-3-one (MK-869), aprepitant, lanepitant, dapitant, and 3-[[2-methoxy-5-(trifluoromethoxy)phenyl]-methylamino]-2-phenylpiperidine (2S,3S);
- muscarinic antagonists, including, but not limited to, oxybutynin, tolterodine, propiverine, trospium chloride, darifenacin, solifenacin, temiverine, and ipratropium;
- 10 cyclooxygenase-2 selective (COX-2) inhibitors, including, but not limited to, celecoxib, rofecoxib, parecoxib, valdecoxib, deracoxib, etoricoxib, and lumiracoxib;
- a coal-tar analgesic, including, but not limited to, paracetamol;
- neuroleptics, including, but not limited to, droperidol, chlorpromazine, haloperidol, perphenazine, thioridazine, mesoridazine, trifluoperazine, fluphenazine,
- 15 clozapine, olanzapine, risperidone, ziprasidone, quetiapine, sertindole, aripiprazole, sonopiprazole, blonanserin, iloperidone, perospirone, raclopride, zotepine, bifeprunox, asenapine, lurasidone, amisulpride, balaperidone, palindore, eplivanserin, osanetant, rimonabant, meclizine, Miraxion[®], and sarizotan;
- vanilloid receptor agonists, including, but not limited to, resiniferatoxin or
- 20 civamide;
- vanilloid receptor antagonists, including, but not limited to, capsazepine or GRC-15300);
- β-adrenergics, including, but not limited to, propranolol;
- local anaesthetics, including, but not limited to, mexiletine;
- 25 corticosteroids, including, but not limited to, dexamethasone and prednisone;
- 5-HT receptor agonists or antagonists, in particular a 5-HT_{1B/1D} agonist, including, but not limited to, eletriptan, sumatriptan, naratriptan, zolmitriptan or rizatriptan;
- 5-HT_{2A} receptor antagonists, including, but not limited to, R(+)-alpha-(2,3-dimethoxy-phenyl)-1-[2-(4-fluorophenylethyl)]-4-piperidinemethanol (MDL-
- 30 100907), eplivanserin, ketanserin, and pimavanserin;
- cholinergic (nicotinic) analgesics, including, but not limited to, ispronicline (TC-1734), (E)-N-methyl-4-(3-pyridinyl)-3-buten-1-amine (RJR-2403), (R)-5-(2-azetidylmethoxy)-2-chloropyridine (ABT-594), and nicotine;

- $\alpha\delta$ ligands, including, but not limited to, gabapentin (Neurontin®), gabapentin GR (Gralise®), gabapentin, enacarbil (Horizant®), pregabalin (Lyrica®), 3-methyl gabapentin, (1[alpha],3[alpha],5[alpha])(3-amino-methyl-bicyclo[3.2.0]hept-3-yl)-acetic acid, (3S,5R)-3-aminomethyl-5-methyl-heptanoic acid, (3S,5R)-3-amino-5-methyl-heptanoic acid, (3S,5R)-3-amino-5-methyl-octanoic acid, (2S,4S)-4-(3-chlorophenoxy)proline, (2S,4S)-4-(3-fluorobenzyl)-proline, [(1R,5R,6S)-6-(aminomethyl)bicyclo[3.2.0]hept-6-yl]acetic acid, 3-(1-aminomethyl-cyclohexylmethyl)-4H-[1,2,4]oxadiazol-5-one, C-[1-(1H-tetrazol-5-ylmethyl)-cycloheptyl]-methylamine, (3S,4S)-(1-aminomethyl-3,4-dimethyl-cyclopentyl)-acetic acid, (3S,5R)-3-aminomethyl-5-methyl-octanoic acid, (3S,5R)-3-amino-5-methyl-nonanoic acid, (3S,5R)-3-amino-5-methyl-octanoic acid, (3R,4R,5R)-3-amino-4,5-dimethyl-heptanoic acid and (3R,4R,5R)-3-amino-4,5-dimethyl-octanoic acid;
- cannabinoid receptor ligands, including, but not limited to, KHK-6188;
- metabotropic glutamate subtype 1 receptor antagonists;
- serotonin reuptake inhibitors, including, but not limited to, sertraline, sertraline metabolite demethylsertraline, fluoxetine, norfluoxetine (fluoxetine desmethyl metabolite), fluvoxamine, paroxetine, citalopram, citalopram metabolite desmethylcitalopram, escitalopram, d,l-fenfluramine, femoxetine, ifoxetine, cyanodothiepin, litoxetine, dapoxetine, nefazodone, cericlamine, and trazodone;
- noradrenaline (norepinephrine) reuptake inhibitors, including, but not limited to, maprotiline, lofepramine, mirtazepine, oxaprotiline, fezolamine, tomoxetine, mianserin, bupropion, bupropion metabolite hydroxybupropion, nomifensine and viloxazine (Vivalan®), especially a selective noradrenaline reuptake inhibitor, such as reboxetine, in particular (S,S)-reboxetine;
- dual serotonin-noradrenaline reuptake inhibitors, including, but not limited to, venlafaxine, venlafaxine metabolite O-desmethylvenlafaxine, clomipramine, clomipramine metabolite desmethylclomipramine, duloxetine (Cymbalta®), milnacipran and imipramine;
- Rho kinase inhibitors;
- inducible nitric oxide synthase (iNOS) inhibitors, including, but not limited to, S-[2-[(1-iminoethyl)amino]ethyl]-L-homocysteine, S-[2-[(1-iminoethyl)-amino]ethyl]-4,4-dioxo-L-cysteine, S-[2-[(1-iminoethyl)amino]ethyl]-2-methyl-L-cysteine, (2S,5Z)-2-amino-2-methyl-7-[(1-iminoethyl)amino]-5-heptenoic acid, 2-[[[(1R,3S)-3-amino-4-hydroxy-1-(5-thiazolyl)-butyl]thio]-S-chloro-S-pyridinecarbonitrile; 2-

- 5 [[(1R,3S)-3-amino-4-hydroxy-1-(5-thiazolyl)butyl]thio]-4-chlorobenzonitrile,
 (2S,4R)-2-amino-4-[[2-chloro-5-(trifluoromethyl)phenyl]thio]-5-thiazolebutanol, 2-
 [[(1R,3S)-3-amino-4-hydroxy-1-(5-thiazolyl) butyl]thio]-6-(trifluoromethyl)-3-
 pyridinecarbonitrile, 2-[[[(1R,3S)-3-amino-4-hydroxy-1-(5-thiazolyl)butyl]thio]-5-
 chlorobenzonitrile, N-[4-[2-(3-chlorobenzylamino)ethyl]phenyl]thiophene-2-
 carboxamide, NXN-462, and guanidinoethyldisulfide;
 acetylcholinesterase inhibitors, including, but not limited to, donepezil;
 prostaglandin E₂ subtype 4 antagonists, including, but not limited to, N-[(2-
 10 [4-(2-ethyl-4,6-dimethyl-1H-imidazo[4,5-c]pyridin-1-yl)phenyl]ethyl)amino)-
 carbonyl]-4-methylbenzenesulfonamide, and 4-[(15)-1-({[5-chloro-2-(3-
 fluorophenoxy)pyridin-3-yl]carbonyl}amino)ethyl]benzoic acid;
 leukotriene B₄ antagonists, including, but not limited to, 1-(3-biphenyl-4-
 ylmethyl-4-hydroxy-chroman-7-yl)-cyclopentanecarboxylic acid (CP-105696), 5-[2-
 (2-Carboxyethyl)-3-[6-(4-methoxyphenyl)-5E-hexenyl]oxyphenoxy]-valeric acid
 15 (ONO-4057), and DPC-11870;
 5-lipoxygenase inhibitors, including, but not limited to, zileuton, 6-[(3-fluoro-
 5-[4-methoxy-3,4,5,6-tetrahydro-2H-pyran-4-yl])phenoxy-methyl]-1-methyl-2-
 quinolone (ZD-2138), and 2,3,5-trimethyl-6-(3-pyridylmethyl)-1,4-benzoquinone
 (CV-6504);
 20 sodium channel blockers, including, but not limited to, lidocaine, lidocaine
 plus tetracaine cream (ZRS-201), and eslicarbazepine acetate;
 5-HT₃ antagonists, including, but not limited to, ondansetron;
 N-methyl-D-aspartic acid receptor antagonists;
 voltage-gated calcium channel blockers (e.g., N-type and T-type), including,
 25 but not limited to ziconotide, Z-160, (R)-2-(4-cyclopropylphenyl)-N-(1-(5-(2,2,2-
 trifluoroethoxy)pyridin-2-yl)ethyl) acetamide;
 KCNQ openers (e.g., KCNQ2/3 (K_v 7.2/3));
 TPRV 1 receptor agonists, including, but not limited to, capsaicin (Neuroges[®],
 Qutenza[®]); and the pharmaceutically acceptable salts and solvates thereof;
 30 nicotinic receptor antagonists, including, but not limited to, varenicline;
 nerve growth factor antagonists, including, but not limited to, tanezumab;
 endopeptidase stimulants, including, but not limited to, senrebotase;
 angiotensin II antagonists, including, but not limited to, EMA-401;
 Tramadol[®], Tramadol ER (Ultram ER[®]), Tapentadol ER (Nucynta[®]);

PDE5 inhibitors, including, but not limited to, 5-[2-ethoxy-5-(4-methyl-1-piperazinyl-sulphonyl)phenyl]-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one (sildenafil), (6R,12aR)-2,3,6,7,12,12a-hexahydro-2-methyl-6-(3,4-methylenedioxyphenyl)-pyrazino[2',1':6,1]-pyrido[3,4-b]indole-1,4-dione (IC-351 or 5
tadalafil), 2-[2-ethoxy-5-(4-ethyl-piperazin-1-yl)-1-sulphonyl]-phenyl]-5-methyl-7-propyl-3H-imidazo[5,1-f][1,2,4]triazin-4-one (vardenafil), 5-(5-acetyl-2-butoxy-3-pyridinyl)-3-ethyl-2-(1-ethyl-3-azetidiny)-2,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one, 5-(5-acetyl-2-propoxy-3-pyridinyl)-3-ethyl-2-(1-isopropyl-3-azetidiny)-2,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one, 5-[2-ethoxy-5-(4-ethylpiperazin-1-ylsulphonyl)pyridin-3-yl]-3-ethyl-2-[2-methoxyethyl]-2,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one, 4-[(3-chloro-4-methoxybenzyl)amino]-2-[(2S)-2-(hydroxymethyl)pyrrolidin-1-yl]-N-(pyrimidin-2-ylmethyl)pyrimidine-5-carboxamide, 3-(1-methyl-7-oxo-3-propyl-6,7-dihydro-1H-pyrazolo[4,3-d]pyrimidin-5-yl)-N-[2-(1-methylpyrrolidin-2-yl)ethyl]-4-propoxybenzenesulfonamide;
15 Nav1.7 blockers, including, but not limited to, XEN-402, XEN403, TV-45070, PF-05089771, CNV1014802, GDC-0276, RG7893 and such as those disclosed in WO2011/140425; WO2012/106499; WO2012/112743; WO2012/125613, WO2012/116440, WO2011026240, U.S. Pat. Nos. 8,883,840, or 8,466,188, or PCT/US2013/21535 the entire contents of each application hereby incorporated by
20 reference; and

Nav1.7 blockers, including, but not limited to, (2-benzylspiro[3,4-dihydropyrrolo[1,2-a]pyrazine-1,4'-piperidine]-1'-yl)-(4-isopropoxy-3-methyl-phenyl)methanone, 2,2,2-trifluoro-1-[1'-[3-methoxy-4-[2-(trifluoromethoxy)ethoxy]benzoyl]-2-,4-dimethyl-spiro[3,4-dihydropyrrolo[1,2-a]pyrazine-1,4'-piperidine]-6-yl]-ethanone, [8-fluoro-2-methyl-6-(trifluoromethyl)spiro[3,4-dihydropyrrolo[1-,2-a]pyrazine-1,4'-piperidine]-1'-yl]-(4-isobutoxy-3-methoxy-phenyl)methanone, 1-(4-benzhydrylpiperazin-1-yl)-3-[2-(3,4-dimethylphenoxy)ethoxy]propan-2-ol, (4-butoxy-3-methoxy-phenyl)-[2-methyl-6-(trifluoromethyl)spiro[3,4-dihydropyrrolo[1,2-a]pyrazine-1,4'-piperidine]-1'-yl]methanone, [8-fluoro-2-methyl-6-(trifluoromethyl)spiro[3,4-dihydropyrrolo[1,2-a]pyrazine-1,4'-piperidine]-1'-yl]-(5-isopropoxy-6-methyl-2-pyridyl)methanone, (4-isopropoxy-3-methyl-phenyl)-[2-methyl-6-(1,1,2,2,2-pentafluoroethyl)spiro[3,4-dihydropyrrolo[1,2-a]pyrazine-1,4'-piperidine]-1'-yl]methanone, 5-[2-methyl-4-[2-methyl-6-(2,2,2-trifluoroacetyl)spiro[3,4-dihydropyrrolo[1,2-a]pyrazine-1,4'-

- piperidine]-1'-carbonyl]phenyl]pyridine-2-carbonitrile, (4-isopropoxy-3-methyl-phenyl)-[6-(trifluoromethyl)spiro[3,4-dihydro-2H-pyrrolo[1,2-a]pyrazine-1,4'-piperidine]-1'-yl]methanone, 2,2,2-trifluoro-1-[1'-(3-methoxy-4-[2-(trifluoromethoxy)ethoxy]benzoyl]-2-methyl-spiro[3,4-dihydropyrrolo[1,2-a]pyrazine-1,4'-piperidine]-6-yl]ethanone, 2,2,2-trifluoro-1-[1'-(5-isopropoxy-6-methyl-pyridine-2-carbonyl)-3,3-dimethyl-spiro[2,4-dihydropyrrolo[1,2-a]pyrazine-1,4'-piperidine]-6-yl]ethanone, 2,2,2-trifluoro-1-[1'-(5-isopentylloxypyridine-2-carbonyl)-2-methyl-spiro[3,4-dihydropyrrolo[1,2-a]pyrazine-1,4'-piperidine]-6-yl]ethanone, (4-isopropoxy-3-methoxy-phenyl)-[2-methyl-6-(trifluoromethyl)spiro[3,4-dihydropyrrolo[1,2-a]pyrazine-1,4'-piperidine]-1'-yl]methanone, 2,2,2-trifluoro-1-[1'-(5-isopentylloxypyridine-2-carbonyl)-2,4-dimethyl-spiro[3,4-dihydropyrrolo[1,2-a]pyrazine-1,4'-piperidine]-6-yl]ethanone, 1-[(3S)-2,3-dimethyl-1'-[4-(3,3,3-trifluoropropoxymethyl)benzoyl]spiro[3,4-dihydropyrrolo[1,2-a]pyrazine-1,4'-piperidine]-6-yl]-2,2,2-trifluoro-ethanone, [8-fluoro-2-methyl-6-(trifluoromethyl)spiro[3,4-dihydropyrrolo[1,2-a]pyrazine-1,4'-piperidine]-1'-yl]-[3-methoxy-4-[(1R)-1-methylpropoxy]phenyl]methanone, 2,2,2-trifluoro-1-[1'-(5-isopropoxy-6-methyl-pyridine-2-carbonyl)-2,4-dimethyl-spiro[3,4-dihydropyrrolo[1,2-a]pyrazine-1,4'-piperidine]-6-yl]ethanone, 1-[1'-[4-methoxy-3-(trifluoromethyl)benzoyl]-2-methyl-spiro[3,4-dihydropyrrolo[1,2-a]pyrazine-1,4'-piperidine]-6-yl]-2,2-dimethyl-propan-1-one, (4-isopropoxy-3-methyl-phenyl)-[2-methyl-6-(trifluoromethyl)spiro[3,4-dihydropyrrolo[1,2-a]pyrazine-1,4'-piperidine]-1'-yl]methanone, [2-methyl-6-(1-methylcyclopropanecarbonyl)spiro[3,4-dihydropyrrolo[1,2-a]pyrazine-1,4'-piperidine]-1'-yl]-[4-(3,3,3-trifluoropropoxymethyl)phenyl]methanone, 4-bromo-N-(4-bromophenyl)-3-[(1-methyl-2-oxo-4-piperidyl)sulfamoyl]benzamide or (3-chloro-4-isopropoxy-phenyl)-[2-methyl-6-(1,1,2,2,2-pentafluoroethyl)spiro[3,4-dihydropyrrolo[1,2-a]pyrazine-1,4'-piperidine]-1'-yl]methanone.

In some embodiments, the method comprises administering to the subject a therapeutically effective amount of a compound described herein, or a pharmaceutically acceptable salt, with or without a pharmaceutically acceptable carrier, in combination with a second therapeutic agent selected from the group consisting of acetaminophen, NSAIDs, opioid analgesics, and combinations thereof.

In some embodiments, the method comprises administering to the subject a therapeutically effective amount of a compound described herein, or a

pharmaceutically acceptable salt, with or without a pharmaceutically acceptable carrier, in combination with one or more additional therapeutic agents for treating pain. In one embodiment, the additional therapeutic agent is selected from the group consisting of acetaminophen, NSAIDs (such as aspirin, ibuprofen, and naproxen), and
5 opioid analgesics. In another embodiment, the additional therapeutic agent is acetaminophen. In another embodiment, the additional therapeutic agent is an NSAID. In another embodiment, the additional therapeutic agent is an opioid analgesic.

C. Pharmaceutical Compositions and Administration

10 In another aspect, the present disclosure provides a pharmaceutical composition including one compound of formula (I) alone or in combination with one or more additional therapeutic agents in admixture with a pharmaceutically acceptable excipient. One of ordinary skill in the art will recognize that the pharmaceutical compositions include the pharmaceutically acceptable salts of the compounds
15 described above. Pharmaceutically acceptable salts are generally well known to those of ordinary skill in the art, and include salts of active compounds which are prepared with relatively nontoxic acids or bases, depending on the particular substituent moieties found on the compounds described herein. When compounds of the present disclosure contain relatively acidic functionalities, base addition salts can be obtained
20 by contacting the neutral form of such compounds with a sufficient amount of the desired base, either neat or in a suitable inert solvent or by ion exchange, whereby one basic counterion (base) in an ionic complex is substituted for another. Examples of pharmaceutically acceptable base addition salts include sodium, potassium, calcium, ammonium, organic amino, or magnesium salt, or a similar salt.

25 When compounds of the present disclosure contain relatively basic functionalities, acid addition salts can be obtained by contacting the neutral form of such compounds with a sufficient amount of the desired acid, either neat or in a suitable inert solvent or by ion exchange, whereby one acidic counterion (acid) in an ionic complex is substituted for another. Examples of pharmaceutically acceptable
30 acid addition salts include those derived from inorganic acids like hydrochloric, hydrobromic, nitric, carbonic, monohydrogencarbonic, phosphoric, monohydrogenphosphoric, dihydrogenphosphoric, sulfuric, monohydrogensulfuric, hydriodic, or phosphorous acids and the like, as well as the salts derived from relatively nontoxic organic acids like acetic, propionic, isobutyric, maleic, malonic,

benzoic, succinic, suberic, fumaric, lactic, mandelic, phthalic, benzenesulfonic, p-toluenesulfonic, citric, tartaric, methanesulfonic, and the like. Also included are salts of amino acids such as arginate and the like, and salts of organic acids like glucuronic or galactunoric acids and the like (see, for example, Berge et al, "Pharmaceutical
5 Salts", Journal of Pharmaceutical Science, 1977, 66, 1-19). Certain specific compounds of the present disclosure contain both basic and acidic functionalities that allow the compounds to be converted into either base or acid addition salts.

Accordingly, pharmaceutically acceptable salts suitable for use with the presently disclosed subject matter include, by way of example but not limitation,
10 acetate, benzenesulfonate, benzoate, bicarbonate, bitartrate, bromide, calcium edetate, camsylate, carbonate, citrate, edetate, edisylate, estolate, esylate, fumarate, gluceptate, gluconate, glutamate, glycolylarsanilate, hexylresorcinate, hydrabamine, hydrobromide, hydrochloride, hydroxynaphthoate, iodide, isethionate, lactate, lactobionate, malate, maleate, mandelate, mesylate, mucate, napsylate, nitrate,
15 pamoate (embonate), pantothenate, phosphate/diphosphate, polygalacturonate, salicylate, stearate, subacetate, succinate, sulfate, tannate, tartrate, or teoclate. Other pharmaceutically acceptable salts may be found in, for example, Remington: The Science and Practice of Pharmacy (20th ed.) Lippincott, Williams & Wilkins (2000).

In therapeutic and/or diagnostic applications, the compounds of the disclosure
20 can be formulated for a variety of modes of administration, including systemic and topical or localized administration. Techniques and formulations generally may be found in Remington: The Science and Practice of Pharmacy (20th ed.) Lippincott, Williams & Wilkins (2000).

Depending on the specific conditions being treated, such agents may be
25 formulated into liquid or solid dosage forms and administered systemically or locally. The agents may be delivered, for example, in a timed- or sustained-slow release form as is known to those skilled in the art. Techniques for formulation and administration may be found in Remington: The Science and Practice of Pharmacy (20th ed.) Lippincott, Williams & Wilkins (2000). Suitable routes may include oral, buccal, by
30 inhalation spray, sublingual, rectal, transdermal, vaginal, transmucosal, nasal or intestinal administration; parenteral delivery, including intramuscular, subcutaneous, intramedullary injections, as well as intrathecal, direct intraventricular, intravenous, intra-articular, intra-sternal, intra-synovial, intra-hepatic, intralesional, intracranial, intraperitoneal, intranasal, or intraocular injections or other modes of delivery.

For injection, the agents of the disclosure may be formulated and diluted in aqueous solutions, such as in physiologically compatible buffers such as Hank's solution, Ringer's solution, or physiological saline buffer. For such transmucosal administration, penetrants appropriate to the barrier to be permeated are used in the
5 formulation. Such penetrants are generally known in the art.

Use of pharmaceutically acceptable inert carriers to formulate the compounds herein disclosed for the practice of the disclosure into dosages suitable for systemic administration is within the scope of the disclosure. With proper choice of carrier and suitable manufacturing practice, the compositions of the present disclosure, in
10 particular, those formulated as solutions, may be administered parenterally, such as by intravenous injection. The compounds can be formulated readily using pharmaceutically acceptable carriers well known in the art into dosages suitable for oral administration. Such carriers enable the compounds of the disclosure to be formulated as tablets, pills, capsules, liquids, gels, syrups, slurries, suspensions and
15 the like, for oral ingestion by a subject (e.g., patient) to be treated.

For nasal or inhalation delivery, the agents of the disclosure also may be formulated by methods known to those of ordinary skill in the art, and may include, for example, but not limited to, examples of solubilizing, diluting, or dispersing substances, such as saline; preservatives, such as benzyl alcohol; absorption
20 promoters; and fluorocarbons.

Pharmaceutical compositions suitable for use in the present disclosure include compositions wherein the active ingredients are contained in an effective amount to achieve its intended purpose. Determination of the effective amounts is well within the capability of those skilled in the art, especially in light of the detailed disclosure
25 provided herein. Generally, the compounds according to the disclosure are effective over a wide dosage range. For example, in the treatment of adult humans, dosages from 0.01 to 1000 mg, from 0.5 to 100 mg, from 1 to 50 mg per day, and from 5 to 40 mg per day are examples of dosages that may be used. A non-limiting dosage is 10 to 30 mg per day. The exact dosage will depend upon the route of administration, the
30 form in which the compound is administered, the subject to be treated, the body weight of the subject to be treated, the bioavailability of the compound(s), the adsorption, distribution, metabolism, and excretion (ADME) toxicity of the compound(s), and the preference and experience of the attending physician.

In addition to the active ingredients, these pharmaceutical compositions may

contain suitable pharmaceutically acceptable carriers comprising excipients and auxiliaries which facilitate processing of the active compounds into preparations which can be used pharmaceutically. The preparations formulated for oral administration may be in the form of tablets, dragees, capsules, or solutions.

5 Pharmaceutical preparations for oral use can be obtained by combining the active compounds with solid excipients, optionally grinding a resulting mixture, and processing the mixture of granules, after adding suitable auxiliaries, if desired, to obtain tablets or dragee cores. Suitable excipients are, in particular, fillers such as sugars, including lactose, sucrose, mannitol, or sorbitol; cellulose preparations, for
10 example, maize starch, wheat starch, rice starch, potato starch, gelatin, gum tragacanth, methyl cellulose, hydroxypropylmethyl-cellulose, sodium carboxymethyl-cellulose (CMC), and/or polyvinylpyrrolidone (PVP: povidone). If desired, disintegrating agents may be added, such as the cross-linked polyvinylpyrrolidone, agar, or alginic acid or a salt thereof such as sodium alginate.

15 Dragee cores are provided with suitable coatings. For this purpose, concentrated sugar solutions may be used, which may optionally contain gum arabic, talc, polyvinylpyrrolidone, carbopol gel, polyethylene glycol (PEG), and/or titanium dioxide, lacquer solutions, and suitable organic solvents or solvent mixtures. Dye-stuffs or pigments may be added to the tablets or dragee coatings for identification or
20 to characterize different combinations of active compound doses.

 Pharmaceutical preparations that can be used orally include push-fit capsules made of gelatin, as well as soft, sealed capsules made of gelatin, and a plasticizer, such as glycerol or sorbitol. The push-fit capsules can contain the active ingredients in admixture with filler such as lactose, binders such as starches, and/or lubricants
25 such as talc or magnesium stearate and, optionally, stabilizers. In soft capsules, the active compounds may be dissolved or suspended in suitable liquids, such as fatty oils, liquid paraffin, or liquid polyethylene glycols (PEGs). In addition, stabilizers may be added.

II. Definitions

30 Although specific terms are employed herein, they are used in a generic and descriptive sense only and not for purposes of limitation. Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this presently described subject matter belongs.

While the following terms in relation to compounds of formula (I) are believed to be well understood by one of ordinary skill in the art, the following definitions are set forth to facilitate explanation of the presently disclosed subject matter. These definitions are intended to supplement and illustrate, not preclude, the definitions that would be apparent to one of ordinary skill in the art upon review of the present disclosure.

The terms substituted, whether preceded by the term “optionally” or not, and substituent, as used herein, refer to the ability, as appreciated by one skilled in this art, to change one functional group for another functional group on a molecule, provided that the valency of all atoms is maintained. When more than one position in any given structure may be substituted with more than one substituent selected from a specified group, the substituent may be either the same or different at every position. The substituents also may be further substituted (e.g., an aryl group substituent may have another substituent off it, such as another aryl group, which is further substituted at one or more positions).

Where substituent groups or linking groups are specified by their conventional chemical formulae, written from left to right, they equally encompass the chemically identical substituents that would result from writing the structure from right to left, e.g., $-\text{CH}_2\text{O}-$ is equivalent to $-\text{OCH}_2-$; $-\text{C}(=\text{O})\text{O}-$ is equivalent to $-\text{OC}(=\text{O})-$; $-\text{OC}(=\text{O})\text{NR}-$ is equivalent to $-\text{NRC}(=\text{O})\text{O}-$, and the like.

When the term “independently selected” is used, the substituents being referred to (e.g., R groups, such as groups R_1 , R_2 , and the like, or variables, such as “m” and “n”), can be identical or different. For example, both R_1 and R_2 can be substituted alkyls, or R_1 can be hydrogen and R_2 can be a substituted alkyl, and the like.

The terms “a,” “an,” or “a(n),” when used in reference to a group of substituents herein, mean at least one. For example, where a compound is substituted with “an” alkyl or aryl, the compound is optionally substituted with at least one alkyl and/or at least one aryl. Moreover, where a moiety is substituted with an R substituent, the group may be referred to as “R-substituted.” Where a moiety is R-substituted, the moiety is substituted with at least one R substituent and each R substituent is optionally different.

A named “R” or group will generally have the structure that is recognized in the art as corresponding to a group having that name, unless specified otherwise

herein. For the purposes of illustration, certain representative “R” groups as set forth above are defined below.

Descriptions of compounds of the present disclosure are limited by principles of chemical bonding known to those skilled in the art. Accordingly, where a group
5 may be substituted by one or more of a number of substituents, such substitutions are selected so as to comply with principles of chemical bonding and to give compounds which are not inherently unstable and/or would be known to one of ordinary skill in the art as likely to be unstable under ambient conditions, such as aqueous, neutral, and several known physiological conditions. For example, a heterocycloalkyl or
10 heteroaryl is attached to the remainder of the molecule via a ring heteroatom in compliance with principles of chemical bonding known to those skilled in the art thereby avoiding inherently unstable compounds.

Unless otherwise explicitly defined, a “substituent group,” as used herein, includes a functional group selected from one or more of the following moieties,
15 which are defined herein:

The term hydrocarbon, as used herein, refers to any chemical group comprising hydrogen and carbon. The hydrocarbon may be substituted or unsubstituted. As would be known to one skilled in this art, all valencies must be satisfied in making any substitutions. The hydrocarbon may be unsaturated, saturated,
20 branched, unbranched, cyclic, polycyclic, or heterocyclic. Illustrative hydrocarbons are further defined herein below and include, for example, methyl, ethyl, *n*-propyl, isopropyl, cyclopropyl, allyl, vinyl, *n*-butyl, *tert*-butyl, ethynyl, cyclohexyl, and the like.

The term “alkyl,” by itself or as part of another substituent, means, unless
25 otherwise stated, a straight (i.e., unbranched) or branched chain, acyclic or cyclic hydrocarbon group, or combination thereof, which may be fully saturated, mono- or polyunsaturated and can include di- and multivalent groups, having the number of carbon atoms designated (i.e., C₁₋₁₀ means one to ten carbons, including 1, 2, 3, 4, 5, 6, 7, 8, 9, and 10 carbons). In particular embodiments, the term “alkyl” refers to C₁₋₂₀
30 inclusive, including 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, and 20 carbons, linear (i.e., “straight-chain”), branched, or cyclic, saturated or at least partially and in some cases fully unsaturated (i.e., alkenyl and alkynyl) hydrocarbon radicals derived from a hydrocarbon moiety containing between one and twenty carbon atoms by removal of a single hydrogen atom.

Representative saturated hydrocarbon groups include, but are not limited to, methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl, isobutyl, *sec*-butyl, *tert*-butyl, *n*-pentyl, *sec*-pentyl, isopentyl, neopentyl, *n*-hexyl, *sec*-hexyl, *n*-heptyl, *n*-octyl, *n*-decyl, *n*-undecyl, dodecyl, cyclohexyl, (cyclohexyl)methyl, cyclopropylmethyl, and homologs
5 and isomers thereof.

“Branched” refers to an alkyl group in which a lower alkyl group, such as methyl, ethyl or propyl, is attached to a linear alkyl chain. “Lower alkyl” refers to an alkyl group having 1 to about 8 carbon atoms (i.e., a C₁₋₈ alkyl), e.g., 1, 2, 3, 4, 5, 6, 7, or 8 carbon atoms. “Higher alkyl” refers to an alkyl group having about 10 to about
10 20 carbon atoms, e.g., 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20 carbon atoms. In certain embodiments, “alkyl” refers, in particular, to C₁₋₈ straight-chain alkyls. In other embodiments, “alkyl” refers, in particular, to C₁₋₈ branched-chain alkyls.

Alkyl groups can optionally be substituted (a “substituted alkyl”) with one or more alkyl group substituents, which can be the same or different. The term “alkyl
15 group substituent” includes but is not limited to alkyl, substituted alkyl, halo, arylamino, acyl, hydroxyl, aryloxy, alkoxy, alkylthio, arylthio, aralkyloxy, aralkylthio, carboxyl, alkoxycarbonyl, oxo, and cycloalkyl. There can be optionally inserted along the alkyl chain one or more oxygen, sulfur or substituted or unsubstituted nitrogen atoms, wherein the nitrogen substituent is hydrogen, lower
20 alkyl (also referred to herein as “alkylaminoalkyl”), or aryl.

Thus, as used herein, the term “substituted alkyl” includes alkyl groups, as defined herein, in which one or more atoms or functional groups of the alkyl group are replaced with another atom or functional group, including for example, alkyl, substituted alkyl, halogen, aryl, substituted aryl, alkoxy, hydroxyl, nitro, amino,
25 alkylamino, dialkylamino, sulfate, cyano, and mercapto.

The term “heteroalkyl,” by itself or in combination with another term, means, unless otherwise stated, a stable straight or branched chain having from 1 to 20 carbon atoms or heteroatoms or a cyclic hydrocarbon group having from 3 to 10 carbon atoms or heteroatoms, or combinations thereof, consisting of at least one carbon atom
30 and at least one heteroatom selected from the group consisting of O, N, P, Si and S, and wherein the nitrogen, phosphorus, and sulfur atoms may optionally be oxidized and the nitrogen heteroatom may optionally be quaternized. The heteroatom(s) O, N, P and S and Si may be placed at any interior position of the heteroalkyl group or at the position at which alkyl group is attached to the remainder of the molecule. Examples

- include, but are not limited to, $-\text{CH}_2-\text{CH}_2-\text{O}-\text{CH}_3$, $-\text{CH}_2-\text{CH}_2-\text{NH}-\text{CH}_3$,
 $-\text{CH}_2-\text{CH}_2-\text{N}(\text{CH}_3)-\text{CH}_3$, $-\text{CH}_2-\text{S}-\text{CH}_2-\text{CH}_3$, $-\text{CH}_2-\text{CH}_2-\text{S}(\text{O})-\text{CH}_3$,
 $-\text{CH}_2-\text{CH}_2-\text{S}(\text{O})_2-\text{CH}_3$, $-\text{CH}=\text{CH}-\text{O}-\text{CH}_3$, $-\text{Si}(\text{CH}_3)_3$, $-\text{CH}_2-\text{CH}=\text{N}-\text{OCH}_3$,
 $-\text{CH}=\text{CH}-\text{N}(\text{CH}_3)-\text{CH}_3$, $\text{O}-\text{CH}_3$, $-\text{O}-\text{CH}_2-\text{CH}_3$, and $-\text{CN}$. Up to two or three
5 heteroatoms may be consecutive, such as, for example, $-\text{CH}_2-\text{NH}-\text{OCH}_3$ and
 $-\text{CH}_2-\text{O}-\text{Si}(\text{CH}_3)_3$.

As described above, heteroalkyl groups, as used herein, include those groups that are attached to the remainder of the molecule through a heteroatom, such as $-\text{C}(\text{O})\text{NR}'$, $-\text{NR}'\text{R}''$, $-\text{OR}'$, $-\text{SR}$, $-\text{S}(\text{O})\text{R}$, and/or $-\text{S}(\text{O}_2)\text{R}'$. Where “heteroalkyl” is
10 recited, followed by recitations of specific heteroalkyl groups, such as $-\text{NR}'\text{R}$ or the like, it will be understood that the terms heteroalkyl and $-\text{NR}'\text{R}''$ are not redundant or mutually exclusive. Rather, the specific heteroalkyl groups are recited to add clarity. Thus, the term “heteroalkyl” should not be interpreted herein as excluding specific heteroalkyl groups, such as $-\text{NR}'\text{R}''$ or the like.

- 15 “Cyclic” and “cycloalkyl” refer to a non-aromatic mono- or multicyclic ring system of about 3 to about 10 carbon atoms, e.g., 3, 4, 5, 6, 7, 8, 9, or 10 carbon atoms. The cycloalkyl group can be optionally partially unsaturated. The cycloalkyl group also can be optionally substituted with an alkyl group substituent as defined herein, oxo, and/or alkylene. There can be optionally inserted along the cyclic alkyl
20 chain one or more oxygen, sulfur or substituted or unsubstituted nitrogen atoms, wherein the nitrogen substituent is hydrogen, unsubstituted alkyl, substituted alkyl, aryl, or substituted aryl, thus providing a heterocyclic group. Representative monocyclic cycloalkyl rings include cyclopentyl, cyclohexyl, and cycloheptyl. Multicyclic cycloalkyl rings include adamantyl, octahydronaphthyl, decalin, camphor,
25 camphane, and noradamantyl, and fused ring systems, such as dihydro- and tetrahydronaphthalene, and the like.

- The term “cycloalkylalkyl,” as used herein, refers to a cycloalkyl group as defined hereinabove, which is attached to the parent molecular moiety through an alkylene moiety, also as defined above, e.g., a C_{1-20} alkylene moiety. Examples of
30 cycloalkylalkyl groups include cyclopropylmethyl and cyclopentylethyl.

The terms “cycloheteroalkyl” or “heterocycloalkyl” refer to a non-aromatic ring system, unsaturated or partially unsaturated ring system, such as a 3- to 10-member substituted or unsubstituted cycloalkyl ring system, including one or more heteroatoms, which can be the same or different, and are selected from the group

consisting of nitrogen (N), oxygen (O), sulfur (S), phosphorus (P), and silicon (Si), and optionally can include one or more double bonds.

The cycloheteroalkyl ring can be optionally fused to or otherwise attached to other cycloheteroalkyl rings and/or non-aromatic hydrocarbon rings. Heterocyclic rings include those having from one to three heteroatoms independently selected from oxygen, sulfur, and nitrogen, in which the nitrogen and sulfur heteroatoms may optionally be oxidized and the nitrogen heteroatom may optionally be quaternized. In certain embodiments, the term heterocyclic refers to a non-aromatic 5-, 6-, or 7-membered ring or a polycyclic group wherein at least one ring atom is a heteroatom selected from O, S, and N (wherein the nitrogen and sulfur heteroatoms may be optionally oxidized), including, but not limited to, a bi- or tri-cyclic group, comprising fused six-membered rings having between one and three heteroatoms independently selected from the oxygen, sulfur, and nitrogen, wherein (i) each 5-membered ring has 0 to 2 double bonds, each 6-membered ring has 0 to 2 double bonds, and each 7-membered ring has 0 to 3 double bonds, (ii) the nitrogen and sulfur heteroatoms may be optionally oxidized, (iii) the nitrogen heteroatom may optionally be quaternized, and (iv) any of the above heterocyclic rings may be fused to an aryl or heteroaryl ring. Representative cycloheteroalkyl ring systems include, but are not limited to pyrrolidinyl, pyrrolinyl, imidazolidinyl, imidazoliny, pyrazolidinyl, pyrazolinyl, piperidinyl, piperazinyl, indolinyl, quinuclidinyl, morpholinyl, thiomorpholinyl, thiadiazinanyl, tetrahydrofuranyl, and the like.

The terms "cycloalkyl" and "heterocycloalkyl", by themselves or in combination with other terms, represent, unless otherwise stated, cyclic versions of "alkyl" and "heteroalkyl", respectively. Additionally, for heterocycloalkyl, a heteroatom can occupy the position at which the heterocycle is attached to the remainder of the molecule. Examples of cycloalkyl include, but are not limited to, cyclopentyl, cyclohexyl, 1-cyclohexenyl, 3-cyclohexenyl, cycloheptyl, and the like. Examples of heterocycloalkyl include, but are not limited to, 1-(1,2,5,6-tetrahydropyridyl), 1-piperidinyl, 2-piperidinyl, 3-piperidinyl, 4-morpholinyl, 3-morpholinyl, tetrahydrofuran-2-yl, tetrahydrofuran-3-yl, tetrahydrothien-2-yl, tetrahydrothien-3-yl, 1-piperazinyl, 2-piperazinyl, and the like. The terms "cycloalkylene" and "heterocycloalkylene" refer to the divalent derivatives of cycloalkyl and heterocycloalkyl, respectively.

An unsaturated hydrocarbon has one or more double bonds or triple bonds.

Examples of unsaturated alkyl groups include, but are not limited to, vinyl, 2-propenyl, crotyl, 2-isopentenyl, 2-(butadienyl), 2,4-pentadienyl, 3-(1,4-pentadienyl), ethynyl, 1- and 3-propynyl, 3-butylnyl, and the higher homologs and isomers. Alkyl groups which are limited to hydrocarbon groups are termed "homoalkyl."

5 More particularly, the term "alkenyl" as used herein refers to a monovalent group derived from a C₂₋₂₀ inclusive straight or branched hydrocarbon moiety having at least one carbon-carbon double bond by the removal of a single hydrogen molecule. Alkenyl groups include, for example, ethenyl (i.e., vinyl), propenyl, butenyl, 1-methyl-2-buten-1-yl, pentenyl, hexenyl, octenyl, allenyl, and butadienyl.

10 The term "cycloalkenyl" as used herein refers to a cyclic hydrocarbon containing at least one carbon-carbon double bond. Examples of cycloalkenyl groups include cyclopropenyl, cyclobutenyl, cyclopentenyl, cyclopentadiene, cyclohexenyl, 1,3-cyclohexadiene, cycloheptenyl, cycloheptatrienyl, and cyclooctenyl.

The term "alkynyl" as used herein refers to a monovalent group derived from
15 a straight or branched C₂₋₂₀ hydrocarbon of a designed number of carbon atoms containing at least one carbon-carbon triple bond. Examples of "alkynyl" include ethynyl, 2-propynyl (propargyl), 1-propynyl, pentynyl, hexynyl, and heptynyl groups, and the like.

The term "alkylene" by itself or a part of another substituent refers to a
20 straight or branched bivalent aliphatic hydrocarbon group derived from an alkyl group having from 1 to about 20 carbon atoms, e.g., 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20 carbon atoms. The alkylene group can be straight, branched or cyclic. The alkylene group also can be optionally unsaturated and/or substituted with one or more "alkyl group substituents." There can be optionally
25 inserted along the alkylene group one or more oxygen, sulfur or substituted or unsubstituted nitrogen atoms (also referred to herein as "alkylaminoalkyl"), wherein the nitrogen substituent is alkyl as previously described. Exemplary alkylene groups include methylene (—CH₂—); ethylene (—CH₂—CH₂—); propylene (—(CH₂)₃—); cyclohexylene (—C₆H₁₀—); —CH=CH—CH=CH—; —CH=CH—CH₂—; —CH₂CH₂CH₂CH₂—,
30 —CH₂CH=CHCH₂—, —CH₂CsCCH₂—, —CH₂CH₂CH(CH₂CH₂CH₃)CH₂—, —(CH₂)_q—N(R)—(CH₂)_r—, wherein each of q and r is independently an integer from 0 to about 20, e.g., 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20, and R is hydrogen or lower alkyl; methylenedioxy (—O—CH₂—O—); and ethylenedioxy (—O—(CH₂)₂—O—). An alkylene group can have about 2 to about 3

carbon atoms and can further have 6-20 carbons. Typically, an alkyl (or alkylene) group will have from 1 to 24 carbon atoms, with those groups having 10 or fewer carbon atoms being some embodiments of the present disclosure. A “lower alkyl” or “lower alkylene” is a shorter chain alkyl or alkylene group, generally having eight or
5 fewer carbon atoms.

The term “heteroalkylene” by itself or as part of another substituent means a divalent group derived from heteroalkyl, as exemplified, but not limited by, -CH₂-CH₂-S-CH₂-CH₂- and -CH₂-S-CH₂-CH₂-NH-CH₂-. For heteroalkylene groups, heteroatoms also can occupy either or both of the chain termini (e.g., alkyleneoxo,
10 alkyleneedioxo, alkyleneamino, alkylene diamino, and the like). Still further, for alkylene and heteroalkylene linking groups, no orientation of the linking group is implied by the direction in which the formula of the linking group is written. For example, the formula -C(O)OR’- represents both -C(O)OR’- and -R’OC(O)-.

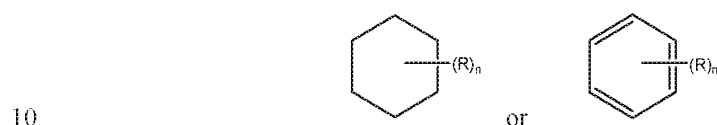
The term “aryl” means, unless otherwise stated, an aromatic hydrocarbon
15 substituent that can be a single ring or multiple rings (such as from 1 to 3 rings), which are fused together or linked covalently. The term “heteroaryl” refers to aryl groups (or rings) that contain from one to four heteroatoms (in each separate ring in the case of multiple rings) selected from N, O, and S, wherein the nitrogen and sulfur atoms are optionally oxidized, and the nitrogen atom(s) are optionally quaternized. A
20 heteroaryl group can be attached to the remainder of the molecule through a carbon or heteroatom. Non-limiting examples of aryl and heteroaryl groups include phenyl, 1-naphthyl, 2-naphthyl, 4-biphenyl, 1-pyrrolyl, 2-pyrrolyl, 3-pyrrolyl, 3-pyrazolyl, 2-imidazolyl, 4-imidazolyl, pyrazinyl, 2-oxazolyl, 4-oxazolyl, 2-phenyl-4-oxazolyl, 5-oxazolyl, 3-isoxazolyl, 4-isoxazolyl, 5-isoxazolyl, 2-thiazolyl, 4-thiazolyl, 5-
25 thiazolyl, 2-furyl, 3-furyl, 2-thienyl, 3-thienyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-pyrimidyl, 4-pyrimidyl, 5-benzothiazolyl, purinyl, 2-benzimidazolyl, 5-indolyl, 1-isoquinolyl, 5-isoquinolyl, 2-quinoxaliny, 5-quinoxaliny, 3-quinolyl, and 6-quinolyl. Substituents for each of above noted aryl and heteroaryl ring systems are selected from the group of acceptable substituents described below. The terms “arylene” and
30 “heteroarylene” refer to the divalent forms of aryl and heteroaryl, respectively.

For brevity, the term “aryl” when used in combination with other terms (e.g., aryloxy, arylthioxy, arylalkyl) includes both aryl and heteroaryl rings as defined above. Thus, the terms “arylalkyl” and “heteroarylalkyl” are meant to include those groups in which an aryl or heteroaryl group is attached to an alkyl group (e.g., benzyl,

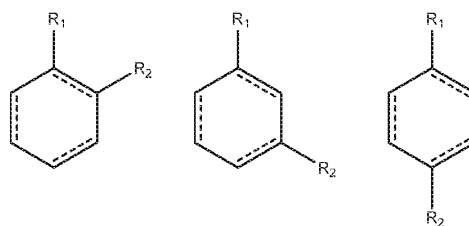
phenethyl, pyridylmethyl, furylmethyl, and the like) including those alkyl groups in which a carbon atom (e.g., a methylene group) has been replaced by, for example, an oxygen atom (e.g., phenoxymethyl, 2-pyridyloxyethyl, 3-(1-naphthoxy)propyl, and the like). However, the term “haloaryl,” as used herein is meant to cover only aryls substituted with one or more halogens.

Where a heteroalkyl, heterocycloalkyl, or heteroaryl includes a specific number of members (e.g., “3 to 7 membered”), the term “member” refers to a carbon or heteroatom.

Further, a structure represented generally by the formula:



as used herein refers to a ring structure, for example, but not limited to a 3-carbon, a 4-carbon, a 5-carbon, a 6-carbon, a 7-carbon, and the like, aliphatic and/or aromatic cyclic compound, including a saturated ring structure, a partially saturated ring structure, and an unsaturated ring structure, comprising a substituent R group, wherein the R group can be present or absent, and when present, one or more R groups can each be substituted on one or more available carbon atoms of the ring structure. The presence or absence of the R group and number of R groups is determined by the value of the variable “n,” which is an integer generally having a value ranging from 0 to the number of carbon atoms on the ring available for substitution. Each R group, if more than one, is substituted on an available carbon of the ring structure rather than on another R group. For example, the structure above where n is 0 to 2 would comprise compound groups including, but not limited to:



and the like.

25 A dashed line representing a bond in a cyclic ring structure indicates that the bond can be either present or absent in the ring. That is, a dashed line representing a bond in a cyclic ring structure indicates that the ring structure is selected from the

group consisting of a saturated ring structure, a partially saturated ring structure, and an unsaturated ring structure.

The symbol () denotes the point of attachment of a moiety to the remainder of the molecule.

5 When a named atom of an aromatic ring or a heterocyclic aromatic ring is defined as being “absent,” the named atom is replaced by a direct bond.

Each of above terms (e.g., “alkyl,” “heteroalkyl,” “cycloalkyl, and “heterocycloalkyl,” “aryl,” “heteroaryl,” “phosphonate,” and “sulfonate” as well as their divalent derivatives) are meant to include both substituted and unsubstituted
10 forms of the indicated group. Optional substituents for each type of group are provided below.

Substituents for alkyl, heteroalkyl, cycloalkyl, heterocycloalkyl monovalent and divalent derivative groups (including those groups often referred to as alkylene, alkenyl, heteroalkylene, heteroalkenyl, alkynyl, cycloalkyl, heterocycloalkyl,
15 cycloalkenyl, and heterocycloalkenyl) can be one or more of a variety of groups selected from, but not limited to: -OR', =O, =NR', =N-OR', -NR'R'', -SR', -halogen, -SiR'R''R''', -OC(O)R', -C(O)R', -CO₂R', -C(O)NR'R'', -OC(O)NR'R'', -NR''C(O)R', -NR'-C(O)NR''R'', -NR''C(O)OR', -NR-C(NR'R'')=NR'', -S(O)R', -S(O)₂R', -S(O)₂NR'R'', -NRSO₂R', -CN, CF₃, fluorinated C₁₋₄ alkyl, and -NO₂ in a
20 number ranging from zero to (2m'+1), where m' is the total number of carbon atoms in such groups. R', R'', R''' and R'''' each may independently refer to hydrogen, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl (e.g., aryl substituted with 1-3 halogens), substituted or unsubstituted alkyl, alkoxy or
25 thioalkoxy groups, or arylalkyl groups. As used herein, an “alkoxy” group is an alkyl attached to the remainder of the molecule through a divalent oxygen. When a compound of the disclosure includes more than one R group, for example, each of the R groups is independently selected as are each R', R'', R''' and R'''' groups when more than one of these groups is present. When R' and R'' are attached to the same
30 nitrogen atom, they can be combined with the nitrogen atom to form a 4-, 5-, 6-, or 7-membered ring. For example, -NR'R'' is meant to include, but not be limited to, 1-pyrrolidinyl and 4-morpholinyl. From the above discussion of substituents, one of ordinary skill in the art will understand that the term “alkyl” is meant to include

groups including carbon atoms bound to groups other than hydrogen groups, such as haloalkyl (e.g., $-\text{CF}_3$ and $-\text{CH}_2\text{CF}_3$) and acyl (e.g., $-\text{C}(\text{O})\text{CH}_3$, $-\text{C}(\text{O})\text{CF}_3$, $-\text{C}(\text{O})\text{CH}_2\text{OCH}_3$, and the like).

Similar to the substituents described for alkyl groups above, exemplary substituents for aryl and heteroaryl groups (as well as their divalent derivatives) are varied and are selected from, for example: halogen, $-\text{OR}'$, $-\text{NR}'\text{R}''$, $-\text{SR}'$, $-\text{SiR}'\text{R}''\text{R}'''$, $-\text{OC}(\text{O})\text{R}'$, $-\text{C}(\text{O})\text{R}'$, $-\text{CO}_2\text{R}'$, $-\text{C}(\text{O})\text{NR}'\text{R}''$, $-\text{OC}(\text{O})\text{NR}'\text{R}''$, $-\text{NR}''\text{C}(\text{O})\text{R}'$, $-\text{NR}'\text{C}(\text{O})\text{NR}''\text{R}'''$, $-\text{NR}''\text{C}(\text{O})\text{OR}'$, $-\text{NR}\text{C}(\text{NR}'\text{R}''\text{R}''')=\text{NR}''''$, $-\text{NR}\text{C}(\text{NR}'\text{R}''')=\text{NR}''''$, $-\text{S}(\text{O})\text{R}'$, $-\text{S}(\text{O})_2\text{R}'$, $-\text{S}(\text{O})_2\text{NR}'\text{R}''$, $-\text{NRSO}_2\text{R}'$, $-\text{CN}$ and $-\text{NO}_2$, $-\text{R}'$, $-\text{N}_3$, $-\text{CH}(\text{Ph})_2$, fluoro(C_{1-4})alkoxo, and fluoro(C_{1-4})alkyl, in a number ranging from zero to the total number of open valences on aromatic ring system; and where R' , R'' , R''' and R'''' may be independently selected from hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl and substituted or unsubstituted heteroaryl. When a compound of the disclosure includes more than one R group, for example, each of the R groups is independently selected as are each R' , R'' , R''' and R'''' groups when more than one of these groups is present.

Two of the substituents on adjacent atoms of aryl or heteroaryl ring may optionally form a ring of the formula $-\text{T}-\text{C}(\text{O})-(\text{CRR}')_q-\text{U}-$, wherein T and U are independently $-\text{NR}-$, $-\text{O}-$, $-\text{CRR}'-$ or a single bond, and q is an integer of from 0 to 3. Alternatively, two of the substituents on adjacent atoms of aryl or heteroaryl ring may optionally be replaced with a substituent of the formula $-\text{A}-(\text{CH}_2)_r-\text{B}-$, wherein A and B are independently $-\text{CRR}'-$, $-\text{O}-$, $-\text{NR}-$, $-\text{S}-$, $-\text{S}(\text{O})-$, $-\text{S}(\text{O})_2-$, $-\text{S}(\text{O})_2\text{NR}'-$ or a single bond, and r is an integer of from 1 to 4.

One of the single bonds of the new ring so formed may optionally be replaced with a double bond. Alternatively, two of the substituents on adjacent atoms of aryl or heteroaryl ring may optionally be replaced with a substituent of the formula $-(\text{CRR}')_s-\text{X}'-(\text{C}''\text{R}''')_d-$, where s and d are independently integers of from 0 to 3, and X' is $-\text{O}-$, $-\text{NR}'-$, $-\text{S}-$, $-\text{S}(\text{O})-$, $-\text{S}(\text{O})_2-$, or $-\text{S}(\text{O})_2\text{NR}'-$. The substituents R , R' , R'' and R''' may be independently selected from hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl.

As used herein, the term “acyl” refers to an organic acid group wherein the -OH of the carboxyl group has been replaced with another substituent and has the general formula $RC(=O)-$, wherein R is an alkyl, alkenyl, alkynyl, aryl, carbocyclic, heterocyclic, or aromatic heterocyclic group as defined herein). As such, the term “acyl” specifically includes arylacyl groups, such as a 2-(furan-2-yl)acetyl- and a 2-phenylacetyl group. Specific examples of acyl groups include acetyl and benzoyl. Acyl groups also are intended to include amides, $-RC(=O)NR'$, esters, $-RC(=O)OR'$, ketones, $-RC(=O)R'$, and aldehydes, $-RC(=O)H$.

The terms “alkoxyl” or “alkoxy” are used interchangeably herein and refer to a saturated (i.e., alkyl-O-) or unsaturated (i.e., alkenyl-O- and alkynyl-O-) group attached to the parent molecular moiety through an oxygen atom, wherein the terms “alkyl,” “alkenyl,” and “alkynyl” are as previously described and can include C_{1-20} inclusive, linear, branched, or cyclic, saturated or unsaturated oxo-hydrocarbon chains, including, for example, methoxyl, ethoxyl, propoxyl, isopropoxyl, *n*-butoxyl, *sec*-butoxyl, *tert*-butoxyl, and *n*-pentoxyl, neopentoxyl, *n*-hexoxyl, and the like.

The term “alkoxyalkyl” as used herein refers to an alkyl-O-alkyl ether, for example, a methoxyethyl or an ethoxymethyl group.

“Aryloxy” refers to an aryl-O- group wherein the aryl group is as previously described, including a substituted aryl. The term “aryloxy” as used herein can refer to phenyloxy or hexyloxy, and alkyl, substituted alkyl, halo, or alkoxy substituted phenyloxy or hexyloxy.

“Aralkyl” refers to an aryl-alkyl-group wherein aryl and alkyl are as previously described, and included substituted aryl and substituted alkyl. Exemplary aralkyl groups include benzyl, phenylethyl, and naphthylmethyl.

“Aralkyloxy” refers to an aralkyl-O- group wherein the aralkyl group is as previously described. An exemplary aralkyloxy group is benzyloxy, i.e., $C_6H_5-CH_2-O-$. An aralkyloxy group can optionally be substituted.

“Alkoxy carbonyl” refers to an alkyl-O-C(=O)- group. Exemplary alkoxy carbonyl groups include methoxy carbonyl, ethoxy carbonyl, butyloxy carbonyl, and *tert*-butyloxy carbonyl.

“Aryloxy carbonyl” refers to an aryl-O-C(=O)- group. Exemplary aryloxy carbonyl groups include phenoxy- and naphthoxy-carbonyl.

“Aralkoxy carbonyl” refers to an aralkyl-O-C(=O)- group. An exemplary aralkoxy carbonyl group is benzyloxy carbonyl.

“Carbamoyl” refers to an amide group of the formula $-C(=O)NH_2$.

“Alkylcarbamoyl” refers to a $R'RN-C(=O)-$ group wherein one of R and R' is hydrogen and the other of R and R' is alkyl and/or substituted alkyl as previously described. “Dialkylcarbamoyl” refers to a $R'RN-C(=O)-$ group wherein each of R
5 and R' is independently alkyl and/or substituted alkyl as previously described.

The term carbonyldioxy, as used herein, refers to a carbonate group of the formula $-O-C(=O)-OR$.

“Acyloxy” refers to an acyl-O- group wherein acyl is as previously described.

The term “amino” refers to the $-NH_2$ group and also refers to a nitrogen
10 containing group as is known in the art derived from ammonia by the replacement of one or more hydrogen radicals by organic groups. For example, the terms “acylamino” and “alkylamino” refer to specific N-substituted organic groups with acyl and alkyl substituent groups respectively.

An “aminoalkyl” as used herein refers to an amino group covalently bound to
15 an alkylene linker. More particularly, the terms alkylamino, dialkylamino, and trialkylamino as used herein refer to one, two, or three, respectively, alkyl groups, as previously defined, attached to the parent molecular moiety through a nitrogen atom. The term alkylamino refers to a group having the structure $-NHR'$ wherein R' is an alkyl group, as previously defined; whereas the term dialkylamino refers to a group
20 having the structure $-NR'R''$, wherein R' and R'' are each independently selected from the group consisting of alkyl groups. The term trialkylamino refers to a group having the structure $-NR'R''R'''$, wherein R', R'', and R''' are each independently selected from the group consisting of alkyl groups. Additionally, R', R'', and/or R''' taken together may optionally be $-(CH_2)_k-$ where k is an integer from 2 to 6.
25 Examples include, but are not limited to, methylamino, dimethylamino, ethylamino, diethylamino, diethylaminocarbonyl, methylethylamino, isopropylamino, piperidino, trimethylamino, and propylamino.

The amino group is $-NR'R''$, wherein R' and R'' are typically selected from hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl,
30 substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl.

The terms alkylthioether and thioalkoxyl refer to a saturated (i.e., alkyl-S-) or unsaturated (i.e., alkenyl-S- and alkynyl-S-) group attached to the parent molecular

moiety through a sulfur atom. Examples of thioalkoxyl moieties include, but are not limited to, methylthio, ethylthio, propylthio, isopropylthio, *n*-butylthio, and the like.

“Acylamino” refers to an acyl-NH– group wherein acyl is as previously described. “Aroylamino” refers to an aroyl-NH– group wherein aroyl is as previously described.

The term “carbonyl” refers to the C(=O) – group, and can include an aldehyde group represented by the general formula R-C(=O)H .

The term “carboxyl” refers to the COOH group. Such groups also are referred to herein as a “carboxylic acid” moiety.

The term “cyano” refers to the $\text{C}\equiv\text{N}$ group.

The terms “halo,” “halide,” or “halogen” as used herein refer to fluoro, chloro, bromo, and iodo groups. Additionally, terms such as “haloalkyl,” are meant to include monohaloalkyl and polyhaloalkyl. For example, the term “halo(C₁₋₄)alkyl” is meant to include, but not be limited to, trifluoromethyl, 2,2,2-trifluoroethyl, 4-chlorobutyl, 3-bromopropyl, and the like.

The term “hydroxyl” refers to the OH group.

The term “hydroxyalkyl” refers to an alkyl group substituted with an OH group.

The term “mercapto” refers to the SH group.

The term “oxo” as used herein means an oxygen atom that is double bonded to a carbon atom or to another element.

The term “nitro” refers to the NO_2 group.

The term “thio” refers to a compound described previously herein wherein a carbon or oxygen atom is replaced by a sulfur atom.

The term “sulfate” refers to the SO_4 group.

The term thiohydroxyl or thiol, as used herein, refers to a group of the formula SH .

More particularly, the term “sulfide” refers to compound having a group of the formula SR .

The term “sulfone” refers to compound having a sulfonyl group $\text{S(O}_2\text{)R'}$.

The term “sulfoxide” refers to a compound having a sulfinyl group S(O)R .

The term ureido refers to a urea group of the formula NHCONH_2 .

Throughout the specification and claims, a given chemical formula or name shall encompass all tautomers, congeners, and optical- and stereoisomers, as well as racemic mixtures where such isomers and mixtures exist.

Certain compounds of the present disclosure may possess asymmetric carbon atoms (optical or chiral centers) or double bonds; the enantiomers, racemates, diastereomers, tautomers, geometric isomers, stereoisometric forms that may be defined, in terms of absolute stereochemistry, as (R)- or (S)- or, as D- or L- for amino acids, and individual isomers are encompassed within the scope of the present disclosure. The compounds of the present disclosure do not include those which are known in art to be too unstable to synthesize and/or isolate. The present disclosure is meant to include compounds in racemic, scalemic, and optically pure forms. Optically active (R)- and (S)-, or D- and L-isomers may be prepared using chiral synthons or chiral reagents, or resolved using conventional techniques. When the compounds described herein contain olefinic bonds or other centers of geometric asymmetry, and unless specified otherwise, it is intended that the compounds include both *E* and *Z* geometric isomers.

Unless otherwise stated, structures depicted herein are also meant to include all stereochemical forms of the structure; i.e., the R and S configurations for each asymmetric center. Therefore, single stereochemical isomers as well as enantiomeric and diastereomeric mixtures of the present compounds are within the scope of the disclosure.

It will be apparent to one skilled in the art that certain compounds of this disclosure may exist in tautomeric forms, all such tautomeric forms of the compounds being within the scope of the disclosure. The term "tautomer," as used herein, refers to one of two or more structural isomers which exist in equilibrium and which are readily converted from one isomeric form to another.

Unless otherwise stated, structures depicted herein are also meant to include compounds which differ only in the presence of one or more isotopically enriched atoms. For example, compounds having the present structures with the replacement of a hydrogen by a deuterium or tritium, or the replacement of a carbon by ¹³C- or ¹⁴C-enriched carbon are within the scope of this disclosure.

The compounds of the present disclosure may also contain unnatural proportions of atomic isotopes at one or more of atoms that constitute such compounds. For example, the compounds may be radiolabeled with radioactive

isotopes, such as for example deuterium (^2H), tritium (^3H), iodine-125 (^{125}I) or carbon-14 (^{14}C). All isotopic variations of the compounds of the present disclosure, whether radioactive or not, are encompassed within the scope of the present disclosure.

5 The compounds of the present disclosure may exist as salts. The present disclosure includes such salts. Examples of applicable salt forms include hydrochlorides, hydrobromides, sulfates, methanesulfonates, nitrates, maleates, acetates, citrates, fumarates, tartrates (e.g. (+)-tartrates, (-)-tartrates or mixtures thereof including racemic mixtures, succinates, benzoates and salts with amino acids
10 such as glutamic acid. These salts may be prepared by methods known to those skilled in art. Also included are base addition salts such as sodium, potassium, calcium, ammonium, organic amino, or magnesium salt, or a similar salt. When compounds of the present disclosure contain relatively basic functionalities, acid addition salts can be obtained by contacting the neutral form of such compounds with
15 a sufficient amount of the desired acid, either neat or in a suitable inert solvent or by ion exchange. Examples of acceptable acid addition salts include those derived from inorganic acids like hydrochloric, hydrobromic, nitric, carbonic, monohydrogencarbonic, phosphoric, monohydrogenphosphoric, dihydrogenphosphoric, sulfuric, monohydrogensulfuric, hydriodic, or phosphorous
20 acids and the like, as well as the salts derived organic acids like acetic, propionic, isobutyric, maleic, malonic, benzoic, succinic, suberic, fumaric, lactic, mandelic, phthalic, benzenesulfonic, p-tolylsulfonic, citric, tartaric, methanesulfonic, and the like. Also included are salts of amino acids such as arginate and the like, and salts of organic acids like glucuronic or galactunoric acids and the like. Certain specific
25 compounds of the present disclosure contain both basic and acidic functionalities that allow the compounds to be converted into either base or acid addition salts.

 The neutral forms of the compounds may be regenerated by contacting the salt with a base or acid and isolating the parent compound in the conventional manner. The parent form of the compound differs from the various salt forms in certain
30 physical properties, such as solubility in polar solvents.

 Certain compounds of the present disclosure can exist in unsolvated forms as well as solvated forms, including hydrated forms. In general, the solvated forms are equivalent to unsolvated forms and are encompassed within the scope of the present disclosure. Certain compounds of the present disclosure may exist in multiple

crystalline or amorphous forms. In general, all physical forms are equivalent for the uses contemplated by the present disclosure and are intended to be within the scope of the present disclosure.

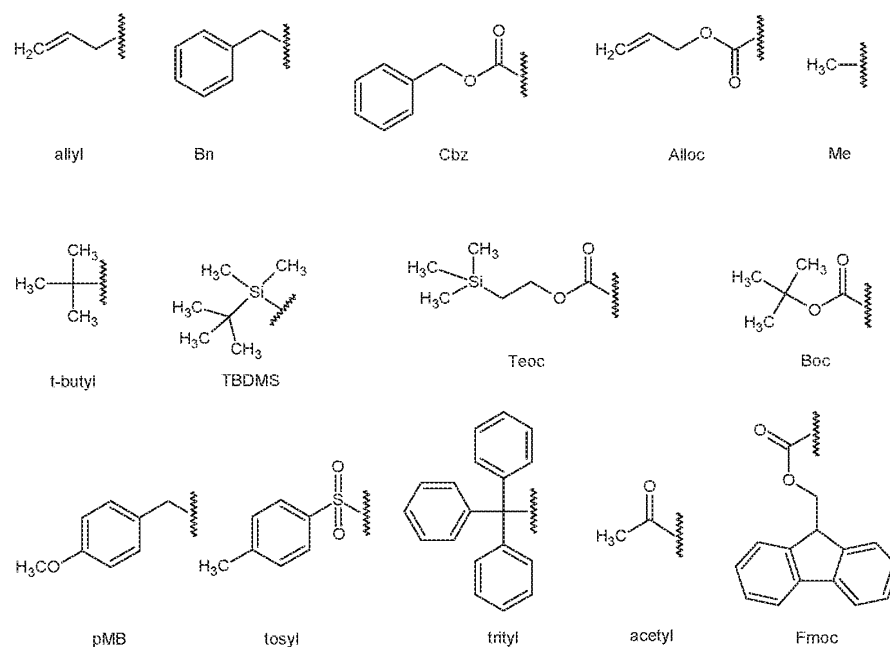
In addition to salt forms, the present disclosure provides compounds, which are in a prodrug form. Prodrugs of the compounds described herein are those compounds that readily undergo chemical changes under physiological conditions to provide the compounds of the present disclosure. Additionally, prodrugs can be converted to the compounds of the present disclosure by chemical or biochemical methods in an ex vivo environment. For example, prodrugs can be slowly converted to the compounds of the present disclosure when placed in a transdermal patch reservoir with a suitable enzyme or chemical reagent.

The term "protecting group" refers to chemical moieties that block some or all reactive moieties of a compound and prevent such moieties from participating in chemical reactions until the protective group is removed, for example, those moieties listed and described in T. W. Greene, P.G.M. Wuts, *Protective Groups in Organic Synthesis*, 3rd ed. John Wiley & Sons (1999). It may be advantageous, where different protecting groups are employed, that each (different) protective group be removable by a different means. Protective groups that are cleaved under totally disparate reaction conditions allow differential removal of such protecting groups. For example, protective groups can be removed by acid, base, and hydrogenolysis. Groups such as trityl, dimethoxytrityl, acetal and tert-butyldimethylsilyl are acid labile and may be used to protect carboxy and hydroxy reactive moieties in the presence of amino groups protected with Cbz groups, which are removable by hydrogenolysis, and Fmoc groups, which are base labile. Carboxylic acid and hydroxy reactive moieties may be blocked with base labile groups such as, without limitation, methyl, ethyl, and acetyl in the presence of amines blocked with acid labile groups such as tert-butyl carbamate or with carbamates that are both acid and base stable but hydrolytically removable.

Carboxylic acid and hydroxy reactive moieties may also be blocked with hydrolytically removable protective groups such as the benzyl group, while amine groups capable of hydrogen bonding with acids may be blocked with base labile groups such as Fmoc. Carboxylic acid reactive moieties may be blocked with oxidatively-removable protective groups such as 2,4-dimethoxybenzyl, while co-existing amino groups may be blocked with fluoride labile silyl carbamates.

Allyl blocking groups are useful in the presence of acid- and base- protecting groups since the former are stable and can be subsequently removed by metal or pi-acid catalysts. For example, an allyl-blocked carboxylic acid can be deprotected with a palladium(O)- catalyzed reaction in the presence of acid labile t-butyl carbamate or base-labile acetate amine protecting groups. Yet another form of protecting group is a resin to which a compound or intermediate may be attached. As long as the residue is attached to the resin, that functional group is blocked and cannot react. Once released from the resin, the functional group is available to react.

Typical blocking/protecting groups include, but are not limited to the following moieties:



Following long-standing patent law convention, the terms “a,” “an,” and “the” refer to “one or more” when used in this application, including the claims. Thus, for example, reference to “a subject” includes a plurality of subjects, unless the context clearly is to the contrary (e.g., a plurality of subjects), and so forth.

Throughout this specification and the claims, the terms “comprise,” “comprises,” and “comprising” are used in a non-exclusive sense, except where the context requires otherwise. Likewise, the term “include” and its grammatical variants

are intended to be non-limiting, such that recitation of items in a list is not to the exclusion of other like items that can be substituted or added to the listed items.

For the purposes of this specification and appended claims, unless otherwise indicated, all numbers expressing amounts, sizes, dimensions, proportions, shapes, formulations, parameters, percentages, quantities, characteristics, and other numerical values used in the specification and claims, are to be understood as being modified in all instances by the term “about” even though the term “about” may not expressly appear with the value, amount or range. Accordingly, unless indicated to the contrary, the numerical parameters set forth in the following specification and attached claims are not and need not be exact, but may be approximate and/or larger or smaller as desired, reflecting tolerances, conversion factors, rounding off, measurement error and the like, and other factors known to those of ordinary skill in the art depending on the desired properties sought to be obtained by the presently disclosed subject matter. For example, the term “about,” when referring to a value can be meant to encompass variations of, in some embodiments, $\pm 100\%$ in some embodiments $\pm 50\%$, in some embodiments $\pm 20\%$, in some embodiments $\pm 10\%$, in some embodiments $\pm 5\%$, in some embodiments $\pm 1\%$, in some embodiments $\pm 0.5\%$, and in some embodiments $\pm 0.1\%$ from the specified amount, as such variations are appropriate to perform the disclosed methods or employ the disclosed compositions.

Further, the term “about” when used in connection with one or more numbers or numerical ranges, should be understood to refer to all such numbers, including all numbers in a range and modifies that range by extending the boundaries above and below the numerical values set forth. The recitation of numerical ranges by endpoints includes all numbers, e.g., whole integers, including fractions thereof, subsumed within that range (for example, the recitation of 1 to 5 includes 1, 2, 3, 4, and 5, as well as fractions thereof, e.g., 1.5, 2.25, 3.75, 4.1, and the like) and any range within that range.

EXAMPLES

The following Examples have been included to provide guidance to one of ordinary skill in the art for practicing representative embodiments of the presently disclosed subject matter. In light of the present disclosure and the general level of skill in the art, those of skill can appreciate that the following Examples are intended to be exemplary only and that numerous changes, modifications, and alterations can

be employed without departing from the scope of the presently disclosed subject matter. The synthetic descriptions and specific examples that follow are only intended for the purposes of illustration, and are not to be construed as limiting in any manner to make compounds of the disclosure by other methods.

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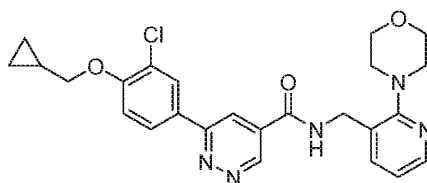
SYNTHETIC PROCEDURES

Exemplary compounds were prepared via several general synthetic routes set forth in the Examples below. Any of the disclosed compounds of the present invention can be prepared according to one or more of these synthetic routes or
10 specific examples, or via modifications thereof accessible to the person of ordinary skill in the art.

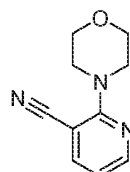
Example 1: 6-[3-chloro-4-(cyclopropylmethoxy)phenyl]-N-[(2-morpholinophenyl)methyl]pyridazine-4-carboxamide

Method A

15

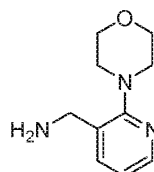


Step 1: Synthesis of 2-morpholinonicotinonitrile



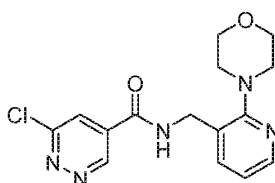
To a 20 mL scintillation vial was added 2-fluoronicotinonitrile (1g, 8.2 mmol) and DCM (15 mL). Morpholine (1.4 mL, 16.4 mmol) was added, and the mixture was
20 stirred at room temperature for ~18 hours. The crude mixture was filtered through a plug of silica gel, and the filtrate was concentrated to give a colorless crystalline solid, which was used without further purification (Yield: 1.1g, 71%).

Step 2: Synthesis of (2-morpholinopyridin-3-yl)methanamine



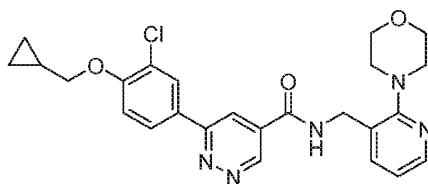
To a round-bottom flask was charged 2-morpholinonicotinonitrile (500 mg, 4.1 mmol) and a suspension of Raney nickel (large excess). This mixture was stirred under a hydrogen atmosphere (balloon) for ~18 hours, and then solids were removed by filtration. The clear filtrate was concentrated under reduced pressure to give an oil containing the title product, which was used without further purification.

Step 3: Synthesis of 6-chloro-N-((2-morpholinopyridin-3-yl)methyl)pyridazine-4-carboxamide



A round-bottom flask was charged with 6-Chloropyridazine-4-carboxylic acid (1.48 g, 9.31 mmol). This was suspended in DCM (45 mL) and then trimethylamine (2.6 mL, 18.6 mmol) was added. HBTU (3.53 g, 9.31 mmol) was added, and the mixture was stirred for 15 minutes. (2-morpholinopyridin-3-yl)methanamine (1.8 g, 9.31 mmol) was added in one portion, and the mixture was stirred at room temperature for 5 hours. The mixture was filtered through a plug of basic alumina, and the filtrate was concentrated. This was purified by preparative reversed-phase MPLC (0-100% ACN in water) to afford the product as an off-white solid. (Yield: 1.8 g, 57.9%).

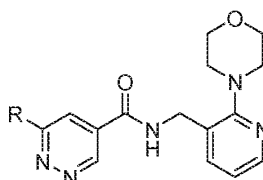
Step 4: Synthesis of 6-(3-chloro-4-(cyclopropylmethoxy)phenyl)-N-((2-morpholinopyridin-3-yl)methyl)pyridazine-4-carboxamide



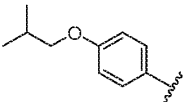
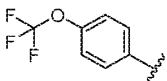
Intermediate A (155 mg, 0.46 mmol) was added to a microwave vial, followed by (3-chloro-4-(cyclopropylmethoxy)phenyl)boronic acid (210 mg, 0.93 mmol), palladium acetate (5.2 mg, 0.02 mmol), SPhos (19 mg, 0.05 mmol), and tribasic potassium phosphate (100 mg, 0.46 mmol). The microwave vial was sealed, evacuated and backfilled with nitrogen three times, and then THF (2.5 mL) and water (0.25 mL) were introduced via syringe. The mixture was heated on a hotplate to 80 °C for ~18 hours, and then diluted with dichloromethane (about 5 mL) and filtered

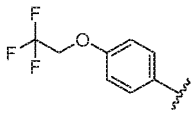
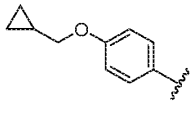
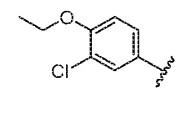
through celite. The filtrate was concentrated under reduced pressure and purified by preparative HPLC, eluting with a 10-100% acetonitrile/water gradient, modified with 0.003M NH₄OH ("high pH method") to afford the desired product as a beige foam (yield: 112 mg, 50%).

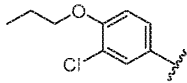
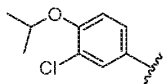
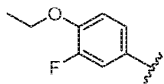
5 The following compounds have been synthesized according to **Method A**:

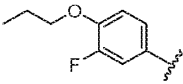
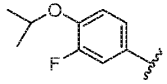


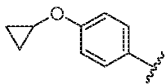
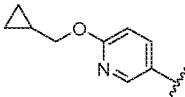
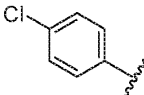
Example	Name	R	Analytical data	Preparation details
2	6-(6-chloro-3-pyridyl)-N-[(2-morpholino-3-pyridyl)methyl]pyridazine-4-carboxamide		MS, ES ⁺ m/z 411 (M+H) ⁺ . ¹ H-NMR (400 MHz, DMSO-d ₆) δ ppm 9.61 (d, J = 2 Hz, 1H), 9.52-9.59 (m, 1H), 9.22 (dd, J = 2.5, 0.8 Hz, 1H), 8.69 (d, J = 2.0 Hz, 1H), 8.62-8.68 (m, 1H), 8.23 (dd, J = 4.8, 1.7 Hz, 1H), 7.76-7.83 (m, 1H), 7.72 (dd, J = 7.6, 1.7 Hz, 1H), 7.07 (dd, J = 7.5, 4.7 Hz, 1H), 4.61 (d, J = 5.6 Hz, 2H), 3.72-3.81 (m, 4H), 3.02-3.13 (m, 4H)	Method A, using (6-chloropyridin-3-yl)boronic acid
3	6-(3-chlorophenyl)-N-[(2-morpholino-3-pyridyl)methyl]pyridazine-4-carboxamide		MS, ES ⁺ m/z 410 (M+H) ⁺ .	Method A, using (3-chlorophenyl)boronic acid
4	6-(4-chloro-2-methyl-phenyl)-N-[(2-morpholino-3-pyridyl)methyl]pyridazine-4-carboxamide		MS, ES ⁺ m/z 424 (M+H) ⁺ . ¹ H-NMR (400 MHz, DMSO-d ₆) δ ppm 9.59 (d, J = 2.3 Hz, 1H), 9.51-9.57 (m, 1H), 8.22 (dd, J = 4.8, 1.7 Hz, 1H), 8.2 (d, J = 2 Hz, 1H), 7.7 (dd, J =	Method A, using (4-chloro-2-methylphenyl)boronic acid

Example	Name	R	Analytical data	Preparation details
			7.5, 1.6 Hz, 1H), 7.52-7.58 (m, 2H), 7.45-7.50 (m, 1H), 7.06 (dd, J = 7.3, 4.8, 1H), 4.58 (d, J = 5.8 Hz, 2H), 3.70-3.81 (m, 4H), 3.0-3.12 (m, 4H), 2.36 (s, 3H)	
5	6-(4-isobutoxyphenyl)-N-[(2-morpholino-3-pyridyl)methyl]pyridazine-4-carboxamide		MS, ES ⁺ m/z 448 (M+H) ⁺ . ¹ H-NMR (400 MHz, DMSO-d ₆) δ ppm 9.52-9.59 (m, 1H), 9.47 (d, J = 2.0 Hz, 1H), 8.51 (d, J = 2.0 Hz, 1H), 8.23 (dd, J = 4.8, 1.8 Hz, 1H), 8.15-8.21 (m, 2H), 7.71 (dd, J = 7.5, 1.9 Hz, 1H), 7.12-7.20 (m, 2H), 7.07 (dd, J = 7.6, 4.8 Hz, 1H), 4.60 (d, J = 5.8 Hz, 2H), 3.86 (d, J = 6.6 Hz, 2H), 3.71-3.81 (m, 4H), 3.03-3.12 (m, 4H), 2.00-2.14 (m, 1H), 1.02 (d, J = 6.6 Hz, 6H)	Method A, using (4-isobutoxyphenyl)boronic acid
6	N-[(2-morpholino-3-pyridyl)methyl]-6-[4-(trifluoromethoxy)phenyl]pyridazine-4-carboxamide		MS, ES ⁺ m/z 460 (M+H) ⁺ . ¹ H-NMR (400 MHz, DMSO-d ₆) δ ppm 9.53-9.62 (m, 2H), 8.62 (d, J = 2.0 Hz, 1H), 8.32-8.40 (m, 2H), 8.24 (dd, J = 4.8, 1.8 Hz, 1H), 7.72 (dd, J = 7.6, 1.8 Hz, 1H), 7.62 (dd, J = 8.8, 1.0 Hz, 2H), 7.07 (dd, J = 7.5, 4.9 Hz, 1H), 4.61 (d, J = 5.8 Hz, 2H), 3.73-3.81 (m, 4H), 3.03-3.11 (m, 4H)	Method A, using (4-(trifluoromethoxy)phenyl)boronic acid

Example	Name	R	Analytical data	Preparation details
7	N-[(2-morpholino-3-pyridyl)methyl]-6-[4-(2,2,2-trifluoroethoxy)phenyl]pyridazine-4-carboxamide		MS, ES ⁺ m/z 474 (M+H) ⁺ . ¹ H-NMR (400 MHz, DMSO-d ₆) δ ppm 9.52-9.59 (m, 1H), 9.50 (d, J = 2.0 Hz, 1H), 8.55 (d, J = 2.0 Hz, 1H), 8.20-8.27 (m, 3H), 7.72 (dd, J = 7.6, 1.8 Hz, 1H), 7.26-7.33 (m, 2H), 7.07 (dd, J = 7.6, 4.8 Hz, 1H), 4.86-4.97 (m, 2H), 4.60 (d, J = 5.8 Hz, 2H), 3.72-3.82 (m, 4H), 3.01-3.13 (m, 4H)	Method A , using (4-(2,2,2-trifluoroethoxy)phenyl)boronic acid
8	6-[4-(cyclopropylmethoxy)phenyl]-N-[(2-morpholino-3-pyridyl)methyl]pyridazine-4-carboxamide		MS, ES ⁺ m/z 446 (M+H) ⁺ . ¹ H-NMR (400 MHz, DMSO-d ₆) δ ppm 9.50-9.59 (m, 1H), 9.47 (d, J = 2.0 Hz, 1H), 8.51 (d, J = 2.0 Hz, 1H), 8.23 (dd, J = 4.8, 2.0 Hz, 1H), 8.18 (m, 2H), 7.71 (dd, J = 7.6, 1.7 Hz, 1H), 7.11-7.18 (m, 2H), 7.07 (dd, J = 7.6, 4.8 Hz, 1H), 4.6 (d, J = 5.6 Hz, 2H), 3.93 (d, J = 6.8 Hz, 2H), 3.71-3.82 (m, 4H), 3.02-3.12 (m, 4H), 1.21-1.33 (m, 1H), 0.56-0.64 (m, 2H), 0.33-0.40 (m, 2H)	Method A , using (4-(cyclopropylmethoxy)phenyl)boronic acid
9	6-(3-chloro-4-ethoxy-phenyl)-N-[(2-morpholino-3-pyridyl)methyl]pyridazine-4-carboxamide		MS, ES ⁺ m/z 454 (M+H) ⁺ . ¹ H-NMR (400 MHz, DMSO-d ₆) δ ppm 9.48-9.59 (m, 2H), 8.57 (d, J = 2.0 Hz, 1H), 8.30 (d, J = 2.2 Hz, 1H), 8.18-8.27 (m, 2H), 7.72 (dd, J = 7.5, 1.9 Hz, 1H), 7.37 (d, J = 8.8 Hz, 1H), 7.07 (dd, J = 7.6 Hz, 1H), 4.60 (d, J = 5.8 Hz, 2H), 4.24	Method A , using (3-chloro-4-ethoxy-phenyl)boronic acid

Example	Name	R	Analytical data	Preparation details
			(quartet, J = 7.1 Hz, 2H), 3.71-3.83 (m, 4H), 3.01-3.15 (m, 4H), 1.41 (t, J = 6.9 Hz)	
10	6-(3-chloro-4-propoxy-phenyl)-N-[(2-morpholino-3-pyridyl)methyl]pyridazine-4-carboxamide		MS, ES ⁺ m/z 468 (M+H) ⁺ . ¹ H-NMR (400 MHz, DMSO-d ₆) δ ppm 9.48-9.60 (m, 2H), 8.57 (d, J = 1.8 Hz, 1H), 8.30 (d, J = 2.3 Hz, 1H), 8.18-8.28 (m, 2H), 7.72 (dd, J = 7.6, 1.8 Hz, 1H), 7.38 (d, J = 8.8 Hz, 1H), 7.07 (dd, J = 7.3, 4.8 Hz, 1H), 4.6 (d, J = 5.6 Hz, 2H), 4.14 (t, J = 6.4 Hz, 2H), 3.71-3.83 (m, 4H), 3.01-3.08 (m, 4H), 1.81 (sextet, J = 6.9 Hz, 2H), 1.04 (t, J = 7.3 Hz, 3H)	Method A, using (3-chloro-4-propoxy-phenyl)boronic acid
11	6-(3-chloro-4-isopropoxy-phenyl)-N-[(2-morpholino-3-pyridyl)methyl]pyridazine-4-carboxamide		MS, ES ⁺ m/z 468 (M+H) ⁺ . ¹ H-NMR (400 MHz, DMSO-d ₆) δ ppm 9.48-9.61 (m, 2H), 8.56 (d, J = 2.0 Hz, 1H), 8.13-8.37 (m, 3H), 7.72 (dd, J = 7.6, 1.8 Hz, 1H), 7.4 (d, J = 8.8 Hz, 1H), 7.07 (dd, J = 7.5, 4.7 Hz, 1H), 4.78-4.91 (m, 1H), 4.6 (d, J = 5.6 Hz, 2H), 3.69-3.85 (m, 4H), 3.01-3.16 (m, 4H), 1.30-1.43 (m, 6H)	Method A, using (3-chloro-4-isopropoxy-phenyl)boronic acid
12	6-(4-ethoxy-3-fluoro-phenyl)-N-[(2-morpholino-3-pyridyl)methyl]pyridazine-4-carboxamide		MS, ES ⁺ m/z 438 (M+H) ⁺ . ¹ H-NMR (400 MHz, DMSO-d ₆) δ ppm 9.47-9.57 (m, 2H), 8.55 (d, J = 2.0 Hz, 1H), 8.23 (dd, J = 4.8, 1.7 Hz, 1H), 8.09-	Method A, using (4-ethoxy-3-fluoro-phenyl)boronic acid

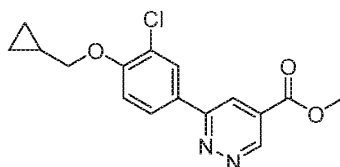
Example	Name	R	Analytical data	Preparation details
			8.13 (m, 1H), 7.68-7.76 (m, 1H), 7.39 (t, J = 8.6 Hz, 1H), 7.07 (dd, J = 7.3, 4.8 Hz, 1H), 4.60 (d, J = 5.8 Hz, 2H), 4.23 (quartet, J = 7.1 Hz, 2H), 3.72-3.81 (m, 4H), 3.03-3.12 (m, 4H), 1.40 (t, J = 6.9 Hz, 3H)	
13	6-(3-fluoro-4-propoxy-phenyl)-N-[(2-morpholino-3-pyridyl)methyl]pyridazine-4-carboxamide		MS, ES ⁺ m/z 452 (M+H) ⁺ . ¹ H-NMR (400 MHz, DMSO-d ₆) δ ppm 9.48-9.58 (m, 2H), 8.55 (d, J = 1.8 Hz, 1H), 8.21-8.27 (m, 1H), 8.02-8.14 (m, 2H), 7.72 (d, J = 7.6 Hz, 1H), 7.35-7.45 (m, 1H), 7.07 (dd, J = 7.5, 4.6 Hz, 1H), 4.6 (d, J = 5.8 Hz, 2H), 4.13 (t, J = 6.7 Hz, 2H), 3.73-3.84 (m, 4H), 3.03-3.14 (m, 4H), 1.80 (sextet, J = 7.3 Hz, 2H)	Method A, using (3-fluoro-4-propoxy-phenyl)boronic acid
14	6-(3-fluoro-4-isopropoxy-phenyl)-N-[(2-morpholino-3-pyridyl)methyl]pyridazine-4-carboxamide		MS, ES ⁺ m/z 452 (M+H) ⁺ . ¹ H-NMR (400 MHz, DMSO-d ₆) δ ppm 9.50-9.56 (m, 2H), 8.56 (d, J = 2 Hz, 1H), 8.23 (dd, J = 5.1, 1.8 Hz, 1H), 8.02-8.11 (m, 2H), 7.72 (dd, J = 7.3, 2.0 Hz, 1H), 7.43 (t, J = 8.3 Hz, 1H), 7.07 (dd, J = 7.3, 4.8 Hz, 1H), 4.78-4.83 (m, 1H), 4.60 (d, J = 5.8 Hz, 2H), 3.73-3.84 (m, 4H), 3.03-3.14 (m, 4H), 1.35 (d, J = 6.1 Hz, 6H)	Method A, using (3-fluoro-4-isopropoxy-phenyl)boronic acid

Example	Name	R	Analytical data	Preparation details
15	6-[4-(cyclopropoxy)phenyl]-N-[(2-morpholino-3-pyridyl)methyl]pyridazine-4-carboxamide		MS, ES+ m/z 432 (M+H) ⁺ . ¹ H-NMR (400 MHz, DMSO-d ₆) δ ppm 9.55 (t, J = 5.6 Hz, 1H), 9.48 (d, J = 2.0 Hz, 1H), 8.51 (d, J = 2.0 Hz, 1H), 8.15-8.27 (m, 3H), 7.72 (dd, J = 7.5, 1.9 Hz, 1H), 7.21-7.30 (m, 2H), 7.07 (dd, J = 7.6, 4.8 Hz, 1H), 4.60 (d, J = 5.6 Hz, 2H), 3.97 (sept., J = 3.1 Hz, 1H), 3.72-3.80 (m, 4H), 3.02-3.12 (m, 4H), 0.80-0.90 (m, 2H), 0.66-0.75 (m, 2H)	Method A, using 4-(cyclopropoxy)phenylboronic acid
16	6-[6-(cyclopropylmethoxy)-3-pyridyl]-N-[(2-morpholino-3-pyridyl)methyl]pyridazine-4-carboxamide		MS, ES+ m/z 447 (M+H) ⁺ . ¹ H-NMR (400 MHz, DMSO-d ₆) δ ppm 9.49-9.56 (m, 2H), 8.98 (dd, J = 2.5, 0.8 Hz, 1H), 8.57 (d, J = 2.0 Hz, 1H), 8.51 (dd, J = 8.8, 2.5 Hz, 1H), 8.23 (dd, J = 4.8, 1.8 Hz, 1H), 7.72 (dd, J = 7.5, 1.9 Hz, 1H), 7.02-7.10 (m, 2H), 4.60 (d, J = 5.6 Hz, 2H), 4.21 (d, J = 7.3 Hz, 2H), 3.72-3.81 (m, 4H), 3.02-3.11 (m, 4H), 1.24-1.35 (m, 1H), 0.55-0.62 (m, 2H), 0.34-0.40 (m, 2H)	Method A, using 6-(cyclopropylmethoxy)-3-pyridylboronic acid
17	6-(4-chlorophenyl)-N-[(2-morpholino-3-pyridyl)methyl]pyridazine-4-carboxamide		MS, ES+ m/z 410 (M+H) ⁺ .	Method A, using 4-chlorophenylboronic acid

Example 18: 6-[3-chloro-4-(cyclopropylmethoxy)phenyl]-N-[(2-(1-methylimino-1-oxo-1,4-thiazinan-4-yl)-3-pyridyl)methyl]pyridazine-4-carboxamide

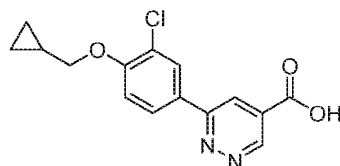
Method B

Step 1: Synthesis of methyl 6-(3-chloro-4-(cyclopropylmethoxy)phenyl)pyridazine-4-carboxylate



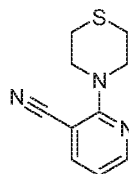
- 5 A microwave vial was charged with methyl 6-chloropyridazine-4-carboxylate (1g, 5.8 mmol), [3-chloro-4-(cyclopropylmethoxy)phenyl]boronic acid (1.44 g, 6.37 mmol), Palladium XPhos G1 precatalyst (214 mg, 0.29 mmol), and tribasic potassium phosphate (2.46 g, 11.59 mmol). The vial was sealed, and evacuated and backfilled with nitrogen three times. THF (10 mL) and water (1 mL) were introduced via
- 10 syringe, and the mixture was heated to 80 °C for about t hours. The crude solution was filtered through celite, concentrated, and purified by silica gel chromatography (0-5% MeOH in DCM) to afford the desired product as a beige solid (Yield: 800 mg, 43%).

- Step 2: Synthesis of 6-(3-chloro-4-(cyclopropylmethoxy)phenyl)pyridazine-4-carboxylic acid*
- 15



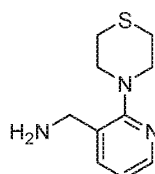
- To a vial equipped with a stir bar was added methyl 6-[3-chloro-4-(cyclopropylmethoxy)phenyl]pyridazine-4-carboxylate (1.25 g, 3.92 mmol). Methanol (15 mL) and water (2 mL) were added, followed by excess solid sodium
- 20 hydroxide. After stirring at room temperature for 3 hours, the solution was diluted with water (about 100 mL) and acidified by addition of 6N HCl. The resultant precipitate was collected by filtration, rinsed with water and dried under reduced pressure to give the desired product as a solid, which was used without further purification. (Yield: 1g, 84%).

- 25 *Step 3: Synthesis of 2-thiomorpholinopyridine-3-carbonitrile*



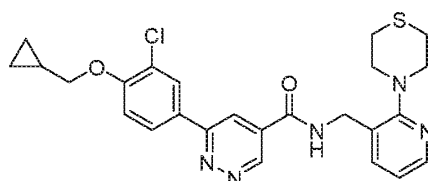
A round bottom flask equipped with a magnetic stir bar was charged with 2-fluoropyridine-3-carbonitrile (2.43 g, 19.9 mmol), and DMSO (10 mL) was added. Triethylamine (2.0 g, 19.9 mmol) and thiomorpholine (2.05 g, 19.9 mmol) were added, and the resulting mixture was heated to 70 °C for 18 hours. The crude mixture was purified directly by preparative MPLC (0-75% ACN/water gradient, 0.1% TFA modifier) to afford the desired product as a light yellow solid. (Yield: 3.65 g, 89%).

Step 4: Synthesis of (2-thiomorpholino-3-pyridyl)methanamine



2-thiomorpholinopyridine-3-carbonitrile (1.0 g, 4.87 mmol) was added to a round-bottom flask with magnetic stir bar and dissolved in methanol (15 mL). Excess Raney nickel was added, and the mixture was stirred under a hydrogen atmosphere (balloon) for 3 hours. The resulting solution was filtered through celite, and the clear filtrate was concentrated to afford a yellow oil containing the desired product. This was used without further purification.

Step 5: Synthesis of 6-[3-chloro-4-(cyclopropylmethoxy)phenyl]-N-[[2-(1-methylimino-1-oxo-1,4-thiazinan-4-yl)-3-pyridyl]methyl]pyridazine-4-carboxamide

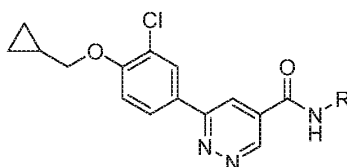


A solution of intermediate B (80 mg, 0.26 mmol) in DCM (2.5 mL) was treated with HATU (74.1 mg, 0.32 mmol) and trimethylamine (0.073 mL, 0.53 mmol). The resulting mixture was stirred at room temperature for about 2 hours, and then (2-thiomorpholino-3-pyridyl)methanamine (83.1 mg, 0.33 mmol) was added. Stirring was continued for an additional 30 minutes, and the crude mixture was concentrated and purified by preparative HPLC (10-100% ACN/water gradient, 0.1%

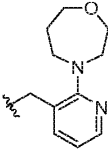
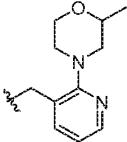
TFA modifier) to afford the desired product as a foam. MS, ES⁺ m/z 497 (M+H)⁺.

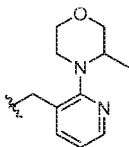
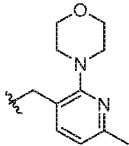
¹H-NMR (400 MHz, DMSO-d₆) δ ppm 9.45-9.57 (m, 2H), 8.57 (d, J = 2.0 Hz, 1H), 8.30 (d, J = 2.3 Hz, 1H), 8.15-8.26 (m, 2H), 7.71 (dd, J = 7.6, 2.0 Hz, 1H), 7.35 (d, J = 8.8 Hz, 1H), 7.07 (dd, J = 7.6, 4.8 Hz, 1H), 4.57 (d, J = 5.6 Hz, 2H), 4.04 (d, J = 7.1 Hz, 2H), 3.24-3.34 (m, 4H), 2.74-2.83 (m, 4H), 1.24-1.35 (m, 1H), 0.55-0.66 (m, 2H), 0.30-0.43 (m, 2H).

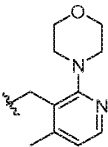
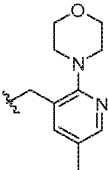
The following compounds have been synthesized according to **Method B**:

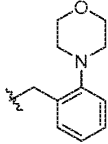
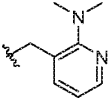
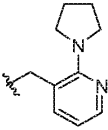


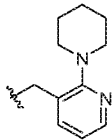
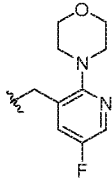
Example	Name	R	Analytical data	Preparation details
19	6-[3-chloro-4-(cyclopropylmethoxy)phenyl]-N-[[2-(2-oxa-6-azaspiro[3.3]heptan-6-yl)-3-pyridyl]methyl]pyridazine-4-carboxamide		MS, ES ⁺ m/z 492 (M+H) ⁺ . ¹ H-NMR (400 MHz, DMSO-d ₆) δ ppm 9.49 (d, J = 1.8 Hz, 1H), 9.39-9.46 (m, 1H), 8.57 (d, J = 2.0 Hz, 1H), 8.31 (d, J = 2.3 Hz, 1H), 8.19 (dd, J = 8.6, 2.2 Hz, 1H), 8.06 (dd, J = 4.8, 1.8 Hz, 1H), 7.51 (dd, J = 7.5, 1.6 Hz, 1H), 7.35 (d, J = 8.8 Hz, 1H), 6.76 (dd, J = 7.5, 4.9 Hz, 1H), 4.73 (s, 4H), 4.42 (d, J = 5.3 Hz, 2H), 4.27 (s, 4H), 4.04 (d, J = 6.8 Hz, 2H), 1.25-1.36 (m, 1H), 0.58-0.66 (m, 2H), 0.35-0.43 (m, 2H)	Method B , using 2-oxa-6-azaspiro[3.3]heptane
20	6-[3-chloro-4-(cyclopropylmethoxy)phenyl]-N-[[2-(2,2,2-trifluoroethoxy)-3-pyridyl]methyl]pyridazine-4-carboxamide		MS, ES ⁺ m/z 493 (M+H) ⁺ . ¹ H-NMR (400 MHz, DMSO-d ₆) δ ppm 9.46-9.55 (m, 2H), 8.56 (d, J = 2.0 Hz, 1H), 8.30 (d, J = 2.3 Hz, 1H), 8.17-8.22 (m, 1H), 8.13-8.16 (m, 1H), 7.79-7.84 (m, 1H), 7.36 (d, J = 8.8 Hz, 1H), 7.13 (dd, J = 7.3,	Method B , using commercially available (2-(2,2,2-trifluoroethoxy)pyridin-3-yl)methanamine in step 5

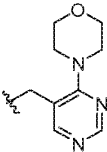
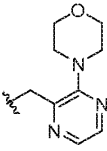
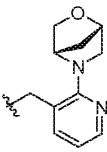
Example	Name	R	Analytical data	Preparation details
			4.8 Hz, 1H), 5.07 (quart., J = 9.1 Hz, 2H), 4.53 (d, J = 5.8 Hz, 2H), 4.05 (d, J = 6.8 Hz, 2H), 1.25-1.35 (m, 1H), 0.58-0.66 (m, 2H), 0.36-0.43 (m, 2H)	
21	6-[3-chloro-4-(cyclopropylmethoxy)phenyl]-N-[[2-(1,4-oxazepan-4-yl)-3-pyridyl]methyl]pyridazine-4-carboxamide		MS, ES ⁺ m/z 496 (M+H) ⁺ . ¹ H-NMR (400 MHz, DMSO-d ₆) δ ppm 9.45-9.55 (m, 2H), 8.57 (d, J = 2.0 Hz, 1H), 8.30 (d, J = 2.3 Hz, 1H), 8.19 (dd, J = 8.8, 2.3 Hz, 1H), 8.14 (dd, J = 4.8, 2.0 Hz, 1H), 7.65 (dd, J = 7.6, 1.8 Hz, 1H), 7.35 (d, J = 8.8 Hz, 1H), 6.95 (dd, J = 7.6, 4.8 Hz, 1H), 4.56 (d, J = 5.8 Hz, 2H), 4.04 (d, J = 7.1 Hz, 2H), 3.72-3.85 (m, 4H), 3.40-3.52 (m, 4H), 1.91-2.02 (m, 2H), 1.24-1.37 (m, 1H), 0.58-0.67 (m, 2H), 0.36-0.44 (m, 2H)	Method B, using 1,4-oxazepane
22	6-[3-chloro-4-(cyclopropylmethoxy)phenyl]-N-[[2-(2-methylmorpholin-4-yl)-3-pyridyl]methyl]pyridazine-4-carboxamide		MS, ES ⁺ m/z 494 (M+H) ⁺ . ¹ H-NMR (400 MHz, DMSO-d ₆) δ ppm 9.47-9.57 (m, 2H), 8.57 (d, J = 1.8 Hz, 1H), 8.30 (d, J = 2.3 Hz, 1H), 8.16-8.25 (m, 2H), 7.71 (dd, J = 7.3, 1.8 Hz, 1H), 7.35 (d, J = 8.8 Hz, 1H), 7.1 (dd, J = 7.6, 4.8 Hz, 1H), 4.6 (d, J = 6.1 Hz, 2H), 4.04 (d, J = 7.1 Hz, 2H), 3.85-3.92 (m, 1H), 3.66-3.78 (m, 2H), 3.34 (s, 1H), 3.15-3.29	Method B, 2-methylmorpholine

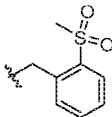
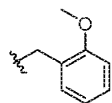
Example	Name	R	Analytical data	Preparation details
			(m, 2H), 2.83-2.93 (m, 1H), 2.55-2.64 (m, 1H), 1.25-1.36 (m, 1H), 1.14 (d, J = 6.1 Hz, 3H), 0.58-0.66 (m, 2H), 0.36-0.43 (m, 2H)	
23	6-[3-chloro-4-(cyclopropylmethoxy)phenyl]-N-[[2-(3-methylmorpholin-4-yl)-3-pyridyl]methyl]pyridazine-4-carboxamide		MS, ES+ m/z 494 (M+H) ⁺ . ¹ H-NMR (400 MHz, DMSO-d ₆) δ ppm 9.49-9.57 (m, 2H), 8.58 (d, J = 2.0 Hz, 1H), 8.29-8.36 (m, 2H), 8.19 (dd, J = 8.6, 2.3 Hz, 1H), 7.76 (dd, J = 7.6, 1.8 Hz, 1H), 7.35 (d, J = 8.6 Hz, 1H), 7.15 (dd, J = 7.6, 4.8 Hz, 1H), 4.64 (d, J = 6.1 Hz, 2H), 4.04 (d, J = 7.1 Hz, 2H), 3.70-3.85 (m, 3H), 3.44-3.54 (m, 1H), 3.31-3.39 (m, 1H), 3.04-3.15 (m, 1H), 2.75-2.85 (m, 1H), 1.25-1.36 (m, 1H), 0.83 (d, J = 6.32, 3H), 0.59-0.65 (m, 2H), 0.37-0.43 (m, 2H).	Method B, using 3-methylmorpholine
24	6-[3-chloro-4-(cyclopropylmethoxy)phenyl]-N-[(6-methyl-2-morpholino-3-pyridyl)methyl]pyridazine-4-carboxamide		MS, ES+ m/z 494 (M+H) ⁺ . ¹ H-NMR (400 MHz, DMSO-d ₆) δ ppm 9.45-9.59 (m, 2H), 8.56 (d, J = 2 Hz, 1H), 8.3 (d, J = 2.3 Hz, 1H), 8.19 (dd, J = 8.8, 2.3 Hz, 1H), 7.59 (d, J = 7.6 Hz, 1H), 7.35 (d, J = 8.8 Hz, 1H), 6.92 (d, J = 7.8 Hz, 1H), 4.56 (d, J = 5.6 Hz, 2H), 4.04 (d, J = 6.8 Hz, 2H), 3.68-3.87 (m, 4H), 2.96-3.15 (m, 4H), 2.38 (s, 3H), 1.24-1.38	Method B, using 2-chloro-6-methylnicotinonitrile

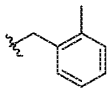
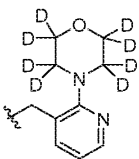
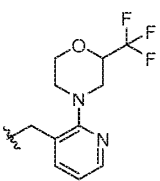
Example	Name	R	Analytical data	Preparation details
			(m, 1H), 0.59-0.70 (m, 2H), 0.35-0.49 (m, 2H).	
25	6-[3-chloro-4-(cyclopropylmethoxy)phenyl]-N-[(4-methyl-2-morpholino-3-pyridyl)methyl]pyridazine-4-carboxamide		MS, ES+ m/z 494 (M+H) ⁺ . ¹ H-NMR (400 MHz, DMSO-d ₆) δ ppm 9.47-9.60 (m, 2H), 8.56 (d, J = 1.8 Hz, 1H), 8.30 (d, J = 2.3 Hz, 1H), 8.19 (dd, J = 8.6, 2.3 Hz, 1H), 7.69 (d, J = 7.6 Hz, 1H), 7.35 (d, J = 8.8 Hz, 1H), 6.97 (d, J = 7.6 Hz, 1H), 4.56 (d, J = 5.6 Hz, 2H), 4.04 (d, J = 7.1 Hz, 2H), 3.71-3.82 (m, 4H), 3.05-3.19 (m, 4H), 2.42 (s, 3H), 1.25-1.36 (m, 1H), 0.58-0.67 (m, 2H), 0.35-0.44 (m, 2H)	Method B, using 2-chloro-4-methylnicotinonitrile
26	6-[3-chloro-4-(cyclopropylmethoxy)phenyl]-N-[(5-methyl-2-morpholino-3-pyridyl)methyl]pyridazine-4-carboxamide		MS, ES+ m/z 494 (M+H) ⁺ . ¹ H-NMR (400 MHz, DMSO-d ₆) δ ppm 9.49-9.57 (m, 2H), 8.58 (d, J = 2.0 Hz, 1H), 8.30 (d, J = 2.3 Hz, 1H), 8.19 (dd, J = 8.7, 2.4 Hz, 1H), 8.08 (d, J = 1.8 Hz, 1H), 7.63 (s, 1H), 7.36 (d, J = 8.84 Hz, 1H), 5.56 (d, J = 5.6 Hz, 2H), 4.04 (d, J = 7.1 Hz, 2H), 3.72-3.81 (m, 4H), 3.02-3.14 (m, 4H), 2.24 (s, 3H), 1.25-1.35 (m, 1H), 0.59-0.66 (m, 2H), 0.36-0.43 (m, 2H)	Method B, using 2-chloro-5-methylnicotinonitrile

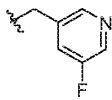
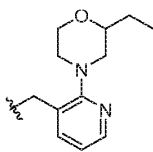
Example	Name	R	Analytical data	Preparation details
27	6-[3-chloro-4-(cyclopropylmethoxy)phenyl]-N-[(2-morpholinophenyl)methyl]pyridazine-4-carboxamide		MS, ES+ m/z 479 (M+H) ⁺ . ¹ H-NMR (400 MHz, DMSO-d ₆) δ ppm 9.43-9.55 (m, 2H), 8.58 (d, J = 2.0 Hz, 1H), 8.30 (d, J = 2.3 Hz, 1H), 8.19 (dd, J = 8.7, 2.2 Hz, 1H), 7.07-7.43 (m, 5H), 4.68 (d, J = 5.6 Hz, 2H), 4.04 (d, J = 6.8 Hz, 2H), 3.71-3.86 (m, 4H), 2.81-2.99 (m, 4H), 1.25-1.39 (m, 1H), 0.54-0.73 (m, 2H), 0.31-0.49 (m, 2H).	Method B , using commercially available (2-morpholinophenyl)methanamine in step 5
28	6-[3-chloro-4-(cyclopropylmethoxy)phenyl]-N-[[2-(dimethylamino)-3-pyridyl]methyl]pyridazine-4-carboxamide		MS, ES+ m/z 438 (M+H) ⁺ . ¹ H-NMR (400 MHz, DMSO-d ₆) δ ppm 9.55-9.65 (m, 1H), 9.48 (d, J = 2.0 Hz, 1H), 8.57 (d, J = 1.8 Hz, 1H), 8.30 (d, J = 2.3 Hz, 1H), 8.18-8.23 (m, 1H), 8.11-8.16 (m, 1H), 7.83-7.90 (s, 1H), 7.36 (d, J = 8.8 Hz, 1H), 7.02-7.09 (m, 1H), 4.61 (d, J = 5.8 Hz, 2H), 4.05 (d, J = 7.1 Hz, 2H), 2.99 (s, 6H), 1.26-1.36 (m, 1H), 0.57-0.68 (m, 2H), 0.35-0.45 (m, 2H).	Method B , using commercially available 3-(aminomethyl)-N,N-dimethylpyridin-2-amine in step 5
29	6-[3-chloro-4-(cyclopropylmethoxy)phenyl]-N-[(2-pyrrolidin-1-yl-3-pyridyl)methyl]pyridazine-4-carboxamide		MS, ES+ m/z 464 (M+H) ⁺ . ¹ H-NMR (400 MHz, DMSO-d ₆) δ ppm 9.53-9.66 (m, 1H), 9.46-9.53 (d, J = 2.0 Hz, 1H), 8.56 (d, J = 2 Hz, 1H), 8.30 (d, J = 2.3 Hz, 1H), 8.19 (dd, J = 8.7, 2.4 Hz, 1H), 7.92-8.10 (m, 2H), 7.36 (d, J = 8.8 Hz, 1H), 6.95 (t, J = 6.6 Hz, 1H), 4.76	Method B , using commercially available (2-pyrrolidin-1-yl)pyridin-3-yl)methanamine in step 5

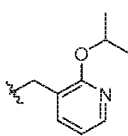
Example	Name	R	Analytical data	Preparation details
			(d, J = 5.1 Hz, 2H), 4.05 (d, J = 7.1 Hz, 2H), 3.65-3.87 (m, 4H), 1.87-2.16 (m, 4H), 1.22-1.42 (m, 1H), 0.54-0.76 (m, 2H), 0.30-0.48 (m, 2H).	
30	6-[3-chloro-4-(cyclopropylmethoxy)phenyl]-N-[[2-(1-piperidyl)-3-pyridyl]methyl]pyridazine-4-carboxamide		MS, ES+ m/z 478 (M+H) ⁺ . ¹ H-NMR (400 MHz, DMSO-d ₆) δ ppm 9.58-9.68 (m, 1H), 9.49 (d, J = 2.0 Hz, 1H), 8.58 (d, J = 2.0 Hz, 1H), 8.30 (d, J = 2.3 Hz, 1H), 8.15-8.25 (m, 2H), 7.85-7.95 (m, 1H), 7.36 (d, J = 8.8 Hz, 1H), 7.10-7.21 (m, 1H), 4.58 (d, J = 5.6 Hz, 2H), 4.04 (d, J = 6.8 Hz, 2H), 3.19 (s, 4H), 1.71 (s, 4H), 1.25-1.36 (m, 1H), 0.57-0.71 (m, 2H), 0.35-0.47 (m, 2H).	Method B, using commercially available (2-(piperidin-1-yl)pyridin-3-yl)methanamine in step 5
31	6-[3-chloro-4-(cyclopropylmethoxy)phenyl]-N-[(5-fluoro-2-morpholino-3-pyridyl)methyl]pyridazine-4-carboxamide		MS, ES+ m/z 498 (M+H) ⁺ . ¹ H-NMR (400 MHz, DMSO-d ₆) δ ppm 9.54-9.64 (m, 1H), 9.49 (d, J = 2.0 Hz, 1H), 8.58 (d, J = 2.0 Hz, 1H), 8.31 (d, J = 2.3 Hz, 1H), 8.16-8.27 (m, 2H), 7.70 (dd, J = 9.2, 2.9 Hz, 1H), 7.36 (d, J = 8.8 Hz, 1H), 4.61 (d, J = 5.8 Hz, 2H), 4.04 (d, J = 6.8 Hz, 2H), 3.70-3.83 (m, 4H), 2.96-3.10 (m, 4H), 1.25-1.36 (m, 1H), 0.58-0.68 (m, 2H), 0.35-0.45 (m, 2H).	Method B, using 2-chloro-5-fluoronicotinonitrile

Example	Name	R	Analytical data	Preparation details
32	6-[3-chloro-4-(cyclopropylmethoxy)phenyl]-N-[(4-morpholinopyrimidin-5-yl)methyl]pyridazine-4-carboxamide		MS, ES+ m/z 481 (M+H) ⁺ . ¹ H-NMR (400 MHz, DMSO-d ₆) δ ppm 9.44-9.55 (m, 2H), 8.63 (s, 1H), 8.55 (d, J = 2.0 Hz, 1H), 8.42 (s, 1H), 8.3 (d, J = 2.3 Hz, 1H), 8.19 (dd, J = 8.8, 2.3 Hz, 1H), 7.35 (d, J = 8.6 Hz, 1H), 4.54 (d, J = 5.1 Hz, 2H), 4.04 (d, J = 7.1 Hz, 2H), 3.64-3.74 (m, 4H), 3.38-3.48 (m, 4H), 1.25-1.36 (m, 1H), 0.57-0.65 (m, 2H), 0.36-0.43 (m, 2H).	Method B, using 4-chloropyrimidine-5-carbonitrile
33	6-[3-chloro-4-(cyclopropylmethoxy)phenyl]-N-[(3-morpholinopyrazin-2-yl)methyl]pyridazine-4-carboxamide		MS, ES+ m/z 481 (M+H) ⁺ . ¹ H-NMR (400 MHz, DMSO-d ₆) δ ppm 9.57 (t, J = 5.7 Hz, 1H), 9.47 (d, J = 2.0 Hz, 1H), 8.57 (d, J = 2.0 Hz, 1H), 8.30 (d, J = 2.3 Hz, 1H), 8.21-8.25 (m, 2H), 8.18 (dd, J = 8.8, 2.3 Hz, 1H), 7.35 (d, J = 8.8 Hz, 1H), 4.72 (d, J = 5.6 Hz, 2H), 4.04 (d, J = 6.8 Hz, 2H), 3.72-3.82 (m, 4H), 3.13-3.24 (m, 4H), 1.25-1.36 (m, 1H), 0.59-0.66 (m, 2H), 0.36-0.43 (m, 2H).	Method B, using 3-chloropyrazine-2-carbonitrile
34	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-		MS, ES+ m/z 492 (M+H) ⁺ . ¹ H-NMR (400 MHz, DMSO-d ₆) δ ppm 9.38-9.52 (m, 2H), 8.56 (d, J = 1.8 Hz, 1H), 8.31 (d, J = 2.0 Hz, 1H), 8.19 (dd, J = 8.6, 2.3 Hz, 1H), 8.01-8.10 (m, 1H), 7.59 (d, J = 7.6 Hz, 1H), 7.35 (d, J = 8.6 Hz, 1H),	Method B, using (1S,4S)-2-oxa-5-azabicyclo[2.2.1]heptane

Example	Name	R	Analytical data	Preparation details
	carboxamide		6.82 (dd, $J = 7.3, 4.8$ Hz, 1H), 4.34-4.64 (m, 4H), 3.89-4.11 (m, 3H), 3.59-3.84 (m, 2H), 3.20-3.38 (m, 2H), 1.72-1.93 (m, 2H), 1.23-1.37 (m, 1H), 0.54-0.68 (m, 2H), 0.30-0.44 (m, 2H).	
35	6-[3-chloro-4-(cyclopropylmethoxy)phenyl]-N-[(2-methylsulfonylphenyl)methyl]pyridazine-4-carboxamide		MS, ES+ m/z 472 (M+H) ⁺ . ¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ ppm 0.36 - 0.43 (m, 2 H) 0.59 - 0.67 (m, 2 H) 1.31 (s, 1 H) 3.41 (s, 3 H) 4.05 (d, $J=7.07$ Hz, 2 H) 4.99 (d, $J=5.66$ Hz, 2 H) 7.36 (d, $J=8.80$ Hz, 1 H) 7.54 - 7.61 (m, 1 H) 7.68 - 7.77 (m, 2 H) 7.98 (dd, $J=7.94, 1.02$ Hz, 1 H) 8.21 (dd, $J=8.72, 2.28$ Hz, 1 H) 8.32 (d, $J=2.20$ Hz, 1 H) 8.61 (d, $J=2.04$ Hz, 1 H) 9.51 (d, $J=2.04$ Hz, 1 H) 9.78 (s, 1 H)	Method B , using commercially available (2-(methylsulfonyl)phenyl)methanamine in step 5
36	6-[3-chloro-4-(cyclopropylmethoxy)phenyl]-N-[(2-methoxyphenyl)methyl]pyridazine-4-carboxamide		MS, ES+ m/z 424 (M+H) ⁺ . ¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ ppm 0.37 - 0.44 (m, 2 H) 0.59 - 0.66 (m, 2 H) 1.25 - 1.36 (m, 1 H) 3.85 (s, 3 H) 4.05 (d, $J=6.92$ Hz, 2 H) 4.53 (d, $J=5.66$ Hz, 2 H) 6.94 (t, $J=7.39$ Hz, 1 H) 7.03 (d, $J=8.17$ Hz, 1 H) 7.23 - 7.39 (m, 3 H) 8.19 (dd, $J=8.65, 2.20$ Hz, 1 H) 8.31 (d, $J=2.20$ Hz, 1 H) 8.57 (d, $J=1.89$ Hz, 1 H) 9.39 (t, $J=5.66$ Hz, 1 H) 9.49 (d, $J=2.04$ Hz, 1 H)	Method B , using commercially available (2-methoxyphenyl)methanamine in step 5

Example	Name	R	Analytical data	Preparation details
37	6-[3-chloro-4-(cyclopropylmethoxy)phenyl]-N-(o-tolylmethyl)pyridazine-4-carboxamide		MS, ES+ m/z 408 (M+H) ⁺ . ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ ppm 0.40 (q, <i>J</i> =4.72 Hz, 2 H) 0.57 - 0.67 (m, 2 H) 1.30 (t, <i>J</i> =7.58 Hz, 1 H) 2.35 (s, 3 H) 4.04 (d, <i>J</i> =7.07 Hz, 2 H) 4.55 (d, <i>J</i> =5.56 Hz, 2 H) 7.14 - 7.25 (m, 3 H) 7.29 - 7.39 (m, 2 H) 8.19 (dd, <i>J</i> =8.72, 2.15 Hz, 1 H) 8.30 (d, <i>J</i> =2.27 Hz, 1 H) 8.56 (d, <i>J</i> =2.02 Hz, 1 H) 9.42 (t, <i>J</i> =5.43 Hz, 1 H) 9.49 (d, <i>J</i> =1.77 Hz, 1 H)	Method B , using commercially available o-tolylmethanamine in step 5
38	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		MS, ES+ m/z 489 (M+H) ⁺ . ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ ppm 0.40 (d, <i>J</i> =6.06 Hz, 2 H) 0.62 (dd, <i>J</i> =8.08, 1.77 Hz, 2 H) 4.05 (d, <i>J</i> =7.07 Hz, 2 H) 4.60 (d, <i>J</i> =5.31 Hz, 2 H) 7.35 (d, <i>J</i> =8.84 Hz, 1 H) 8.30 (d, <i>J</i> =2.27 Hz, 1 H) 8.57 (d, <i>J</i> =2.02 Hz, 1 H) 9.49 (d, <i>J</i> =2.02 Hz, 1 H)	Method B , using (2-(morpholino- <i>d</i> ₈)pyridin-3-yl)methanamine
39	6-[3-chloro-4-(cyclopropylmethoxy)phenyl]-N-[[2-(2-(trifluoromethyl)morpholin-4-yl)-3-pyridyl]methyl]pyridazine-4-carboxamide		MS, ES+ m/z 548 (M+H) ⁺ . ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ ppm 0.35 - 0.43 (m, 2 H) 0.59 - 0.66 (m, 2 H) 1.25 - 1.36 (m, 1 H) 2.90 - 3.09 (m, 2 H) 3.29 (d, <i>J</i> =12.63 Hz, 1 H) 3.46 (d, <i>J</i> =11.62 Hz, 1 H) 3.80 - 3.91 (m, 1 H) 4.44 (t, <i>J</i> =7.07 Hz, 1 H) 4.55 - 4.68 (m, 2 H) 7.15 (dd, <i>J</i> =7.58, 4.80 Hz, 1 H) 7.35 (d, <i>J</i> =8.84 Hz, 1 H)	Method B , using (2-(trifluoromethyl)morpholino)pyridin-3-yl)methanamine

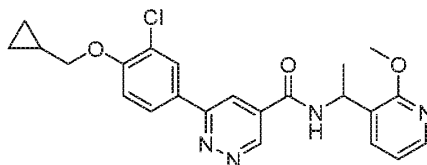
Example	Name	R	Analytical data	Preparation details
			H) 7.78 (d, $J=7.58$ Hz, 1 H) 8.19 (dd, $J=8.84, 2.27$ Hz, 1 H) 8.24 - 8.34 (m, 2 H) 8.57 (d, $J=1.77$ Hz, 1 H) 9.49 (d, $J=1.77$ Hz, 1 H) 9.56 (t, $J=5.68$ Hz, 1 H)	
40	6-[3-chloro-4-(cyclopropylmethoxy)phenyl]-N-[(5-fluoro-3-pyridyl)methyl]pyridazine-4-carboxamide		MS, ES+ m/z 413 (M+H) ⁺ . ¹ H NMR (400 MHz, DMSO- <i>d</i> 6) δ ppm 0.33 - 0.43 (m, 2 H) 0.57 - 0.67 (m, 2 H) 1.24 - 1.37 (m, 1 H) 4.04 (d, $J=7.07$ Hz, 2 H) 4.64 (d, $J=5.81$ Hz, 2 H) 7.35 (d, $J=8.59$ Hz, 1 H) 7.72 - 7.80 (m, 1 H) 8.19 (dd, $J=8.59, 2.27$ Hz, 1 H) 8.30 (d, $J=2.27$ Hz, 1 H) 8.48 - 8.59 (m, 3 H) 9.48 (d, $J=1.77$ Hz, 1 H) 9.65 (t, $J=5.56$ Hz, 1 H)	Method B , using commercially available (5-fluoropyridin-3-yl)methanamine in step 5
41	6-[3-chloro-4-(cyclopropylmethoxy)phenyl]-N-[[2-(2-ethylmorpholin-4-yl)-3-pyridyl)methyl]pyridazine-4-carboxamide		MS, ES+ m/z 509 (M+H) ⁺ . ¹ H NMR (400 MHz, DMSO- <i>d</i> 6) δ ppm 0.35 - 0.43 (m, 2 H) 0.58 - 0.66 (m, 2 H) 0.92 (t, $J=7.45$ Hz, 3 H) 1.31 (s, 1 H) 1.44 - 1.54 (m, 2 H) 2.62 (dd, $J=12.51, 10.23$ Hz, 1 H) 2.89 (d, $J=2.27$ Hz, 1 H) 3.16 - 3.29 (m, 2 H) 3.70 (d, $J=2.53$ Hz, 1 H) 3.91 (d, $J=9.85$ Hz, 1 H) 4.04 (d, $J=7.07$ Hz, 2 H) 4.60 (d, $J=6.06$ Hz, 2 H) 7.07 (dd, $J=7.58, 4.80$ Hz, 1 H) 7.35 (d, $J=8.84$ Hz, 1 H) 7.71 (dd, $J=7.58, 1.77$ Hz, 1 H) 8.15 - 8.26 (m, 2 H) 8.30 (d, $J=2.27$ Hz, 1 H) 8.57 (d, $J=2.02$ Hz, 1 H) 9.46 - 9.59 (m, 2 H)	Method B , using (2-(2-ethylmorpholino)pyridin-3-yl)methanamine

Example	Name	R	Analytical data	Preparation details
42	6-[3-chloro-4-(cyclopropylmethoxy)phenyl]-N-[(2-isopropoxy-3-pyridyl)methyl]pyridazine-4-carboxamide		MS, ES+ m/z 453 (M+H) ⁺ . ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ ppm 0.36 - 0.43 (m, 2 H) 0.57 - 0.66 (m, 2 H) 1.25 - 1.36 (m, 7 H) 4.05 (d, <i>J</i> =7.07 Hz, 2 H) 4.47 (d, <i>J</i> =5.56 Hz, 2 H) 5.26 - 5.38 (m, 1 H) 6.94 (dd, <i>J</i> =7.20, 4.93 Hz, 1 H) 7.35 (d, <i>J</i> =8.84 Hz, 1 H) 7.67 (dd, <i>J</i> =7.20, 1.89 Hz, 1 H) 8.08 (dd, <i>J</i> =5.05, 1.77 Hz, 1 H) 8.19 (dd, <i>J</i> =8.72, 2.15 Hz, 1 H) 8.31 (d, <i>J</i> =2.27 Hz, 1 H) 8.56 (d, <i>J</i> =2.02 Hz, 1 H) 9.41 (t, <i>J</i> =5.68 Hz, 1 H) 9.48 (d, <i>J</i> =2.02 Hz, 1 H)	Method B , using commercially available (2-isopropoxypyridin-3-yl)methanamine in step 5

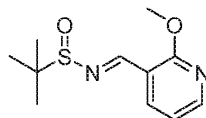
Example 43, 6-(3-chloro-4-(cyclopropylmethoxy)phenyl)-N-(1-(2-methoxypyridin-3-yl)ethyl)pyridazine-4-carboxamide

Method C

5



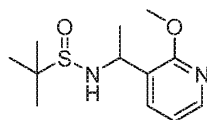
Step 1: Synthesis of (E)-N-((2-methoxypyridin-3-yl)methylene)-2-methylpropane-2-sulfonamide



10 2-methoxypyridine-3-carbaldehyde (2.35 g, 17.1 mmol) was added to a round-bottom flask and dissolved in DCM (25 mL). 2-methyl-2-propanesulfonamide (3.1 g, 25.7 mmol) was added, followed by titanium tetraisopropoxide (10.1 mL, 34.3 mmol). The resulting mixture was stirred at room temperature for ~18 hours, and

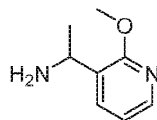
poured into brine (about 250 mL) with vigorous stirring. The biphasic mixture was filtered through celite, and the organic layer was collected, dried and concentrated to afford the product as a yellow oil (yield: 3.1 g, 75%).

Step 2: Synthesis of N-(1-(2-methoxypyridin-3-yl)ethyl)-2-methylpropane-2-sulfinamide



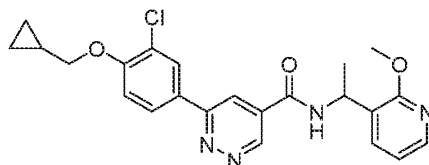
(E)-N-(1-(2-methoxypyridin-3-yl)methylene)-2-methylpropane-2-sulfinamide (531 mg, 2.2 mmol) was added to a round-bottom flask and dissolved in THF (10 mL). The mixture was cooled to -78 °C, and methylmagnesium chloride (3M in THF, 1.1 mL, 3.3 mmol) was added dropwise. After stirring at -78 °C for 10 minutes, the mixture was allowed to warm to room temperature, and the reaction was quenched by the careful addition of water (about 2 mL). The mixture was diluted with dichloromethane, filtered through celite, and the filtrate was concentrated to give a colorless oil containing the desired product. This was used without further purification.

Step 3: Synthesis of 1-(2-methoxy-3-pyridyl)ethanamine



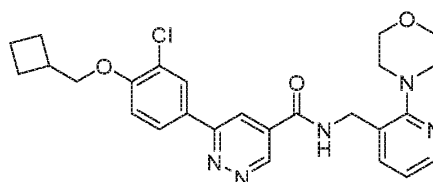
A solution of N-(1-(2-methoxypyridin-3-yl)ethyl)-2-methylpropane-2-sulfinamide (566 mg, 2.2 mmol) in DCM (10 mL) was treated with 4M HCl in dioxane (1.66 mL, 6.63 mmol) and allowed to stir at room temperature for 1.5 hours. Methanol (5 mL) was added to dissolve solids, and volatiles were evaporated under reduced pressure to give a yellow solid. This was re-dissolved in saturated sodium bicarbonate solution (25 mL) and extracted with dichloromethane. Organic layers were collected, dried, and concentrated under reduced pressure, affording a light yellow oil, which was used without further characterization.

Step 4: Synthesis of 6-(3-chloro-4-(cyclopropylmethoxy)phenyl)-N-(1-(2-methoxypyridin-3-yl)ethyl)pyridazine-4-carboxamide (Example 43)

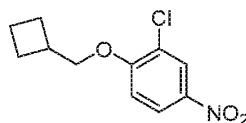


To a suspension of Intermediate B (50 mg, 0.16 mmol) in DCM (2.5 mL) was added trimethylamine (0.046 mL, 0.73 mmol) and HBTU (68.5 mg, 0.18 mmol) and the resulting mixture was stirred at room temperature for 2 hours. 1-(2-methoxy-3-pyridyl)ethanamine (30 mg, 0.2 mmol) was added as a solution in DCM (1mL), and stirring was continued for an additional hour. The mixture was filtered through a plug of basic alumina, concentrated, and purified by preparative HPLC (10-100% ACN/water gradient, 0.1% TFA modifier) to afford the desired product as a solid (43 mg, 60%). ES⁺ m/z 439.0 [M+H]⁺. ¹H NMR (400 MHz, DMSO-d₆) δ ppm 9.45 (d, J=2.02 Hz, 1 H), 8.57 (d, J=2.02 Hz, 1 H), 8.33 (d, J=2.27 Hz, 1 H), 8.21 (dd, J=8.84, 2.27 Hz, 1 H), 8.09 (dd, J=5.05, 1.77 Hz, 1 H), 7.36 (d, J=8.59 Hz, 1 H), 7.00 (dd, J=7.33, 4.80 Hz, 1 H), 4.05 (d, J=6.82 Hz, 2 H), 3.94 (s, 3 H), 1.48 (d, J=7.07 Hz, 3 H), 0.63 (dd, J=8.08, 1.77 Hz, 2 H), 0.41 (dd, J=4.67, 1.64 Hz, 2 H)

Example 44: 6-[3-chloro-4-(cyclobutylmethoxy)phenyl]-N-[(2-morpholino-3-pyridyl)methyl]pyridazine-4-carboxamide
Method D



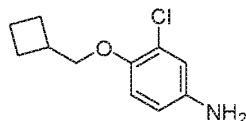
Step 1: Synthesis of 2-chloro-1-(cyclobutylmethoxy)-4-nitrobenzene



To a solution of 2-chloro-4-nitrophenol (2.0 g, 11.5 mmol) in DMSO (10 mL) was added cesium carbonate (5.63 g, 17.3 mmol) and bromomethylcyclobutane (1.94 mL, 17.3 mmol). This mixture was heated to 100 °C for ~18 hours, and then poured into about 100 mL water. pH was adjusted to ~2 by addition of 6N HCl solution, and the aqueous emulsion was extracted with diethyl ether. Organic layers were collected,

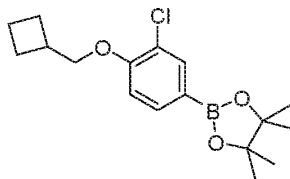
dried, and concentrated to give a dark oil, which was used without further purification.

Step 2: Synthesis of 3-chloro-4-(cyclobutylmethoxy)aniline



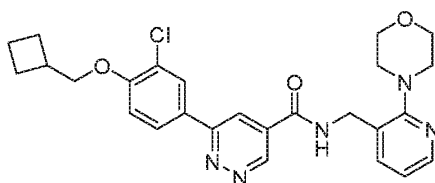
5 A round-bottom flask was charged with 2-chloro-1-(cyclobutylmethoxy)-4-nitrobenzene (2.79 g, 11.5 mmol) and dissolved in 25 mL methanol. 6N HCl solution (5 mL) was added, followed by excess metallic tin. The mixture was heated to reflux for approximately 30 minutes, and then filtered to remove unreacted tin. The filtrate was made strongly basic by addition of concentrated ammonium hydroxide solution, and filtered through celite. The clear filtrate was then extracted with dichloromethane, and organic layers were collected, dried, and concentrated to give an oil containing the desired product. This oil was used without further purification.

Step 3: Synthesis of 2-(3-chloro-4-(cyclobutylmethoxy)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane



15 To a round-bottom flask was added 3-chloro-4-(cyclobutylmethoxy)aniline (2.44 g, 11.5 mmol) and acetonitrile (25 mL). To this solution was added 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (3.22 g, 12.7 mmol) and tert-butyl nitrite (2.1 mL, 17.3 mmol). The mixture was heated to 75 °C until gas evolution stopped (about 35 minutes) and was then concentrated. The resulting residue was purified by silica gel chromatography (0-10% Ethyl acetate in heptane gradient) to afford the desired product as a light yellow oil (yield: 2.3 g, 62%).

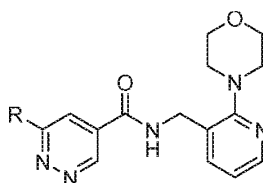
Step 4: Synthesis of 6-(3-chloro-4-(cyclobutylmethoxy)phenyl)-N-((2-morpholinopyridin-3-yl)methyl)pyridazine-4-carboxamide



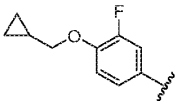
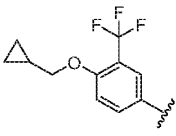
25

A microwave vial was charged with Intermediate A (100 mg, 0.3 mmol), 2-(3-chloro-4-(cyclobutylmethoxy)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (145 mg, 0.5 mmol), [1,1'-Bis(diphenylphosphino)ferrocene]dichloropalladium(II) – dichloromethane complex (24 mg, 0.03 mmol), and cesium carbonate (195 mg, 0.6 mmol). The vial was sealed, evacuated and backfilled with nitrogen three times, and then THF (2.5 mL) and water (0.25 mL) were introduced via syringe and the mixture was heated under microwave irradiation to 160 °C for 10 minutes. The crude mixture was diluted with ethyl acetate and filtered through celite, and then through a plug of basic alumina. The filtrate was concentrated and purified by preparative HPLC (10-100% ACN/water gradient, 0.1% TFA modifier) to afford the desired product as a foam (73 mg, 49%). ES⁺ m/z 494.2 [M+H]⁺. ¹H-NMR (400 MHz, DMSO-d₆) δ ppm 9.54 (t, J = 5.8 Hz, 1H), 9.50 (d, J = 1.8 Hz, 1H), 8.57 (d, J = 2 Hz, 1H), 8.30 (d, J = 2.3 Hz, 1H), 8.17-8.27 (m, 2H), 7.72 (dd, J = 7.6, 1.8 Hz, 1H), 7.38 (d, J = 8.8 Hz, 1H), 7.08 (dd, J = 7.6, 4.8 Hz, 1H), 4.61 (d, J = 5.8 Hz, 2H), 4.16 (d, J = 6.3 Hz, 2H), 3.71-3.81 (m, 4H), 3.01-3.12 (m, 4H), 2.73-2.84 (m, 1H), 2.05-2.15 (m, 2H), 1.86-1.97 (m, 4H).

The following compounds have been synthesized according to Method D:

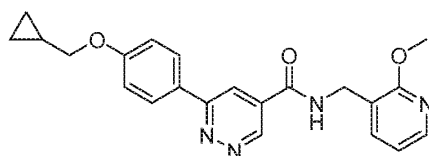


Example	Name	R	Analytical data	Preparation details
45	6-[3-chloro-4-(1-cyclopropylethoxy)phenyl]-N-[(2-morpholino-3-pyridyl)methyl]pyridine-4-carboxamide		MS, ES ⁺ m/z 494 (M+H) ⁺ . ¹ H-NMR (400 MHz, DMSO-d ₆) δ ppm 9.47-9.58 (m, 2H), 8.56 (d, J = 1.8 Hz, 1H), 8.28 (d, J = 2.3 Hz, 1H), 8.23 (dd, J = 4.8, 1.8 Hz, 1H), 8.16 (dd, J = 8.6, 2.3 Hz, 1H), 7.72 (dd, J = 7.6, 1.8 Hz, 1H), 7.39 (d, J = 9.1 Hz, 1H), 7.07 (dd, J = 7.6, 4.8 Hz, 1H), 4.6 (d, J = 5.8 Hz, 2H), 4.17-4.27 (m, 1H), 3.71-	Method D , using (1-bromoethyl)cyclopropane

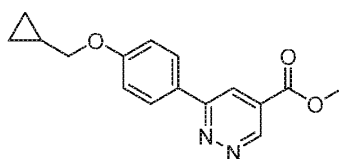
Example	Name	R	Analytical data	Preparation details
			3.83 (m, 4H), 3.0-3.12 (m, 4H), 1.37 (d, J = 6.1 Hz, 3H), 1.12-1.22 (m, 1H), 0.54 (dt, J = 7.9, 1.4 Hz, 2H), 0.30-0.44 (m, 2H).	
46	6-[4-(cyclopropylmethoxy)-3-fluoro-phenyl]-N-[(2-morpholino-3-pyridyl)methyl]pyridazine-4-carboxamide		MS, ES+ m/z 464 (M+H) ⁺ . ¹ H-NMR (400 MHz, DMSO-d ₆) δ ppm 9.46-9.57 (m, 2H), 8.55 (d, J = 2.0 Hz, 1H), 8.23 (dd, J = 4.8, 1.8 Hz, 1H), 8.1 (dd, J = 12.8, 2.1 Hz, 1H), 8.04 (dt, J = 8.6, 1.1 Hz, 1H), 7.72 (dd, J = 7.6, 2.0 Hz, 1H), 7.37 (t, J = 8.7 Hz, 1H), 7.07 (dd, J = 7.6, 4.8 Hz, 1H), 4.60 (d, J = 5.6 Hz, 2H), 4.02 (d, J = 7.1 Hz, 2H), 3.72-3.81 (m, 4H), 3.01-3.12 (m, 4H), 1.23-1.34 (m, 1H), 0.57-0.65 (m, 2H), 0.34-0.41 (m, 2H).	Method D, using 2-fluoro-4-nitrophenol
47	6-[4-(cyclopropylmethoxy)-3-(trifluoromethyl)phenyl]-N-[(2-morpholino-3-pyridyl)methyl]pyridazine-4-carboxamide		MS, ES+ m/z 514 (M+H) ⁺ . ¹ H-NMR (400 MHz, DMSO-d ₆) δ ppm 9.50-9.61 (m, 2H), 8.61 (d, J = 2.0 Hz, 1H), 8.42-8.52 (m, 2H), 8.23 (dd, J = 4.8, 1.8 Hz, 1H), 7.72 (dd, J = 7.6, 1.8 Hz, 1H), 7.49 (d, J = 9.6 Hz, 1H), 7.08 (dd, J = 7.5, 4.9 Hz, 1H), 4.61 (d, J = 5.8 Hz, 2H), 4.13 (d, J = 6.8 Hz, 2H), 3.72-3.81 (m, 4H), 3.0-3.12 (m, 4H), 1.21-1.33 (m, 1H), 0.53-0.64 (m, 2H), 0.33-0.43 (m, 2H).	Method D, using 4-nitro-2-(trifluoromethyl)phenol

Example 48: 6-[4-(cyclopropylmethoxy)phenyl]-N-[(2-methoxy-3-pyridyl)methyl]pyridazine-4-carboxamide

Method E

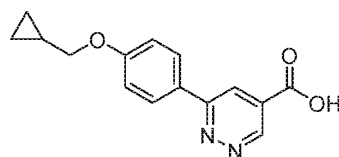


- 5 *Step 1: Synthesis of methyl 6-[4-(cyclopropylmethoxy)phenyl]pyridazine-4-carboxylate*



- A microwave vial containing a magnetic stir bar was charged with methyl 6-chloropyridazine-4-carboxylate (1.50 g, 8.70 mmol), [4-(cyclopropylmethoxy)phenyl]boronic acid (1.84 g, 9.56 mmol), Bis(diphenylphosphino)ferrocene[dichloropalladium(II) – dichloromethane complex (709 mg, 0.869 mmol), and cesium carbonate (5.66 g, 17.4 mmol) and the vial was sealed, evacuated and backfilled with nitrogen three times. THF (6 mL) and water (0.6 mL) were introduced via syringe, and the mixture was heated to 145 °C for 35 minutes. The crude mixture was diluted with ethyl acetate (20 mL) and filtered through celite, and the filtrate was concentrated and purified by silica gel chromatography (0-100% EtOAc in heptane gradient) to afford the desired product as a solid (1.6 g, 65%).

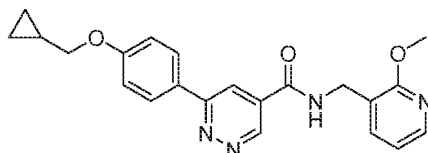
Step 2: Synthesis of 6-[4-(cyclopropylmethoxy)phenyl]pyridazine-4-carboxylic acid



- Methyl 6-[4-(cyclopropylmethoxy)phenyl]pyridazine-4-carboxylate (1.6 g, 5.63 mmol) was added to a round-bottom flask equipped with a stir bar and dissolved in methanol (10 mL). Water (1 mL) was added, followed by excess solid sodium hydroxide, and the resulting mixture was stirred at room temperature for ~2 hours.
- 25 The mixture was diluted with water (50 mL), and pH was adjusted to about 3 by

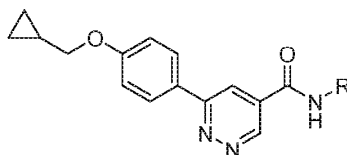
addition of 6N HCl solution. The resultant precipitate was collected by filtration, rinsed with water, and dried under reduced pressure to give the title compound as a white powder, which was used without further purification. (1.43 g, 94%)

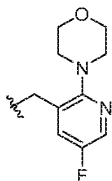
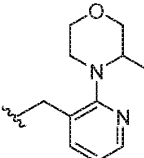
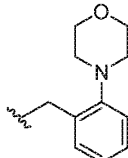
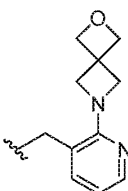
5 *Step 3: Synthesis of 6-[4-(cyclopropylmethoxy)phenyl]-N-[(2-methoxy-3-pyridyl)methyl]pyridazine-4-carboxamide*



- 6-[4-(cyclopropylmethoxy)phenyl]pyridazine-4-carboxylic acid (100 mg, 0.37 mmol) was charged to a screw-top vial and suspended in dichloromethane (2.5 mL). Oxalyl chloride (0.04 mL, 0.41 mmol) was added, followed by a drop of DMF. After stirring for 1 hour at room temperature, volatiles were evaporated under reduced pressure, and the residue was re-dissolved in DCM (2.5 mL), and the mixture was cooled in an ice bath. (2-methoxy-3-pyridyl)methanamine (56 mg, 0.41 mmol) and trimethylamine (0.1 mL, 0.74 mmol) were added dropwise as a solution in DCM, and the mixture was allowed to reach room temperature. The crude mixture was filtered through a plug of basic alumina and concentrated to give an oil. This was purified by preparative HPLC (10-100% ACN/water gradient, 0.1% TFA modifier) to give the title product as a glass (56 mg, 38%). MS, ES+ m/z 391 (M+H)⁺. ¹H-NMR (400 MHz, DMSO- d_6) δ 9.43-9.54 (m, 2H), 8.51 (d, J = 2.0 Hz, 1H), 8.15-8.23 (m, 2H), 8.10 (dd, J = 4.9, 1.9 Hz, 1H), 7.65-7.72 (m, 1H), 7.11-7.17 (m, 2H), 6.99 (dd, J = 7.2, 4.9 Hz, 1H), 4.48 (d, J = 5.3 Hz, 2H), 3.87-3.97 (m, 5H), 1.21-1.32 (m, 1H), 0.55-0.64 (m, 2H), 0.32-0.40 (m, 2H).

The following compounds have been synthesized according to **Method E**:

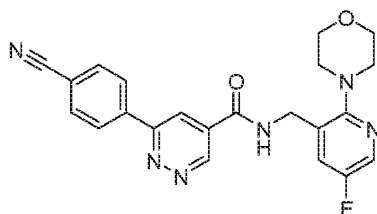


Example	Name	R	Analytical data	Preparation details
49	6-[4-(cyclopropylmethoxy)phenyl]-N-[(5-fluoro-2-morpholino-3-pyridyl)methyl]pyridazine-4-carboxamide		MS, ES+ m/z 464 (M+H) ⁺	Method E, using (5-fluoro-2-morpholino-3-pyridyl)methanamine
50	6-[4-(cyclopropylmethoxy)phenyl]-N-[[2-(3-methylmorpholin-4-yl)-3-pyridyl]methyl]pyridazine-4-carboxamide		MS, ES+ m/z 460 (M+H) ⁺	Method E, using (2-(3-methylmorpholino)pyridin-3-yl)methanamine
51	6-[4-(cyclopropylmethoxy)phenyl]-N-[(2-morpholinophenyl)methyl]pyridazine-4-carboxamide		MS, ES+ m/z 445 (M+H) ⁺ ¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ ppm 0.29 - 0.43 (m, 2 H) 0.52 - 0.66 (m, 2 H) 1.18 - 1.34 (m, 1 H) 2.80 - 2.94 (m, 4 H) 3.77 (br. s., 4 H) 3.93 (d, <i>J</i> =6.92 Hz, 2 H) 4.68 (d, <i>J</i> =5.50 Hz, 2 H) 7.05 - 7.23 (m, 4 H) 7.23 - 7.32 (m, 1 H) 7.36 (d, <i>J</i> =7.55 Hz, 1 H) 8.18 (d, <i>J</i> =8.65 Hz, 2 H) 8.51 (d, <i>J</i> =1.57 Hz, 1 H) 9.35 - 9.56 (m, 2 H)	Method E, using (2-morpholinophenyl)methanamine
52	6-[4-(cyclopropylmethoxy)phenyl]-N-[[2-(2-oxa-6-azaspiro[3.3]heptan-6-yl)-3-pyridyl]methyl]py		MS, ES+ m/z 458 (M+H) ⁺ ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ ppm 0.32 - 0.39 (m, 2 H) 0.56 - 0.65 (m, 2 H) 1.27 (ddd, <i>J</i> =7.96, 4.67, 3.28 Hz, 1 H) 3.92 (d, <i>J</i> =6.82 Hz, 2 H)	Method E, (2-(2-oxa-6-azaspiro[3.3]heptan-6-yl)pyridin-3-yl)methanamine

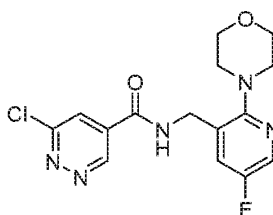
	ridazine-4-carboxamide		4.26 (s, 4 H) 4.42 (d, $J=5.31$ Hz, 2 H) 4.73 (s, 4 H) 6.76 (dd, $J=7.45, 4.93$ Hz, 1 H) 7.11 - 7.20 (m, 2 H) 7.51 (dd, $J=7.45, 1.64$ Hz, 1 H) 8.06 (dd, $J=4.80, 1.77$ Hz, 1 H) 8.14 - 8.23 (m, 2 H) 8.51 (d, $J=2.02$ Hz, 1 H) 9.36 - 9.53 (m, 2 H)	
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Example 53: 6-(4-cyanophenyl)-N-[(5-fluoro-2-morpholino-3-pyridyl)methyl]pyridazine-4-carboxamide

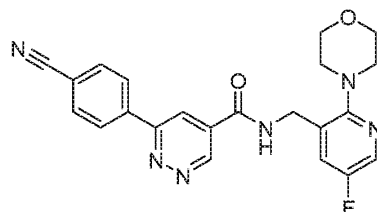
Method F



- 5 *Step 1: Synthesis of 6-chloro-N-[(5-fluoro-2-morpholino-3-pyridyl)methyl]pyridazine-4-carboxamide*



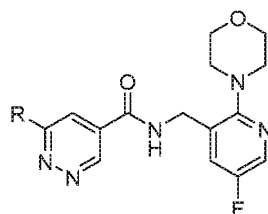
- 6-chloropyridazine-4-carboxylic acid (250 mg, 1.58 mmol) was added to a round bottom flask and dissolved in dichloromethane (10 mL). Oxalyl chloride (152 μ L, 1.73 mmol) was added, followed by a drop of DMF, and the mixture was allowed to stir at room temperature for 1 hour. Solvents were evaporated under reduced pressure, and the residue was dissolved in dichloromethane (5 mL). Triethylamine (242 μ L, 0.73 mmol) and (5-fluoro-2-morpholino-3-pyridyl)methanamine were added dropwise as a solution in dichloromethane (5 mL). The crude mixture was concentrated under reduced pressure and purified by preparative reversed-phase HPLC (high pH method) to give the title compound (403 mg, 1.3 mmol) as a foam. MS, ES⁺ m/z 352 (M+H)⁺
- 10 *Step 2: Synthesis of 6-(4-cyanophenyl)-N-[(5-fluoro-2-morpholino-3-pyridyl)methyl]pyridazine-4-carboxamide*



To a microwave vial equipped with a magnetic stir bar were added 6-chloro-N-[(5-fluoro-2-morpholino-3-pyridyl)methyl]pyridazine-4-carboxamide (82 mg, 0.23 mmol), 4-cyanophenylboronic acid (51 mg, 0.35 mmol), [1,1'-

- 5 Bis(diphenylphosphino)ferrocene]dichloropalladium(II) (19 mg, 0.02 mmol), and cesium carbonate (152 mg, 0.47 mmol). THF (2.5 mL) and water (0.25 mL) were added, the vial was sealed, and the mixture was heated to 160 °C under microwave irradiation for 10 minutes. The crude mixture was filtered through celite, concentrated and purified by preparative reversed-phase HPLC (high pH method) to afford the
- 10 desired product as a solid. (40 mg, 0.1 mmol). MS, ES+ m/z 419 (M+H)⁺. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 2.95 - 3.10 (m, 4 H) 3.67 - 3.82 (m, 4 H) 4.62 (d, J =5.81 Hz, 2 H) 7.70 (dd, J =9.09, 3.03 Hz, 1 H) 8.07 - 8.15 (m, 2 H) 8.24 (d, J =2.78 Hz, 1 H) 8.36 - 8.47 (m, 2 H) 8.70 (d, J =2.02 Hz, 1 H) 9.54 - 9.68 (m, 2 H).

The following compounds have been synthesized according to **Method F**:

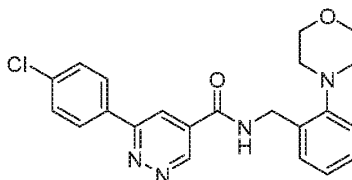


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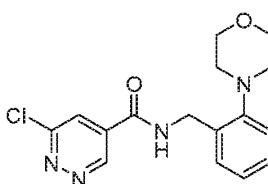
Example	Name	R	Analytical data	Prep details
54	6-(4-chlorophenyl)-N-[(5-fluoro-2-morpholino-3-pyridyl)methyl]pyridazine-4-carboxamide		MS, ES+ m/z 428 (M+H) ⁺	Method F, using 4-chlorophenylboronic acid

Example 55: 6-(4-chlorophenyl)-N-[(2-morpholinophenyl)methyl]pyridazine-4-carboxamide

Method G

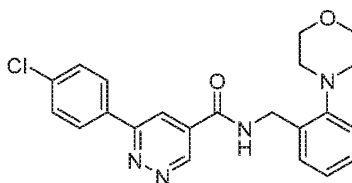


5 *Step 1: Synthesis of 6-chloro-N-[(2-morpholinophenyl)methyl]pyridazine-4-carboxamide*



A round-bottom flask was charged with 6-chloropyridazine-4-carboxylic acid (165 mg, 1.04 mmol), and dichloromethane (5 mL) was added. Oxalyl chloride (91 μ L, 1.04 mmol) was added, followed by a drop of DMF, and the mixture was stirred at room temperature for 1.5 hours. Volatiles were removed under reduced pressure, and the residue was dissolved in 5 mL dichloromethane. Triethylamine (145 μ L, 1.04 mmol) and (2-morpholinophenyl)methanamine (200 mg, 1.04 mmol) were added dropwise as a solution in 3 mL dichloromethane. After stirring for an additional five minutes, the mixture was concentrated and purified by silica gel chromatography, eluting with a 0-5% gradient of methanol in dichloromethane to afford the desired product (200 mg, 0.6 mmol, 58% yield) as a colorless solid. MS, ES+ m/z 333 (M+H)⁺

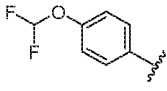
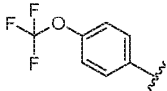
Step 2: Synthesis of 6-(4-chlorophenyl)-N-[(2-morpholinophenyl)methyl]pyridazine-4-carboxamide

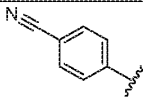


20 To a microwave vial equipped with a magnetic stir bar were added 6-chloro-N-[(2-morpholinophenyl)methyl]pyridazine-4-carboxamide (100 mg, 0.3 mmol), 4-chlorophenylboronic acid (70 mg, 0.45 mmol), [1,1'-

- Bis(diphenylphosphino)ferrocene]dichloropalladium(II) (25 mg, 0.03 mmol), and cesium carbonate (152 mg, 0.47 mmol). THF (2.5 mL) and water (0.25 mL) were added, the vial was sealed, and the mixture was heated to 160 °C under microwave irradiation for 10 minutes. The crude mixture was filtered through celite, concentrated and purified by preparative reversed-phase HPLC (high pH method) to afford the desired product as a solid. MS, ES+ m/z 409 (M+H)⁺. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 2.84 - 3.02 (m, 4 H) 3.69 - 3.88 (m, 4 H) 4.68 (d, J =5.81 Hz, 2 H) 7.06 - 7.23 (m, 2 H) 7.23 - 7.46 (m, 2 H) 7.65 - 7.84 (m, 2 H) 8.22 - 8.39 (m, 2 H) 8.61 (d, J =2.02 Hz, 1 H) 9.45 - 9.54 (m, 1 H) 9.57 (d, J =1.77 Hz, 1 H).

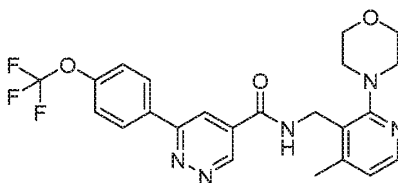
- 10 The following compounds have been synthesized according to **Method G**:

Example	Name	R	Analytical data	Prep details
56	6-[4-(difluoromethoxy)phenyl]-N-[(2-morpholinophenyl)methyl]pyridazine-4-carboxamide		MS, ES+ m/z 409 (M+H) ⁺ . ¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ ppm 2.81 - 2.94 (m, 4 H) 3.77 (br. s., 4 H) 4.69 (d, J =5.66 Hz, 2 H) 7.11 (t, J =7.31 Hz, 1 H) 7.18 (d, J =7.55 Hz, 1 H) 7.22 - 7.33 (m, 1 H) 7.33 - 7.48 (m, 3 H) 8.30 (d, J =8.80 Hz, 2 H) 8.58 (d, J =1.73 Hz, 1 H) 9.48 (t, J =5.50 Hz, 1 H) 9.55 (d, J =1.89 Hz, 1 H)	Method G , using (4-(difluoromethoxy)phenyl)boronic acid
57	6-[4-(trifluoromethoxy)phenyl]-N-[(2-morpholinophenyl)methyl]pyridazine-4-carboxamide		MS, ES+ m/z 459 (M+H) ⁺ . ¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ ppm 2.83 - 2.93 (m, 4 H) 3.72 - 3.81 (m, 4 H) 4.69 (d, J =5.66 Hz, 2 H) 7.11 (t, J =7.39 Hz, 1 H) 7.18 (d, J =7.55 Hz, 1 H) 7.29 (t, J =7.07 Hz, 1 H) 7.37 (d, J =7.23 Hz, 1 H) 7.61 (m, J =8.17 Hz, 2 H) 8.36 (m, J =8.80 Hz, 2 H) 8.62 (d, J =1.73 Hz, 1 H) 9.48 (t, J =5.42 Hz, 1 H) 9.58 (d, J =1.73 Hz, 1 H)	Method G , using (4-(trifluoromethoxy)phenyl)boronic acid

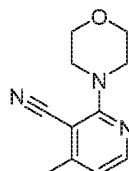
58	6-(4-cyanophenyl)-N-[(2-morpholinophenyl)methyl]pyridazine-4-carboxamide		MS, ES+ m/z 400 (M+H) ⁺ 1H NMR (500 MHz, DMSO- <i>d</i> ₆) δ ppm 2.81 - 2.94 (m, 4 H) 3.77 (br. s., 4 H) 4.69 (d, J =5.50 Hz, 2 H) 7.11 (t, J =7.23 Hz, 1 H) 7.18 (d, J =7.70 Hz, 1 H) 7.29 (t, J =7.39 Hz, 1 H) 7.37 (d, J =7.55 Hz, 1 H) 8.10 (m, J =8.33 Hz, 2 H) 8.42 (m, J =8.33 Hz, 2 H) 8.69 (d, J =1.57 Hz, 1 H) 9.49 (t, J =5.50 Hz, 1 H) 9.62 (d, J =1.73 Hz, 1 H)	Method G , using (4-cyanophenyl)boronic acid
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Example 59: N-[(4-methyl-2-morpholino-3-pyridyl)methyl]-6-[4-(trifluoromethoxy)phenyl]pyridazine-4-carboxamide

Method H

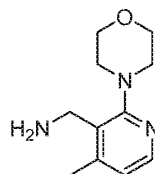


5 Step 1: Synthesis of 4-methyl-2-morpholino-pyridine-3-carbonitrile



A 20 L scintillation vial equipped with a magnetic stir bar was charged with 2-chloro-4-methyl-pyridine-3-carbonitrile (1.0 g, 6.6 mmol) and DMSO (5 mL). Morpholine (1.1 g, 13.1 mmol) was added, and the resulting mixture was stirred at 50 °C for 18
 10 hours. After cooling to room temperature, the crude mixture was purified directly by preparative MPLC (high pH method) to afford the desired product (1.3 g, 6.6 mmol, 100% yield) as a light yellow oil. MS, ES+ m/z 204 (M+H)⁺.

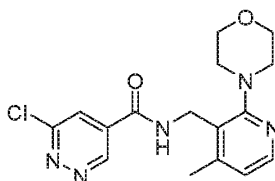
Step 2: Synthesis of (4-methyl-2-morpholino-3-pyridyl)methanamine



A round-bottom flask was charged with 4-methyl-2-morpholino-pyridine-3-carbonitrile (1.3 g, 6.6 mmol) and methanol (25 mL) was added. Excess Raney nickel was added as an aqueous slurry and the resulting mixture was stirred under an atmosphere of hydrogen (balloon) for about 18 hours. Solids were removed by filtration through celite, and the clear filtrate was concentrated to give an oil containing the desired product. Product was used without further purification. MS, ES+ m/z 208 (M+H)⁺

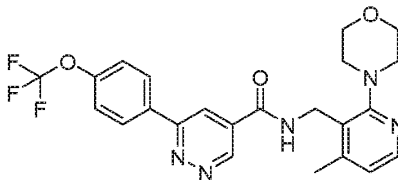
Step 3: Synthesis of 6-chloro-N-[(4-methyl-2-morpholino-3-

pyridyl)methyl]pyridazine-4-carboxamide



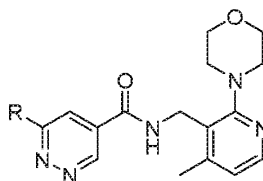
To a round-bottom flask were added 6-chloropyridazine-4-carboxylic acid (325 mg, 2.05 mmol) and dichloromethane (5 mL). Oxalyl chloride (270 μ L, 3.08 mmol) and DMF (1 drop) were added, and the mixture was stirred at room temperature for 1.5 hours. Triethylamine (572 μ L, 4.1 mmol) and (4-methyl-2-morpholino-3-pyridyl)methanamine (425 mg, 2.05 mmol) were added dropwise as a solution in dichloromethane (5 mL). The crude mixture was concentrated and purified by silica gel chromatography (eluting with a 0-5% methanol in DCM gradient) to afford the desired product (539 mg, 1.55 mmol, 76% yield) as a colorless solid. MS, ES+ m/z 348 (M+H)⁺.

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



- To a microwave vial equipped with a magnetic stir bar were added 6-chloro-N-[(4-methyl-2-morpholino-3-pyridyl)methyl]pyridazine-4-carboxamide (100 mg, 0.29 mmol), 4-trifluoromethoxyphenylboronic acid (89 mg, 0.43 mmol), [1,1'-Bis(diphenylphosphino)ferrocene]dichloropalladium(II) (23 mg, 0.03 mmol), and cesium carbonate (187 mg, 0.58 mmol). THF (2.5 mL) and water (0.25 mL) were added, the vial was sealed, and the mixture was heated to 160 °C under microwave irradiation for 10 minutes. The crude mixture was filtered through celite, concentrated and purified by preparative reversed-phase HPLC (high pH method) to afford the desired product (41 mg, 0.09 mmol, 30% yield) as a solid. MS, ES+ m/z 474 (M+H)⁺.
¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 2.39 (s, 3 H) 2.98 - 3.12 (m, 4 H) 3.69 - 3.81 (m, 4 H) 4.57 (d, J =5.34 Hz, 2 H) 6.92 (d, J =7.70 Hz, 1 H) 7.55-7.66 (m, 3 H) 8.35 (d, J =8.80 Hz, 2 H) 8.60 (d, J =1.89 Hz, 1 H) 9.50 (t, J =5.42 Hz, 1 H) 9.57 (d, J =1.73 Hz, 1 H).

The following examples have been synthesized according to **Method H**:

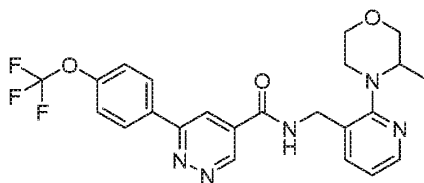


15

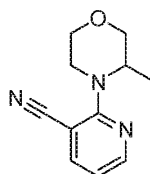
Example	Name	R	Analytical data	Prep details
60	6-(4-chlorophenyl)-N-[(4-methyl-2-morpholino-3-pyridyl)methyl]pyridazine-4-carboxamide		MS, ES+ m/z 400 (M+H) ⁺ ¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ ppm 2.39 (s, 3 H) 2.99 - 3.11 (m, 4 H) 3.69 - 3.80 (m, 4 H) 4.56 (d, J =5.50 Hz, 2 H) 6.92 (d, J =7.70 Hz, 1 H) 7.59 (d, J =7.55 Hz, 1 H) 7.69 (m, J =8.49 Hz, 2 H) 8.25 (m, J =8.65 Hz, 2 H) 8.54 - 8.63 (m, 1 H) 9.50 (t, J =5.27 Hz, 1 H) 9.55 (d, J =1.73 Hz, 1 H)	Method H , using 4-chlorophenylboronic acid

Example 61: N-[[2-(3-methylmorpholin-4-yl)-3-pyridyl]methyl]-6-[4-(trifluoromethoxy)phenyl]pyridazine-4-carboxamide

Method I

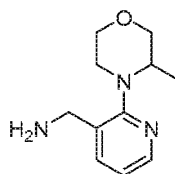


Step 1: Synthesis of 2-(3-methylmorpholin-4-yl)pyridine-3-carbonitrile



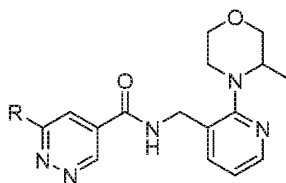
To a round-bottom flask equipped with a magnetic stir bar was added 2-
 5 fluoropyridine-3-carbonitrile (1.2 g, 9.9 mmol) and DMSO (5 mL). Triethylamine
 (1.4 mL, 9.9 mmol) and 3-methylmorpholine were added, and the resulting mixture
 was heated to 50 °C with stirring for 18 hours. After cooling to room temperature, the
 crude mixture was purified directly by preparative MPLC (high pH method) to afford
 the desired product (1.7 g, 8.4 mmol, 85% yield) as an oil, which solidified on
 10 standing. MS, ES+ m/z 204 (M+H)⁺.

Step 2: Synthesis of [2-(3-methylmorpholin-4-yl)-3-pyridyl]methanamine



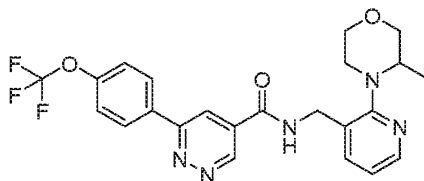
A round-bottom flask was charged with 2-(3-methylmorpholin-4-yl)pyridine-3-
 carbonitrile (1.7 g, 8.4 mmol) and methanol (25 mL) was added. Excess Raney nickel
 15 was added as an aqueous slurry and the resulting mixture was stirred under an
 atmosphere of hydrogen (balloon) for about 18 hours. Solids were removed by
 filtration through celite, and the clear filtrate was concentrated to give an oil
 containing the desired product. Product was used without further purification. MS,
 ES+ m/z 208 (M+H)⁺.

20 Step 3: Synthesis of 6-chloro-N-[[2-(3-methylmorpholin-4-yl)-3-
 pyridyl]methyl]pyridazine-4-carboxamide



- To a round-bottom flask equipped with a magnetic stir bar was added 6-chloropyridazine-4-carboxylic acid (250mg, 1.58 mmol) and dichloromethane (10 mL). Oxalyl chloride (152 μ L, 1.73 mmol) and DMF (1 drop) were added, and the mixture was stirred at room temperature for 1 hour, and then concentrated to dryness. The residue was dissolved in DCM (5 mL), and then trimethylamine (242 μ L, 1.73 mmol) and [2-(3-methylmorpholin-4-yl)-3-pyridyl]methanamine (360 mg, 1.73 mmol) were added dropwise as a solution in DCM (5 mL). The crude mixture was concentrated under reduced pressure and purified by preparative MPLC (high pH method) to give the desired product as a foam (241 mg, 0.7 mmol, 44% yield). MS, ES+ m/z 348 (M+H)⁺.

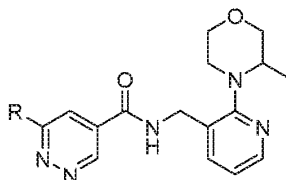
Step 4: Synthesis of N-[[2-(3-methylmorpholin-4-yl)-3-pyridyl]methyl]-6-[4-(trifluoromethoxy)phenyl]pyridazine-4-carboxamide



- To a microwave vial equipped with a magnetic stir bar were added 6-chloro-N-[[2-(3-methylmorpholin-4-yl)-3-pyridyl]methyl]pyridazine-4-carboxamide (100 mg, 0.29 mmol), 4-trifluoromethoxyphenylboronic acid (89 mg, 0.43 mmol), [1,1'-Bis(diphenylphosphino)ferrocene]dichloropalladium(II) (23 mg, 0.03 mmol), and cesium carbonate (187 mg, 0.58 mmol). THF (2.5 mL) and water (0.25 mL) were added, the vial was sealed, and the mixture was heated to 160 °C under microwave irradiation for 10 minutes. The crude mixture was filtered through celite, concentrated and purified by preparative reversed-phase HPLC (high pH method) to afford the desired product as a solid (61 mg, 0.13 mmol, 45% yield). MS, ES+ m/z 348 (M+H)⁺. ¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 0.83 (d, *J*=6.13 Hz, 3 H) 2.76 - 2.86 (m, 1 H) 3.11 (d, *J*=12.26 Hz, 1 H) 3.34 - 3.41 (m, 1 H) 3.45 - 3.54 (m, 1 H) 3.68 - 3.87 (m, 3 H) 4.65 (d, *J*=5.50 Hz, 2 H) 7.15 (dd, *J*=7.55, 4.72 Hz, 1 H) 7.62 (d, *J*=8.17 Hz, 2 H)

7.77 (d, $J=7.55$ Hz, 1 H) 8.27 - 8.41 (m, 3 H) 8.61 (d, $J=1.89$ Hz, 1 H) 9.48 - 9.61 (m, 2 H).

The following compounds have been synthesized according to **Method I**:



Example	Name	R	Analytical data	Prep details
62	6-(4-chlorophenyl)-N-[[2-(3-methylmorpholin-4-yl)-3-pyridyl]methyl]pyridazine-4-carboxamide		MS, ES+ m/z 400 (M+H) ⁺ ¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ ppm 0.83 (d, $J=6.29$ Hz, 3 H) 2.75 - 2.85 (m, 1 H) 3.11 (d, $J=12.58$ Hz, 1 H) 3.34 - 3.40 (m, 1 H) 3.44 - 3.54 (m, 1 H) 3.69 - 3.86 (m, 3 H) 4.65 (d, $J=5.66$ Hz, 2 H) 7.15 (dd, $J=7.55$, 4.72 Hz, 1 H) 7.69 (m, $J=8.65$ Hz, 2 H) 7.76 (d, $J=7.39$ Hz, 1 H) 8.26 (m, $J=8.65$ Hz, 2 H) 8.32 (dd, $J=4.48$, 1.49 Hz, 1 H) 8.60 (d, $J=1.73$ Hz, 1 H) 9.48 - 9.60 (m, 2 H)	Method I, using 4-chlorophenylboronic acid

5

Assay Methods

The ability of pyridine carboxamide derivatives exemplified above to inhibit the Nav1.8 channel was determined using one or more of the methods described below.

10 HEK Nav1.8 $\beta 1/\beta 2$ stably expressing cell line

A HEK293 cell line stably expressing the human Nav1.8 (hNav1.8) ion channel with $\beta 1/\beta 2$ subunits was constructed. The cell line is suitable for IC₅₀ determination in fluorescence and electrophysiological based assays. It is also suitable

to conduct mechanism of action pharmacology studies in electrophysiological assays. HEK293 Nav1.8 cells are grown as adherent monolayers in DMEM/high glucose media, 10% fetal bovine serum, Na pyruvate (2 mM), Hepes (10 mM) with selection agents G418 (400 mg/L) and puromycin (0.5 mg/L) at 37 degrees C, 10% CO₂.

5 Na_v1.8 Fluorescence Inhibition Assay

Compounds were made up to or supplied as a 10-mM stock solution using DMSO as the vehicle. Concentration-response curves were generated using a Matrix multichannel pipettor. Compound source plates were made by diluting 10mM compound stocks to create 500 μ M (100x) solutions in DMSO in 96-well v-bottom plates. Compounds were then serially diluted in 100% DMSO to generate a 5 point, 4-fold dilution scheme dose response curve. 2 μ L of the 100x dose response curves were then added to preincubation and stimulation assay plates. 100 μ L of pre-incubation buffer and 200 μ L of stimulation buffer was then added to the plates resulting in a final assay test concentration range of 5 μ M to 0.02 μ M with a final DMSO concentration of 1%.

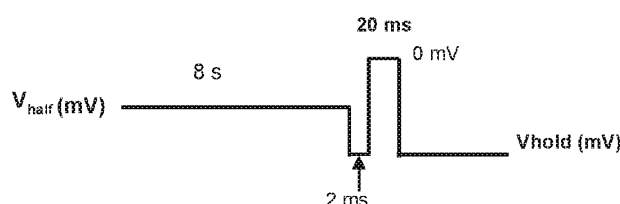
On the day of assay, plates were washed to remove cell culture media using 2K EBSS buffer (135 mM NaCl, 2 mM KCl, 5 mM Glucose, 2mM CaCl₂, 1 mM MgCl₂, 10 mM HEPES, pH 7.4). The Na-sensitive fluorescent dye, Asante Natrium Green-2 (ANG-2) was incubated for 60 min to allow equilibration and then washed with 2K EBSS. Plates were then transferred to a fluorescence plate reader (FLIPR™, Molecular Devices) for fluorescence measurement using an excitation wavelength of 490 nm and an emission wavelength of 565 nm. Compounds were pre-incubated for 5 min at final test concentration in the presence of ouabain (30 μ M) to inhibit Na⁺ efflux through Na⁺/K⁺ exchanger. Following the pre-incubation phase, hNav1.8 channels were stimulated with 10 μ M of the pyrethroid deltamethrin to prevent channel inactivation. The assay was run for 15 minutes with vehicle and 30 μ M tetracaine serving as negative and positive controls, respectively. The peak change in fluorescence relative to negative and positive control wells was calculated and fit with a logistic equation to determine IC₅₀.

30

PatchXpress Nav1.8 Inhibition Assay

HEK-Nav1.8 $\beta 1/\beta 2$ cells were recorded in whole cell patch-clamp using the PatchXpress automated patch clamp platforms (Molecular Devices). Cell suspensions were obtained by trypsinization of adherent monolayers, followed by gentle rocking
 5 for minimally 30 min. Compounds were prepared from 10 mM DMSO stocks.

PROTOCOL 1



Nav1.8 channel variants were evaluated using **Protocol 1** in which cells were initially voltage clamped at a holding potential of -100 mV to maintain Nav1.8 in a closed resting state. After current amplitude becomes stable, the mid-point voltage of steady state inactivation was determined for each cell using a series of 5 sec
 10 conditioning steps to increasingly depolarized voltages (-100 to 0 mV). The holding potential was then reset to a voltage that produces ~50% inactivation (V_{half} - set automatically via PatchXpress scripts) so that closed and inactivated channel inhibition could be assessed. Protocol 1 was run at a frequency of 0.1 Hz until current amplitude is steady (automatically determined by PatchXpress scripts). The effect of
 15 test reagent on Nav current amplitude was monitored using custom PatchXpress stability scripts which determines the timing of compound addition and washout.

Data were processed and analyzed using DataXpress 2.0 (Molecular Devices). Percent inhibition was calculated using Microsoft Excel such that compound block was normalized to the average of control and washout currents according to the
 20 formula, % Inhibition = $\frac{(((\text{Ctrl} + \text{Wash})/2) - \text{Drug})}{((\text{Ctrl} + \text{Wash})/2)} \times 100$ (see schematic diagram hereinabove). Normalized concentration-response relationships were fit using XLfit software (IDBS) 4 Parameter Logistic Model or Sigmoidal Dose-Response Model.

hNav1.8 Automated Patch Clamp-IonFlux^{HT} Assay

25 The IonFlux HT automated whole-cell patch-clamp instrument (Fluxion Biosciences, Inc., Alameda, CA USA) was used to record the inward sodium currents.

Cells HEK-293 cells were stably transfected with human Nav1.8 cDNA (type X voltage-gated sodium channel alpha subunit, accession# NM_006514) and the human beta subunit 1 (accession# NM_001037). The cells were harvested with trypsin and maintained in serum free medium at room temperature before recording.

- 5 The cells were washed and re-suspended in the Extracellular Solution before being applied to the instrument.

Test concentrations: Stock solution was prepared in DMSO at 300X the final assay concentrations, and stored at -80°C until the day of assay. On the day of the assay, an aliquot of the stock solution was thawed and diluted into external solution to
10 make final test concentrations. A final concentration of 0.33% DMSO was maintained for each concentration of the assay compounds and controls.

Recording conditions: Intracellular Solution (mM): 100 CsF, 45 CsCl, 5 NaCl, 10 HEPES, 5 EGTA (pH 7.3, titrated with 1M CsOH).

Extracellular Solution (mM): 150 NaCl, 4 BaCl, 1 MgCl₂, 1.8 CaCl₂, 10
15 HEPES, 5 Glucose, (pH 7.4, titrated with 10M NaOH).

When sodium channels are held at a depolarized membrane potential, the channels open and inactivate and remain inactivated until the membrane potential is stepped back to a hyperpolarized membrane potential, when the inactivated channels recover into the closed state. Compounds that show more inhibition at pulse 2
20 compared to pulse 1 are state-dependent inhibitors. An example is Tetracaine, which is a much more potent inhibitor in the inactivated state than in the tonic or open state.

Cells were held at -120mV for 50ms before stepping to -10mV for 2s to completely inactivate the sodium channels (pulse 1), and stepped back to -120mV for 10ms (to completely recover from inactivation, however, channels that have inhibitors
25 bound to them may not recover from inactivation) before stepping to -10mV for 50ms (pulse 2). The sweep interval is 20s (0.05Hz). Each concentration of compound was applied for two minutes. The assay was performed at room temperature.

Reference compounds: Tetracaine was used as the positive control and was tested concurrently with the test compound.

30 *Data analysis:* Only current amplitudes in excess of 3nA at the control stage were analyzed. The amplitude of the sodium current was calculated by measuring the difference between the peak inward current on stepping to -10mV (i.e., peak of the current) and remaining current at the end of the step. The sodium current was assessed in vehicle control conditions and then at the end of each two (2) minute compound

application. Individual cell trap results were normalized to the vehicle control amplitude and the mean $\pm$ SEM calculated for each compound concentration. These values were then plotted and estimated IC₅₀ curve fits calculated.

Estimated IC₅₀ values for pyridine carboxamide compounds exemplified

5 above are listed in Table 1.

Table 1.					
Example	Activity range	Example	Activity range	Example	Activity range
1	+++	23	+++	45	+++
2	+	24	+++	46	+++
3	++	25	+++	47	+++
4	+++	26	+	48	+
5	+++	27	+++	49	+
6	+++	28	+++	50	+
7	+++	29	+++	51	
8	+++	30	+++	52	+
9	+++	31	+++	53	++
10	+++	32	+	54	
11	+++	33	+++	55	+++
12	+++	34	+++	56	+++
13	+++	35	++	57	+++
14	+++	36	+++	58	+++
15	+++	37	+++	59	+++
16	+++	38	+++	60	+++
17	+	39	++		
18	+++	40	+++		
19	+++	41	+++		
20	+++	42	+++		
21	+++	43	++		
22	+++	44	+++		

+ IC₅₀ > 1 μM
 ++ IC₅₀ 500 nM – 1 μM
 +++ IC₅₀ < 500 nM

REFERENCES

All publications, patent applications, patents, and other references mentioned in the specification are indicative of the level of those skilled in the art to which the presently disclosed subject matter pertains. All publications, patent applications, patents, and other references are herein incorporated by reference to the same extent as if each individual publication, patent application, patent, and other reference was specifically and individually indicated to be incorporated by reference. It will be understood that, although a number of patent applications, patents, and other references are referred to herein, such reference does not constitute an admission that any of these documents forms part of the common general knowledge in the art.

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Although the foregoing subject matter has been described in some detail by way of illustration and example for purposes of clarity of understanding, it will be understood by those skilled in the art that certain changes and modifications can be practiced within the scope of the appended claims.