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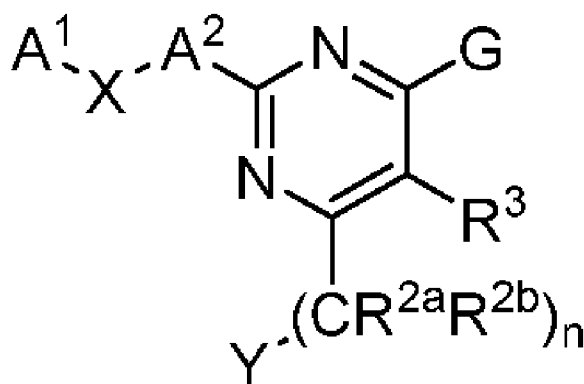
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(54) Title: PYRIMIDINES AND USE THEREOF

**I**

(57) Abstract: The present disclosure provides pyrimidines of Formula I: and pharmaceutically acceptable salts and solvates thereof, wherein A¹, X, A², G, Y, n, R^{2a}, R^{2b}, and R³ are defined as set forth in the specification. The present disclosure is also directed to the use of compounds of Formula I and the pharmaceutically acceptable salts and solvates thereof to treat a disorder responsive to the blockade of one or more sodium channels. In one embodiment, compounds of the present disclosure are useful for treating pain.

PYRIMIDINES AND USE THEREOF

BACKGROUND OF THE INVENTION

Field of the Invention

This invention is in the field of medicinal chemistry. The invention provides novel pyrimidines and the use of these compounds thereof. In certain embodiments, the compounds are useful as blockers of one or more voltage-gated sodium (Na^+) channels.

5

Background Art

Voltage-gated sodium channels (VGSCs) are found in all excitable cells. In neuronal cells of the central nervous system (CNS) and peripheral nervous system (PNS) sodium channels are primarily responsible for generating the rapid upstroke of the action potential.

10 In this manner sodium channels are essential to the initiation and propagation of electrical signals in the nervous system. Proper function of sodium channels is therefore necessary for normal function of the neuron. Consequently, aberrant sodium channel function is thought to underlie a variety of medical disorders (See Hubner *et al.*, *Hum. Mol. Genet.* 11:2435-2445 (2002) for a general review of inherited ion channel disorders) including epilepsy
15 (Yogeeswari *et al.*, *Curr. Drug Target* 5:589-602 (2004)), arrhythmia (Noble, *Proc. Natl. Acad. Sci. USA* 99:5755-5756 (2002)), myotonia (Cannon, *Kidney Int.* 57:772-779 (2000)), and pain (Wood *et al.*, *J. Neurobiol.*, 61:55-71 (2004)).

VGSCs are composed of one α -subunit, which forms the core of the channel and is responsible for voltage-dependent gating and ion permeation, and several auxiliary β -
20 subunits (see, *e.g.*, Chahine *et al.*, *CNS & Neurological Disorders-Drug Targets* 7:144-158 (2008) and Kyle and Ilyin, *J. Med. Chem.* 50:2583-2588 (2007)). α -Subunits are large proteins composed of four homologous domains. Each domain contains six α -helical transmembrane spanning segments. There are currently nine known members of the family of voltage-gated sodium channel α -subunits. Names for this family include SCN x , SCNA x ,
25 and Na v . x (see TABLE 1, below). The VGSC family has been phylogenetically divided into two subfamilies Na v 1. x (all but SCN6A) and Na v 2. x (SCN6A). The Na v 1. x subfamily can be functionally subdivided into two groups, those which are sensitive to blocking by tetrodotoxin (TTX-sensitive or TTX-s) and those which are resistant to blocking by tetrodotoxin (TTX-resistant or TTX-r).

There are three members of the subgroup of TTX-resistant sodium channels. The SCN5A gene product (Na_v1.5, H1) is almost exclusively expressed in cardiac tissue and has been shown to underlie a variety of cardiac arrhythmias and other conduction disorders (Liu *et al.*, *Am. J. Pharmacogenomics* 3:173-179 (2003)). Consequently, blockers of Na_v1.5 have found clinical utility in treatment of such disorders (Srivatsa *et al.*, *Curr. Cardiol. Rep.* 4:401-410 (2002)). The remaining TTX-resistant sodium channels, Na_v1.8 (SCN10A, PN3, SNS) and Na_v1.9 (SCN11A, NaN, SNS2) are expressed in the peripheral nervous system and show preferential expression in primary nociceptive neurons. Human genetic variants of these channels have not been associated with any inherited clinical disorder. However, aberrant expression of Na_v1.8 has been found in the CNS of human multiple sclerosis (MS) patients and also in a rodent model of MS (Black *et al.*, *Proc. Natl. Acad. Sci. USA* 97:11598-115602 (2000)). Evidence for involvement in nociception is both associative (preferential expression in nociceptive neurons) and direct (genetic knockout). Na_v1.8-null mice exhibited typical nociceptive behavior in response to acute noxious stimulation but had significant deficits in referred pain and hyperalgesia (Laird *et al.*, *J. Neurosci.* 22:8352-8356 (2002)).

TABLE 1
Voltage-gated sodium channel gene family

Type	Gene Symbol	Tissue Distribution	TTX IC ₅₀ (nM)	Disease Association	Indications
Na _v 1.1	SCN1A	CNS/PNS	10	Epilepsy	Pain, seizures, neurodegeneration
Na _v 1.2	SCN2A	CNS	10	Epilepsy	Epilepsy, neurodegeneration
Na _v 1.3	SCN3A	CNS	15	-	Pain
Na _v 1.4	SCN4A	Skeletal muscle	25	Myotonia	Myotonia
Na _v 1.5	SCN5A	Heart muscle	2,000	Arrhythmia	Arrhythmia
Na _v 1.6	SCN8A	CNS/PNS	6	-	Pain, movement disorders
Na _v 1.7	SCN9A	PNS	25	Erythralgia	Pain
Na _v 1.8	SCN10A	PNS	50,000	-	Pain
Na _v 1.9	SCN11A	PNS	1,000	-	Pain

The Na_v1.7 (PNI, SCN9A) VGSC is sensitive to blocking by tetrodotoxin and is preferentially expressed in peripheral sympathetic and sensory neurons. The SCN9A gene has been cloned from a number of species, including human, rat, and rabbit and shows ~90 % amino acid identity between the human and rat genes (Toledo-Aral *et al.*, *Proc. Natl. Acad. Sci. USA* 94:1527-1532 (1997)).

An increasing body of evidence suggests that Na_v1.7 plays a key role in various pain states, including acute, inflammatory and/or neuropathic pain. Deletion of the SCN9A gene in nociceptive neurons of mice led to an increase in mechanical and thermal pain thresholds and reduction or abolition of inflammatory pain responses (Nassar *et al.*, *Proc. Natl. Acad. Sci. USA* 101:12706-12711 (2004)).

Sodium channel-blocking agents have been reported to be effective in the treatment of various disease states, and have found particular use as local anesthetics, *e.g.*, lidocaine and bupivacaine, and in the treatment of cardiac arrhythmias, *e.g.*, propafenone and amiodarone, and epilepsy, *e.g.*, lamotrigine, phenytoin and carbamazepine (see Clare *et al.*, *Drug Discovery Today* 5:506-510 (2000); Lai *et al.*, *Annu. Rev. Pharmacol. Toxicol.* 44:371-397 (2004); Anger *et al.*, *J. Med. Chem.* 44:115-137 (2001), and Catterall, *Trends Pharmacol. Sci.* 8:57-65 (1987)). Each of these agents is believed to act by interfering with the rapid influx of sodium ions.

Other sodium channel blockers such as BW619C89 and lifarizine have been shown to be neuroprotective in animal models of global and focal ischemia (Graham *et al.*, *J. Pharmacol. Exp. Ther.* 269:854-859 (1994); Brown *et al.*, *British J. Pharmacol.* 115:1425-1432 (1995)).

It has also been reported that sodium channel-blocking agents can be useful in the treatment of pain, including acute, chronic, inflammatory, neuropathic, and other types of pain such as rectal, ocular, and submandibular pain typically associated with paroxysmal extreme pain disorder; see, for example, Kyle and Ilyin, *J. Med. Chem.* 50:2583-2588 (2007); Wood *et al.*, *J. Neurobiol.* 61:55-71 (2004); Baker *et al.*, *TRENDS in Pharmacological Sciences* 22:27-31 (2001); and Lai *et al.*, *Current Opinion in Neurobiology* 13:291-297 (2003); the treatment of neurological disorders such as epilepsy, seizures, epilepsy with febrile seizures, epilepsy with benign familial neonatal infantile seizures, inherited pain disorders, *e.g.*, primary erthermalgia and paroxysmal extreme pain disorder,

familial hemiplegic migraine, and movement disorder; and the treatment of other psychiatric disorders such as autism, cerebellar atrophy, ataxia, and mental retardation; see, for example, Chahine *et al.*, *CNS & Neurological Disorders-Drug Targets* 7:144-158 (2008) and Meisler and Kearney, *J. Clin. Invest.* 115:2010-2017 (2005). In addition to the above-mentioned
5 clinical uses, carbamazepine, lidocaine and phenytoin are used to treat neuropathic pain, such as from trigeminal neuralgia, diabetic neuropathy and other forms of nerve damage (Taylor and Meldrum, *Trends Pharmacol. Sci.* 16:309-316 (1995)). Furthermore, based on a number of similarities between chronic pain and tinnitus, (Moller, *Am. J. Otol.* 18:577-585 (1997); Tonndorf, *Hear. Res.* 28:271-275 (1987)) it has been proposed that tinnitus should be viewed
10 as a form of chronic pain sensation (Simpson, *et al.*, *Tip.* 20:12-18 (1999)). Indeed, lidocaine and carbamazepine have been shown to be efficacious in treating tinnitus (Majumdar, B. *et al.*, *Clin. Otolaryngol.* 8:175-180 (1983); Donaldson, *Laryngol. Otol.* 95:947-951 (1981)).

Many patients with either acute or chronic pain disorders respond poorly to current pain therapies, and the development of resistance or insensitivity to opiates is common. In
15 addition, many of the currently available treatments have undesirable side effects.

In view of the limited efficacy and/or unacceptable side-effects of the currently available agents, there is a pressing need for more effective and safer analgesics that work by blocking sodium channels.

BRIEF SUMMARY OF THE INVENTION

In one aspect, the present disclosure provides pyrimidines represented by Formulae I-VI, below, and the pharmaceutically acceptable salts and solvates thereof, collectively referred to herein as "Compounds of the Disclosure."

In another aspect, the present disclosure provides the use of Compounds of the
25 Disclosure as blockers of one or more sodium (Na^+) channels.

In another aspect, the present disclosure provides compounds as synthetic intermediates that can be used to prepare blockers of one or more sodium (Na^+) channels.

In another aspect, the present disclosure provides a method for treating a disorder responsive to the blockade of one or more sodium channels in a mammal, comprising
30 administering to the mammal an effective amount of a Compound of the Disclosure.

In another aspect, the present disclosure provides a method for treating pain (*e.g.*, acute pain, chronic pain, which includes but is not limited to, neuropathic pain, postoperative

pain, and inflammatory pain, or surgical pain), comprising administering an effective amount of a Compound of the Disclosure to a mammal in need of such treatment. Specifically, the present disclosure provides a method for preemptive or palliative treatment of pain by administering an effective amount of a Compound of the Disclosure to a mammal in need of such treatment.

In another aspect, the present disclosure provides a method for treating stroke, neuronal damage resulting from head trauma, epilepsy, seizures, general epilepsy with febrile seizures, severe myoclonic epilepsy in infancy, neuronal loss following global and focal ischemia, migraine, familial primary erythromelalgia, paroxysmal extreme pain disorder, cerebellar atrophy, ataxia, dystonia, tremor, mental retardation, autism, a neurodegenerative disorder (*e.g.*, Alzheimer's disease, amyotrophic lateral sclerosis (ALS), or Parkinson's disease), manic depression, tinnitus, myotonia, a movement disorder, or cardiac arrhythmia, or providing local anesthesia, comprising administering an effective amount of a Compound of the Disclosure to a mammal in need of such treatment.

In another aspect, the present disclosure provides a pharmaceutical composition comprising a Compound of the Disclosure and one or more pharmaceutically acceptable carriers.

In another aspect, the present disclosure provides a pharmaceutical composition for treating a disorder responsive to the blockade of sodium ion channels, wherein the pharmaceutical composition comprises an effective amount of a Compound of the Disclosure in a mixture with one or more pharmaceutically acceptable carriers.

In another aspect, the present disclosure provides a method of modulating sodium channels in a mammal, comprising administering to the mammal an effective amount of at least one Compound of the Disclosure.

In another aspect, the present disclosure provides Compounds of the Disclosure for use in treating pain in a mammal, *e.g.*, acute pain, chronic pain, which includes but is not limited to, neuropathic pain, postoperative pain, and inflammatory pain, or surgical pain.

In another aspect, the present disclosure provides Compounds of the Disclosure for use in treating stroke, neuronal damage resulting from head trauma, epilepsy, seizures, general epilepsy with febrile seizures, severe myoclonic epilepsy in infancy, neuronal loss following global and focal ischemia, migraine, familial primary erythromelalgia, paroxysmal extreme pain disorder, cerebellar atrophy, ataxia, dystonia, tremor, mental retardation,

autism, a neurodegenerative disorder (*e.g.*, Alzheimer's disease, amyotrophic lateral sclerosis (ALS), or Parkinson's disease), manic depression, tinnitus, myotonia, a movement disorder, or cardiac arrhythmia, or providing local anesthesia, in a mammal.

In another aspect, the present disclosure provides a radiolabeled Compound of the
5 Disclosure and the use of such compounds as radioligands in any appropriately selected competitive binding assays and screening methodologies. Thus, the present disclosure further provides a method for screening a candidate compound for its ability to bind to a sodium channel or sodium channel subunit using a radiolabeled Compound of the Disclosure. In certain embodiments, the compound is radiolabeled with ^3H , ^{11}C , or ^{14}C . This competitive
10 binding assay can be conducted using any appropriately selected methodology. In one embodiment, the screening method comprises: i) introducing a fixed concentration of the radiolabeled compound to an in vitro preparation comprising a soluble or membrane-associated sodium channel, subunit or fragment under conditions that permit the radiolabeled compound to bind to the channel, subunit or fragment, respectively, to form a conjugate; ii)
15 titrating the conjugate with a candidate compound; and iii) determining the ability of the candidate compound to displace the radiolabeled compound from said channel, subunit or fragment.

In another aspect, the present disclosure provides a Compound of the Disclosure for use in the manufacture of a medicament for treating pain in a mammal. In one embodiment,
20 the present disclosure provides the use of a Compound of the Disclosure in the manufacture of a medicament for palliative or preemptive treatment of pain, such as acute pain, chronic pain, or surgical pain.

In another aspect, the present disclosure provides a Compound of the Disclosure for use in the manufacture of a medicament for treating stroke, neuronal damage resulting from
25 head trauma, epilepsy, seizures, general epilepsy with febrile seizures, severe myoclonic epilepsy in infancy, neuronal loss following global and focal ischemia, migraine, familial primary erythromelalgia, paroxysmal extreme pain disorder, cerebellar atrophy, ataxia, dystonia, tremor, mental retardation, autism, a neurodegenerative disorder (*e.g.*, Alzheimer's disease, amyotrophic lateral sclerosis (ALS), or Parkinson's disease), manic depression,
30 tinnitus, myotonia, a movement disorder, or cardiac arrhythmia, or providing local anesthesia, in a mammal.

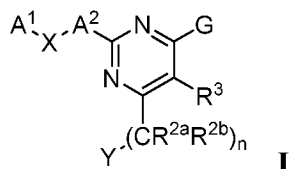
Additional embodiments and advantages of the disclosure will be set forth, in part, in the description that follows, and will flow from the description, or can be learned by practice of the disclosure. The embodiments and advantages of the disclosure will be realized and attained by means of the elements and combinations particularly pointed out in the appended
 5 claims.

It is to be understood that both the foregoing summary and the following detailed description are exemplary and explanatory only, and are not restrictive of the invention as claimed.

DETAILED DESCRIPTION OF THE INVENTION

One aspect of the present disclosure is based on the use of Compounds of the Disclosure as blockers of sodium (Na^+) channels. In view of this property, the Compounds of the Disclosure are useful for treating disorders responsive to the blockade of sodium ion channels.

In one embodiment, Compounds of the Disclosure are compounds represented by
 15 Formula I:



and the pharmaceutically acceptable salts and solvates thereof,
 wherein:

A^1 is selected from the group consisting of optionally substituted phenyl, optionally substituted 5- or 6-membered heteroaryl, optionally substituted cycloalkyl, optionally substituted heterocyclo, and aralkyl;

X is selected from the group consisting of $-\text{O}-$, $-\text{S}-$, $-\text{SO}_2-$, $-\text{CH}_2-$, $-\text{CH}(\text{OH})-$, $-\text{C}(=\text{O})-$, $-\text{C}(=\text{O})\text{N}(\text{H})-$, and $-\text{SO}_2(\text{H})\text{N}-$;

A^2 is selected from the group consisting of optionally substituted aryl, optionally substituted heteroaryl, optionally substituted heterocyclo, and optionally substituted cycloalkyl;

G is selected from the group consisting of dihydroxyalkyl, $-\text{CH}(\text{OH})\text{CH}(\text{OH})\text{C}(=\text{O})\text{E}$, and $-\text{C}(=\text{O})\text{E}$;

E is selected from the group consisting of hydroxy, alkoxy, hydroxyalkyl, and -NR^{1a}R^{1b};

R^{1a} is selected from the group consisting of hydrogen, alkyl, aralkyl, (heterocyclo)alkyl, (heteroaryl)alkyl, (amino)alkyl, (alkylamino)alkyl, (dialkylamino)alkyl, (carboxamido)alkyl, (cyano)alkyl, alkoxyalkyl, hydroxyalkyl, and heteroalkyl;

R^{1b} is selected from the group consisting of hydrogen and alkyl; or

R^{1a} and R^{1b} taken together with the nitrogen atom to which they are attached form a 3- to 8-membered optionally substituted heterocyclo;

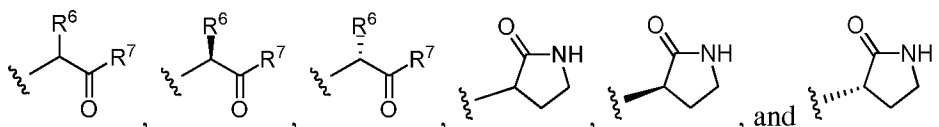
R^{2a} and R^{2b} are independently selected from the group consisting of hydrogen and alkyl;

n is 1, 2, or 3;

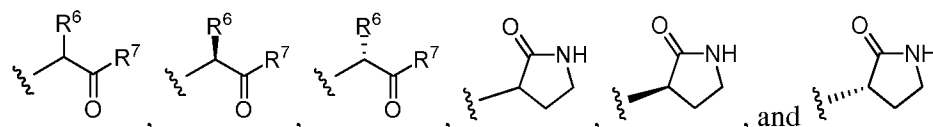
Y is selected from the group consisting of -OR^{4a} and -NR^{4b}R⁵;

R³ selected from the group consisting of hydrogen, alkyl, halo, nitro, cyano, hydroxy, amino, alkylamino, dialkylamino, haloalkyl, hydroxyalkyl, alkoxy, haloalkoxy, and alkoxyalkyl;

R^{4a} is selected from the group consisting of hydrogen, alkyl, (heterocyclo)alkyl, (heteroaryl)alkyl, (amino)alkyl, (alkylamino)alkyl, (dialkylamino)alkyl, (carboxamido)alkyl, (cyano)alkyl, alkoxyalkyl, hydroxyalkyl, heteroalkyl,



R^{4b} is selected from the group consisting of hydrogen, alkyl, (heterocyclo)alkyl, (heteroaryl)alkyl, (amino)alkyl, (alkylamino)alkyl, (dialkylamino)alkyl, (carboxamido)alkyl, (cyano)alkyl, alkoxyalkyl, hydroxyalkyl, heteroalkyl:



R⁶ is selected from the group consisting of hydrogen, alkyl, and hydroxyalkyl;

R⁷ is selected from the group consisting of hydroxy, alkoxy, and -NR^{8a}R^{8b};

R^{8a} is selected from the group consisting of hydrogen, alkyl, aralkyl, (heterocyclo)alkyl, (heteroaryl)alkyl, (amino)alkyl, (alkylamino)alkyl, (dialkylamino)alkyl, (carboxamido)alkyl, (cyano)alkyl, alkoxyalkyl, hydroxyalkyl, and heteroalkyl;

R^{8b} is selected from the group consisting of hydrogen and alkyl; or

R^{8a} and R^{8b} taken together with the nitrogen atom to which they are attached form a 3- to 8-membered optionally substituted heterocycle; and

R^5 is selected from the group consisting of hydrogen and alkyl; or

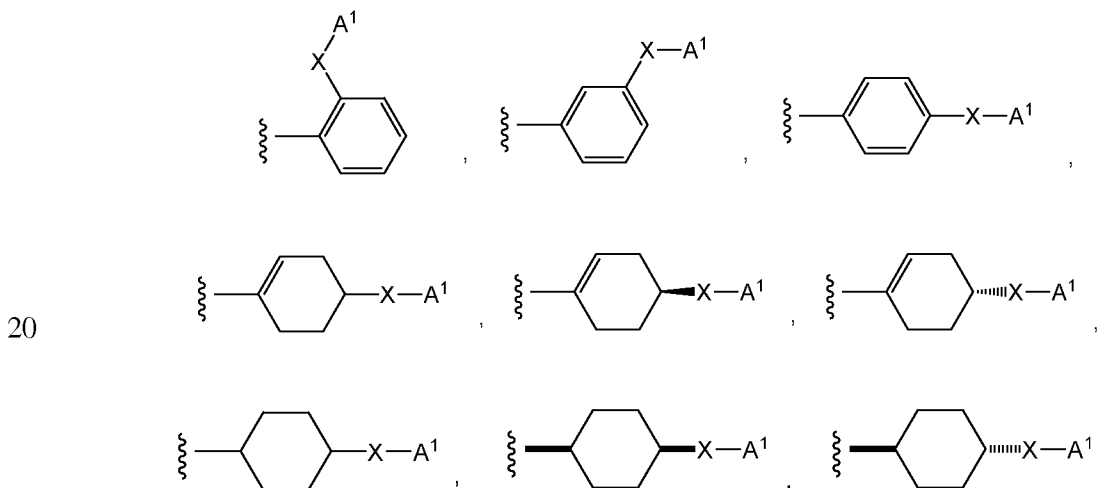
5 R^{4b} and R^5 taken together with the nitrogen atom to which they are attached form a 3- to 8-membered optionally substituted heterocycle.

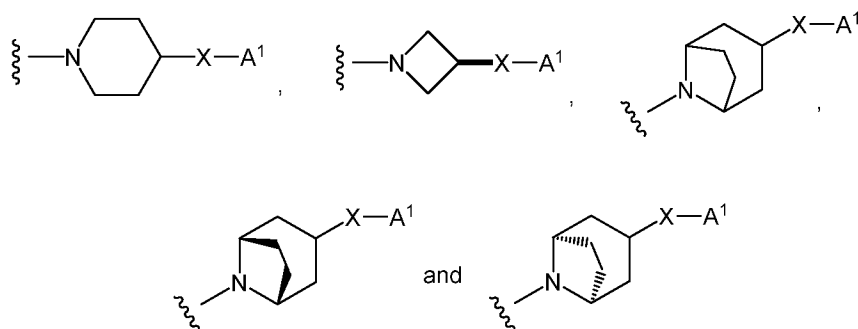
It is well appreciated by one skilled in the art that when X is $-C(=O)N(H)-$, either the carbon or the nitrogen atom can be directly attached to A^1 . Likewise, when X is $-SO_2(H)N-$,
 10 either the sulfur or the nitrogen atom can be directly attached to A^1 .

In another embodiment, Compounds of the Disclosure are compounds having Formula I, wherein A^2 is selected from the group consisting of phenyl, cyclohexyl, cyclohexenyl, azetidiny, pyrrolidinyl, and piperidinyl, and the pharmaceutically acceptable salts and solvates thereof.

15 In another embodiment, Compounds of the Disclosure are compounds having Formula I, wherein A^2 is selected from the group consisting of phenyl, cyclohexyl, and cyclohexenyl, and the pharmaceutically acceptable salts and solvates thereof.

In another embodiment, Compounds of the Disclosure are compounds having Formula I, wherein $-A^2-X-A^1$ is selected from the group consisting of:

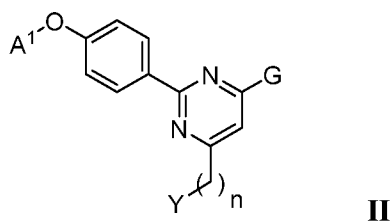




and the pharmaceutically acceptable salts and solvates thereof.

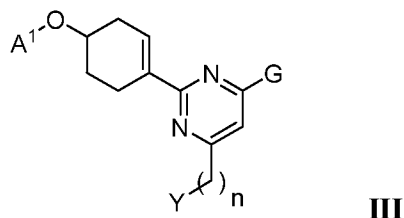
In another embodiment, Compounds of the Disclosure are compounds having
 5 Formula **I**, wherein X is -O-, and the pharmaceutically acceptable salts and solvates thereof.

In another embodiment, Compounds of the Disclosure are compounds having
 Formula **II**:



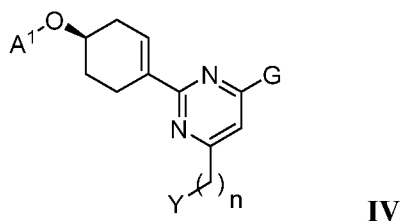
wherein A¹, n, G, and Y are as defined above in connection with Formula **I**, and the
 10 pharmaceutically acceptable salts and solvates thereof.

In another embodiment, Compounds of the Disclosure are compounds having
 Formula **III**:



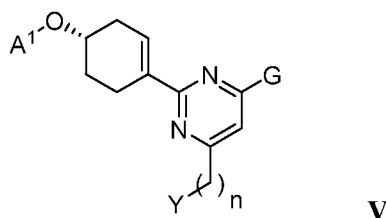
wherein A¹, n, G, and Y are as defined above in connection with Formula **I**, and the
 15 pharmaceutically acceptable salts and solvates thereof.

In another embodiment, Compounds of the Disclosure are compounds having
 Formula **IV**:



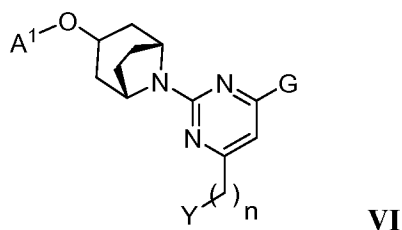
wherein A¹, n, G, and Y are as defined above in connection with Formula **I**, and the pharmaceutically acceptable salts and solvates thereof.

In another embodiment, Compounds of the Disclosure are compounds having
5 Formula **V**:



wherein A¹, n, G, and Y are as defined above in connection with Formula **I**, and the pharmaceutically acceptable salts and solvates thereof.

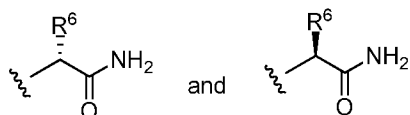
In another embodiment, Compounds of the Disclosure are compounds having
10 Formula **VI**:



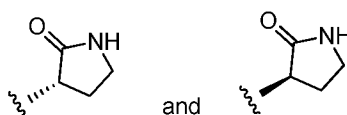
wherein A¹, n, G, and Y are as defined above in connection with Formula **I**, and the pharmaceutically acceptable salts and solvates thereof.

In another embodiment, Compounds of the Disclosure are compounds having any one
15 of Formulae **I-VI**, wherein n is 1, and the pharmaceutically acceptable salts and solvates thereof.

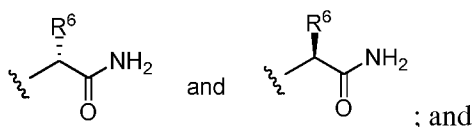
In another embodiment, Compounds of the Disclosure are compounds having any one of Formulae **I-VI**, wherein Y is -OR^{4a}, and the pharmaceutically acceptable salts and solvates thereof. In one embodiment, R^{4a} is selected from the group consisting of:



In another embodiment, R^6 is selected from the group consisting of methyl, isopropyl, and hydroxymethyl, and the pharmaceutically acceptable salts and solvates thereof. In another embodiment R^{4a} is:

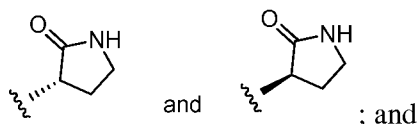


In another embodiment, Compounds of the Disclosure are compounds having any one of Formulae **I-VI**, wherein Y is $-NR^{4b}R^5$, and the pharmaceutically acceptable salts and solvates thereof. In one embodiment, R^{4b} is selected from the group consisting of:



10 R^5 is hydrogen. In another embodiment, R^6 is selected from the group consisting of methyl, isopropyl, hydroxyethyl, and hydroxymethyl. In one embodiment, R^6 is methyl. In another embodiment, R^6 is isopropyl. In another embodiment, R^6 is hydroxymethyl. In still another embodiment, R^6 is hydroxyethyl, such as (1-hydroxy)ethyl. In certain embodiments, R^5 is hydrogen. In another embodiment, R^5 is (C_1-C_3) alkyl.

15 In another embodiment of Formulae **I-VI**, Y is $-NR^{4b}R^5$, and R^{4b} is selected from the group consisting of:

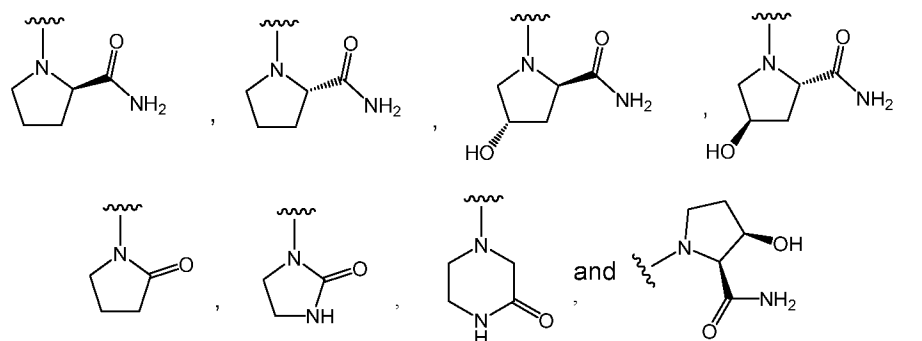


R^5 is hydrogen. In still another embodiment, R^{4b} and R^5 taken together with the nitrogen atom to which they are attached form a 3- to 8-membered optionally substituted heterocycle.

20 In another embodiment, R^{4b} and R^5 taken together with the nitrogen atom to which they are attached form a 5- or 6-membered optionally substituted heterocycle. In another embodiment, R^{4b} and R^5 taken together with the nitrogen atom to which they are attached form a 5- or 6-membered heterocycle that is optionally substituted by one to three substituents selected from the group consisting of halo, hydroxy, alkoxy, and carboxamido.

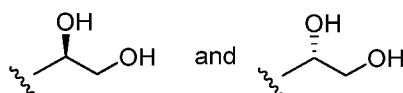
25 In another embodiment, R^{4b} and R^5 taken together with the nitrogen atom to which they are

attached form a 5- or 6-membered optionally substituted heterocycle selected from the group consisting of:

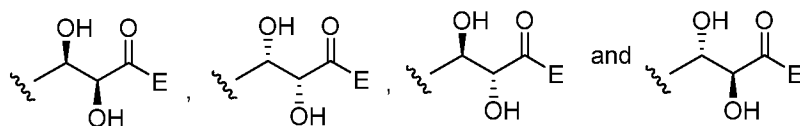


In another embodiment, Compounds of the Disclosure are compounds having any one of Formulae **I-VI**, wherein Y is -OH, and the pharmaceutically acceptable salts and solvates thereof.

In another embodiment, Compounds of the Disclosure are compounds having any one of Formulae **I-VI**, wherein G is dihydroxyalkyl, and the pharmaceutically acceptable salts and solvates thereof. In one embodiment, G is dihydroxyalkyl selected from the group consisting of:



In another embodiment, Compounds of the Disclosure are compounds having any one of Formulae **I-VI**, wherein G is -CH(OH)CH(OH)C(=O)E, and the pharmaceutically acceptable salts and solvates thereof. In another embodiment, G is -CH(OH)CH(OH)C(=O)E selected from the group consisting of:



In another embodiment, E is -NR^{1a}R^{1b}. In one embodiment, R^{1a} and R^{1b} are hydrogen.

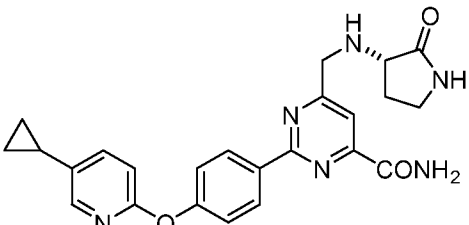
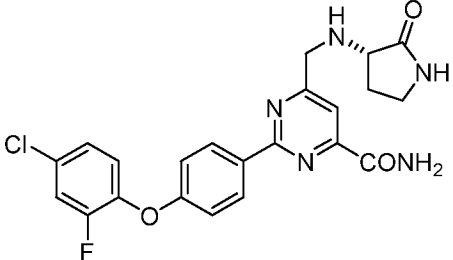
In another embodiment, Compounds of the Disclosure are compounds having any one of Formulae **I-VI** wherein G is -C(=O)E, and the pharmaceutically acceptable salts and solvates thereof. In another embodiment, E is -NR^{1a}R^{1b}. In one embodiment, R^{1a} and R^{1b} are hydrogen.

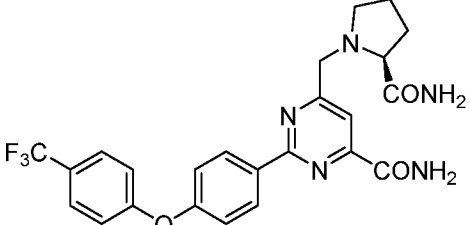
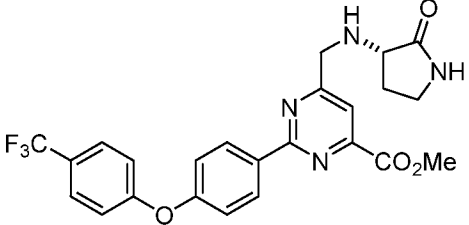
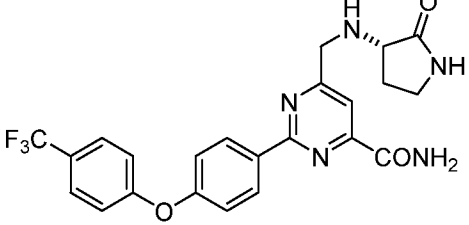
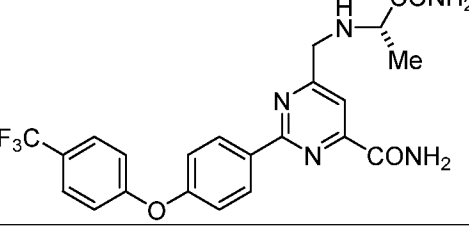
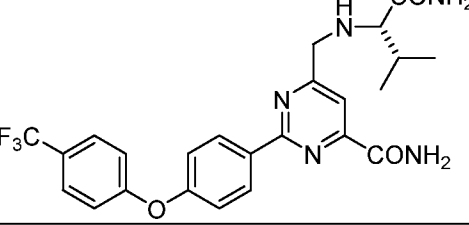
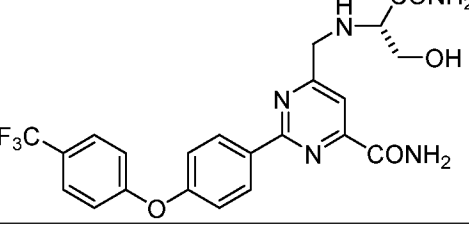
In another embodiment, Compounds of the Disclosure are compounds having any one of Formulae **I-V**, wherein A¹ is selected from the group consisting of optionally substituted

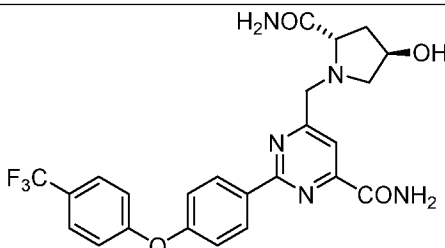
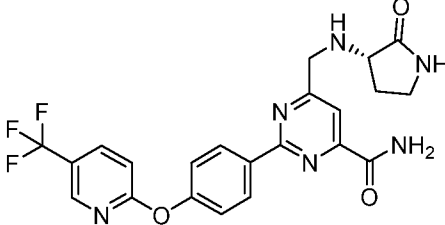
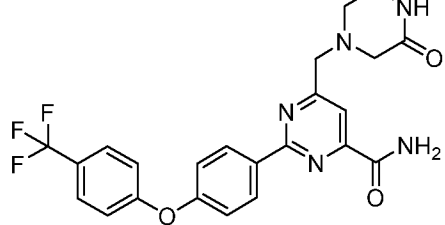
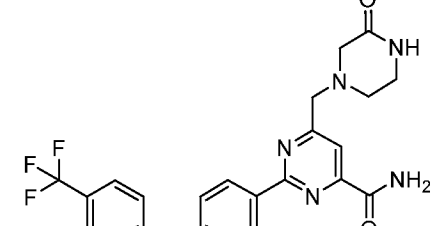
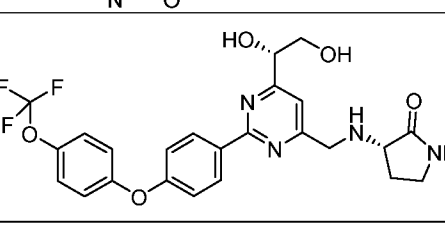
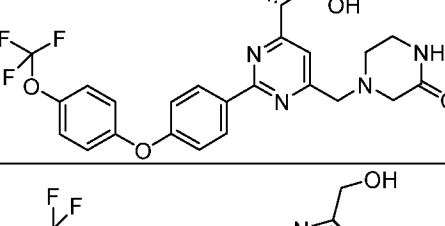
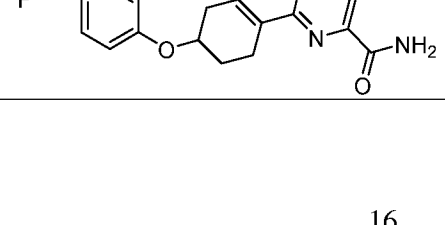
phenyl and optionally substituted 5- or 6-membered heteroaryl, and the pharmaceutically acceptable salts and solvates thereof. In another embodiment, A¹ is optionally substituted pyridyl. In another embodiment, A¹ is optionally substituted phenyl. In certain embodiments, the optional substituents are independently selected from the group consisting of halo, nitro, cyano, hydroxy, amino, alkylamino, dialkylamino, haloalkyl, hydroxyalkyl, alkoxy, haloalkoxy, aryloxy, heteroaryloxy, aralkyloxy, alkylthio, carboxamido, sulfonamido, alkylcarbonyl, arylcarbonyl, alkylsulfonyl, arylsulfonyl, ureido, guanidino, carboxy, carboxyalkyl, alkyl, cycloalkyl, alkenyl, alkynyl, aryl, heteroaryl, heterocyclo, alkoxyalkyl, (amino)alkyl, hydroxyalkylamino, (alkylamino)alkyl, (dialkylamino)alkyl, (cyano)alkyl, (carboxamido)alkyl, mercaptoalkyl, (heterocyclo)alkyl, (cycloalkylamino)alkyl, (halo(C₁-C₄)alkoxy)alkyl, and (heteroaryl)alkyl. In one embodiment, the optional substituents for pyridyl or phenyl are independently selected from the group consisting of halo, cyano, hydroxy, amino, alkylamino, dialkylamino, haloalkyl, hydroxyalkyl, alkoxy, haloalkoxy, alkyl, and cycloalkyl.

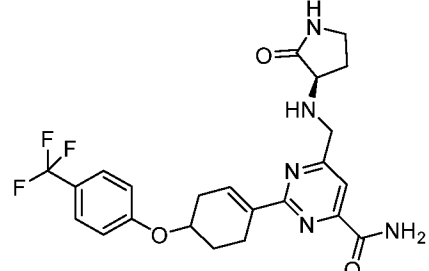
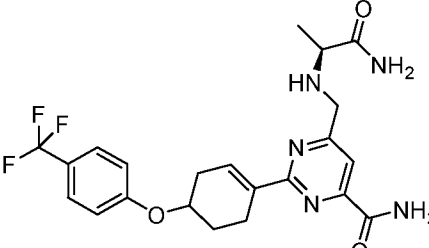
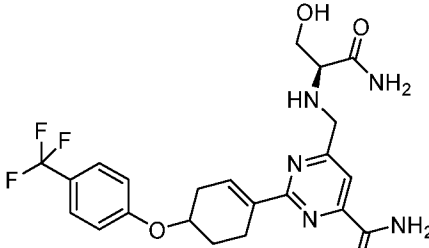
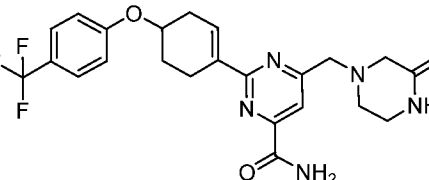
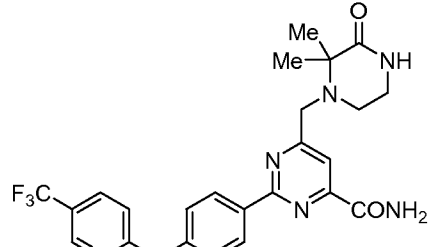
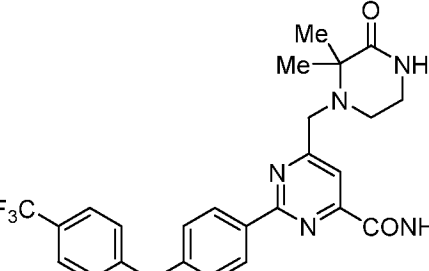
In another embodiment, Compounds of the Disclosure are compounds of TABLE 2, and the pharmaceutically acceptable salts and solvates thereof.

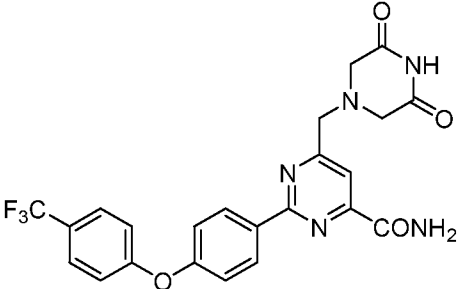
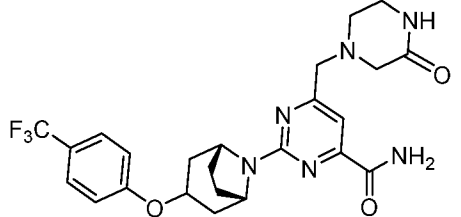
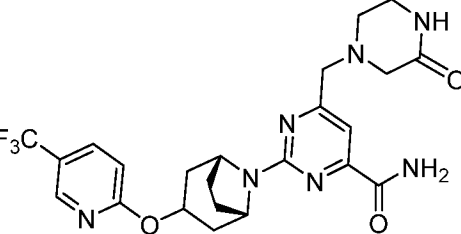
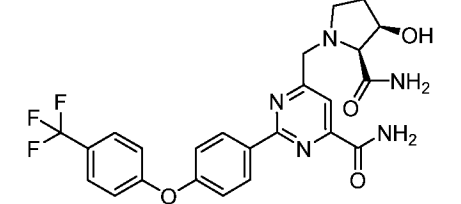
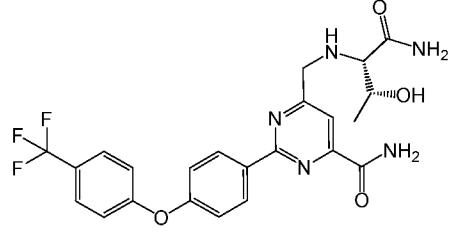
TABLE 2

Cpd #	Structure	Name
14		(S)-2-(4-((5-cyclopropylpyridin-2-yl)oxy)phenyl)-6-(((2-oxopyrrolidin-3-yl)amino)-methyl)pyrimidine-4-carboxamide
15		(S)-2-(4-(4-chloro-2-fluorophenoxy)phenyl)-6-(((2-oxopyrrolidin-3-yl)amino)-methyl)pyrimidine-4-carboxamide

16		(S)-6-((2-carbamoylpyrrolidin-1-yl)methyl)-2-(4-(4-(trifluoromethyl)phenoxy)phenyl)pyrimidine-4-carboxamide
19		methyl (S)-6-(((2-oxopyrrolidin-3-yl)amino)methyl)-2-(4-(4-(trifluoromethyl)phenoxy)phenyl)pyrimidine-4-carboxylate
20		(S)-6-(((2-oxopyrrolidin-3-yl)amino)methyl)-2-(4-(4-(trifluoromethyl)phenoxy)phenyl)pyrimidine-4-carboxamide
21		(S)-6-(((1-amino-1-oxopropan-2-yl)amino)methyl)-2-(4-(4-(trifluoromethyl)phenoxy)phenyl)pyrimidine-4-carboxamide
22		(S)-6-(((1-amino-3-methyl-1-oxobutan-2-yl)amino)methyl)-2-(4-(4-(trifluoromethyl)phenoxy)phenyl)pyrimidine-4-carboxamide
23		(S)-6-(((1-amino-3-hydroxy-1-oxopropan-2-yl)amino)methyl)-2-(4-(4-(trifluoromethyl)phenoxy)phenyl)pyrimidine-4-carboxamide

24		6-(((2S,4R)-2-carbamoyl-4-hydroxypyrrolidin-1-yl)methyl)-2-(4-(4-(trifluoromethyl)phenoxy)phenyl)pyrimidine-4-carboxamide
26		(S)-6-(((2-oxopyrrolidin-3-yl)amino)methyl)-2-(4-((5-(trifluoromethyl)pyridin-2-yl)oxy)phenyl)pyrimidine-4-carboxamide
27		6-((3-oxopiperazin-1-yl)methyl)-2-(4-(4-(trifluoromethyl)phenoxy)phenyl)pyrimidine-4-carboxamide
28		6-((3-oxopiperazin-1-yl)methyl)-2-(4-((5-(trifluoromethyl)pyridin-2-yl)oxy)phenyl)pyrimidine-4-carboxamide
40		(S)-3-(((6-((S)-1,2-dihydroxyethyl)-2-(4-(4-(trifluoromethoxy)phenoxy)phenyl)pyrimidin-4-yl)methyl)amino)pyrrolidin-2-one
41		(S)-4-(((6-(1,2-dihydroxyethyl)-2-(4-(4-(trifluoromethoxy)phenoxy)phenyl)pyrimidin-4-yl)methyl)piperazin-2-one
54		6-(hydroxymethyl)-2-(4-(4-(trifluoromethyl)phenoxy)cyclohex-1-en-1-yl)pyrimidine-4-carboxamide

56		6-((((R)-2-oxopyrrolidin-3-yl)amino)methyl)-2-(4-(4-(trifluoromethyl)phenoxy)cyclohex-1-en-1-yl)pyrimidine-4-carboxamide
57		6-((((S)-1-amino-1-oxopropan-2-yl)amino)methyl)-2-(4-(4-(trifluoromethyl)phenoxy)cyclohex-1-en-1-yl)pyrimidine-4-carboxamide
58		6-((((S)-1-amino-3-hydroxy-1-oxopropan-2-yl)amino)-methyl)-2-(4-(4-(trifluoromethyl)phenoxy)cyclohex-1-en-1-yl)pyrimidine-4-carboxamide
59		6-((3-oxopiperazin-1-yl)methyl)-2-(4-(4-(trifluoromethyl)phenoxy)cyclohex-1-en-1-yl)pyrimidine-4-carboxamide
60		6-((2,2-dimethyl-3-oxopiperazin-1-yl)methyl)-2-(4-((5-(trifluoromethyl)pyridin-2-yl)oxy)phenyl)pyrimidine-4-carboxamide
61		6-((2,2-dimethyl-3-oxopiperazin-1-yl)methyl)-2-(4-(4-(trifluoromethyl)phenoxy)phenyl)pyrimidine-4-carboxamide

62		6-((3,5-dioxopiperazin-1-yl)methyl)-2-(4-(4-(trifluoromethyl)phenoxy)phenyl)pyrimidine-4-carboxamide
63		6-((3-oxopiperazin-1-yl)methyl)-2-((1R,5S)-3-(4-(trifluoromethyl)phenoxy)-8-azabicyclo[3.2.1]octan-8-yl)pyrimidine-4-carboxamide
64		6-((3-oxopiperazin-1-yl)methyl)-2-((1R,5S)-3-((5-(trifluoromethyl)pyridin-2-yl)oxy)-8-azabicyclo[3.2.1]octan-8-yl)pyrimidine-4-carboxamide
65		6-(((2S,3R)-2-carbamoyl-3-hydroxypyrrolidin-1-yl)methyl)-2-(4-(4-(trifluoromethyl)phenoxy)phenyl)pyrimidine-4-carboxamide
66		6-((((2S,3R)-1-amino-3-hydroxy-1-oxobutan-2-yl)amino)methyl)-2-(4-(4-(trifluoromethyl)phenoxy)phenyl)pyrimidine-4-carboxamide

For the purpose of the present disclosure, the term "alkyl" as used by itself or as part of another group refers to a straight- or branched-chain aliphatic hydrocarbon containing one to twelve carbon atoms (*i.e.*, C₁₋₁₂ alkyl) or the number of carbon atoms designated (*i.e.*, a C₁ alkyl such as methyl, a C₂ alkyl such as ethyl, a C₃ alkyl such as propyl or isopropyl, etc.). In one embodiment, the alkyl group is chosen from a straight chain C₁₋₁₀ alkyl group. In another embodiment, the alkyl group is chosen from a branched chain C₃₋₁₀ alkyl group. In another embodiment, the alkyl group is chosen from a straight chain C₁₋₆ alkyl group. In another

embodiment, the alkyl group is chosen from a branched chain C₃₋₆ alkyl group. In another embodiment, the alkyl group is chosen from a straight chain C₁₋₄ alkyl group. In another embodiment, the alkyl group is chosen from a branched chain C₃₋₄ alkyl group. In another embodiment, the alkyl group is chosen from a straight or branched chain C₃₋₄ alkyl group.

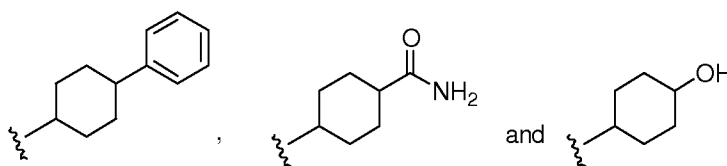
5 Non-limiting exemplary C₁₋₁₀ alkyl groups include methyl, ethyl, propyl, isopropyl, butyl, *sec*-butyl, *tert*-butyl, *iso*-butyl, 3-pentyl, hexyl, heptyl, octyl, nonyl, decyl, and the like. Non-limiting exemplary C₁₋₄ alkyl groups include methyl, ethyl, propyl, isopropyl, butyl, *sec*-butyl, *tert*-butyl, and *iso*-butyl.

For the purpose of the present disclosure, the term "optionally substituted alkyl" as
10 used by itself or as part of another group means that the alkyl as defined above is either unsubstituted or substituted with one, two, or three substituents independently chosen from nitro, haloalkoxy, aryloxy, aralkyloxy, alkylthio, sulfonamido, alkylcarbonyl, arylcarbonyl, alkylsulfonyl, arylsulfonyl, ureido, guanidino, carboxy, carboxyalkyl, cycloalkyl, and the like. In one embodiment, the optionally substituted alkyl is substituted with two substituents.
15 In another embodiment, the optionally substituted alkyl is substituted with one substituent. Non-limiting exemplary optionally substituted alkyl groups include -CH₂CH₂NO₂, -CH₂CH₂CO₂H, -CH₂CH₂SO₂CH₃, -CH₂CH₂COPh, -CH₂C₆H₁₁, and the like.

For the purpose of the present disclosure, the term "cycloalkyl" as used by itself or as part of another group refers to saturated and partially unsaturated (containing one or two
20 double bonds) cyclic aliphatic hydrocarbons containing one to three rings having from three to twelve carbon atoms (*i.e.*, C₃₋₁₂ cycloalkyl) or the number of carbons designated. In one embodiment, the cycloalkyl group has two rings. In one embodiment, the cycloalkyl group has one ring. In another embodiment, the cycloalkyl group is chosen from a C₃₋₈ cycloalkyl group. In another embodiment, the cycloalkyl group is chosen from a C₃₋₆ cycloalkyl group.
25 Non-limiting exemplary cycloalkyl groups include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, norbornyl, decalin, adamantyl, cyclohexenyl, cyclopentenyl, cyclohexenyl and the like.

For the purpose of the present disclosure, the term "optionally substituted cycloalkyl" as used by itself or as part of another group means that the cycloalkyl as defined above is
30 either unsubstituted or substituted with one, two, or three substituents independently chosen from halo, nitro, cyano, hydroxy, amino, alkylamino, dialkylamino, haloalkyl, hydroxyalkyl, alkoxy, haloalkoxy, aryloxy, aralkyloxy, alkylthio, carboxamido, sulfonamido, alkylcarbonyl,

arylcarbonyl, alkylsulfonyl, arylsulfonyl, ureido, guanidino, carboxy, carboxyalkyl, alkyl, cycloalkyl, alkenyl, alkynyl, aryl, heteroaryl, heterocyclo, alkoxyalkyl, (amino)alkyl, hydroxyalkylamino, (alkylamino)alkyl, (dialkylamino)alkyl, (cyano)alkyl, (carboxamido)alkyl, mercaptoalkyl, (heterocyclo)alkyl, and (heteroaryl)alkyl. In one embodiment, the optionally substituted cycloalkyl is substituted with two substituents. In another embodiment, the optionally substituted cycloalkyl is substituted with one substituent. Non-limiting exemplary optionally substituted cycloalkyl groups include:



For the purpose of the present disclosure, the term "alkenyl" as used by itself or as part of another group refers to an alkyl group as defined above containing one, two or three carbon-to-carbon double bonds. In one embodiment, the alkenyl group is chosen from a C₂₋₆ alkenyl group. In another embodiment, the alkenyl group is chosen from a C₂₋₄ alkenyl group. Non-limiting exemplary alkenyl groups include ethenyl, propenyl, isopropenyl, butenyl, *sec*-butenyl, pentenyl, and hexenyl.

For the purpose of the present disclosure, the term "optionally substituted alkenyl" as used herein by itself or as part of another group means the alkenyl as defined above is either unsubstituted or substituted with one, two or three substituents independently chosen from halo, nitro, cyano, hydroxy, amino, alkylamino, dialkylamino, haloalkyl, hydroxyalkyl, alkoxy, haloalkoxy, aryloxy, aralkyloxy, alkylthio, carboxamido, sulfonamido, alkylcarbonyl, arylcarbonyl, alkylsulfonyl, arylsulfonyl, ureido, guanidino, carboxy, carboxyalkyl, alkyl, cycloalkyl, alkenyl, alkynyl, aryl, heteroaryl, or heterocyclo.

For the purpose of the present disclosure, the term "alkynyl" as used by itself or as part of another group refers to an alkyl group as defined above containing one to three carbon-to-carbon triple bonds. In one embodiment, the alkynyl has one carbon-to-carbon triple bond. In one embodiment, the alkynyl group is chosen from a C₂₋₆ alkynyl group. In another embodiment, the alkynyl group is chosen from a C₂₋₄ alkynyl group. Non-limiting exemplary alkynyl groups include ethynyl, propynyl, butynyl, 2-butynyl, pentynyl, and hexynyl groups.

For the purpose of the present disclosure, the term "optionally substituted alkynyl" as used herein by itself or as part of another group means the alkynyl as defined above is either

unsubstituted or substituted with one, two or three substituents independently chosen from halo, nitro, cyano, hydroxy, amino, alkylamino, dialkylamino, haloalkyl, hydroxyalkyl, alkoxy, haloalkoxy, aryloxy, aralkyloxy, alkylthio, carboxamido, sulfonamido, alkylcarbonyl, arylcarbonyl, alkylsulfonyl, arylsulfonyl, ureido, guanidino, carboxy, carboxyalkyl, alkyl, cycloalkyl, alkenyl, alkynyl, aryl, heteroaryl, or heterocyclo.

For the purpose of the present disclosure, the term "haloalkyl" as used by itself or as part of another group refers to an alkyl group substituted by one or more fluorine, chlorine, bromine and/or iodine atoms. In one embodiment, the alkyl group is substituted by one, two, or three fluorine and/or chlorine atoms. In another embodiment, the haloalkyl group is chosen from a C₁₋₄ haloalkyl group. Non-limiting exemplary haloalkyl groups include fluoromethyl, difluoromethyl, trifluoromethyl, pentafluoroethyl, 1,1-difluoroethyl, 2,2-difluoroethyl, 2,2,2-trifluoroethyl, 3,3,3-trifluoropropyl, 4,4,4-trifluorobutyl, and trichloromethyl groups.

For the purpose of the present disclosure, the term "hydroxyalkyl" as used by itself or as part of another group refers to an alkyl group substituted with one or more, e.g., one, two, or three, hydroxy groups. In one embodiment, the hydroxyalkyl group is a monohydroxyalkyl group, *i.e.*, substituted with one hydroxy group. In another embodiment, the hydroxyalkyl group is a dihydroxyalkyl group, *i.e.*, substituted with two hydroxy groups. In another embodiment, the hydroxyalkyl group is chosen from a hydroxy(C₁-C₄) alkyl group. Non-limiting exemplary hydroxyalkyl groups include hydroxymethyl, hydroxyethyl, hydroxypropyl and hydroxybutyl groups, such as 1-hydroxyethyl, 2-hydroxyethyl, 1,2-dihydroxyethyl, 2-hydroxypropyl, 3-hydroxypropyl, 3-hydroxybutyl, 4-hydroxybutyl, 2-hydroxy-1-methylpropyl, and 1,3-dihydroxyprop-2-yl.

For the purpose of the present disclosure, the term "alkoxy" as used by itself or as part of another group refers to an optionally substituted alkyl, optionally substituted cycloalkyl, optionally substituted alkenyl or optionally substituted alkynyl attached to a terminal oxygen atom. In one embodiment, the alkoxy group is chosen from a C₁₋₄ alkoxy group. In another embodiment, the alkoxy group is chosen from a C₁₋₄ alkyl attached to a terminal oxygen atom, *e.g.*, methoxy, ethoxy, and *tert*-butoxy.

For the purpose of the present disclosure, the term "alkylthio" as used by itself or as part of another group refers to a sulfur atom substituted by an optionally substituted alkyl group. In one embodiment, the alkylthio group is chosen from a C₁₋₄ alkylthio group. Non-limiting exemplary alkylthio groups include -SCH₃, and -SCH₂CH₃.

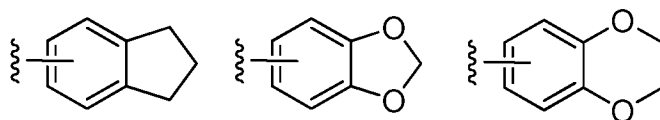
For the purpose of the present disclosure, the term "alkoxyalkyl" as used by itself or as part of another group refers to an alkyl group substituted with an alkoxy group. Non-limiting exemplary alkoxyalkyl groups include methoxymethyl, methoxyethyl, methoxypropyl, methoxybutyl, ethoxymethyl, ethoxyethyl, ethoxypropyl, ethoxybutyl, 5 propoxymethyl, iso-propoxymethyl, propoxyethyl, propoxypropyl, butoxymethyl, tert-butoxymethyl, isobutoxymethyl, sec-butoxymethyl, and pentyloxymethyl.

For the purpose of the present disclosure, the term "haloalkoxy" as used by itself or as part of another group refers to a haloalkyl attached to a terminal oxygen atom. Non-limiting exemplary haloalkoxy groups include fluoromethoxy, difluoromethoxy, trifluoromethoxy, 10 and 2,2,2-trifluoroethoxy.

For the purpose of the present disclosure, the term "aryl" as used by itself or as part of another group refers to a monocyclic or bicyclic aromatic ring system having from six to fourteen carbon atoms (*i.e.*, C₆-C₁₄ aryl). Non-limiting exemplary aryl groups include phenyl (abbreviated as "Ph"), naphthyl, phenanthryl, anthracyl, indenyl, azulenyl, biphenyl, 15 biphenylenyl, and fluorenyl groups. In one embodiment, the aryl group is chosen from phenyl or naphthyl.

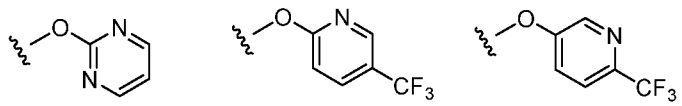
For the purpose of the present disclosure, the term "optionally substituted aryl" as used herein by itself or as part of another group means that the aryl as defined above is either unsubstituted or substituted with one to five substituents independently chosen from halo, 20 nitro, cyano, hydroxy, amino, alkylamino, dialkylamino, haloalkyl, hydroxyalkyl, alkoxy, haloalkoxy, aryloxy, heteroaryloxy, aralkyloxy, alkylthio, carboxamido, sulfonamido, alkylcarbonyl, arylcarbonyl, alkylsulfonyl, arylsulfonyl, ureido, guanidino, carboxy, carboxyalkyl, alkyl, cycloalkyl, alkenyl, alkynyl, aryl, heteroaryl, heterocyclo, alkoxyalkyl, (amino)alkyl, hydroxyalkylamino, (alkylamino)alkyl, (dialkylamino)alkyl, (cyano)alkyl, 25 (carboxamido)alkyl, mercaptoalkyl, (heterocyclo)alkyl, (cycloalkylamino)alkyl, (halo(C₁-C₄)alkoxy)alkyl, or (heteroaryl)alkyl. In one embodiment, the optionally substituted aryl is an optionally substituted phenyl. In one embodiment, the optionally substituted phenyl has four substituents. In another embodiment, the optionally substituted phenyl has three substituents. In another embodiment, the optionally substituted phenyl has two substituents. 30 In another embodiment, the optionally substituted phenyl has one substituent. Non-limiting exemplary substituted aryl groups include 2-methylphenyl, 2-methoxyphenyl, 2-fluorophenyl, 2-chlorophenyl, 2-bromophenyl, 3-methylphenyl, 3-methoxyphenyl, 3-

fluorophenyl, 3-chlorophenyl, 4-methylphenyl, 4-ethylphenyl, 4-methoxyphenyl, 4-fluorophenyl, 4-chlorophenyl, 2,6-di-fluorophenyl, 2,6-di-chlorophenyl, 2-methyl, 3-methoxyphenyl, 2-ethyl, 3-methoxyphenyl, 3,4-di-methoxyphenyl, 3,5-di-fluorophenyl, 3,5-di-methylphenyl, 3,5-dimethoxy, 4-methylphenyl, 2-fluoro-3-chlorophenyl, and 3-chloro-4-fluorophenyl. The term optionally substituted aryl is meant to include groups having fused optionally substituted cycloalkyl and fused optionally substituted heterocyclo rings. Examples include



For the purpose of the present disclosure, the term "aryloxy" as used by itself or as part of another group refers to an optionally substituted aryl attached to a terminal oxygen atom. A non-limiting exemplary aryloxy group is PhO-.

For the purpose of the present disclosure, the term "heteroaryloxy" as used by itself or as part of another group refers to an optionally substituted heteroaryl attached to a terminal oxygen atom. Non-limiting exemplary heteroaryloxy groups include:



For the purpose of the present disclosure, the term "aralkyloxy" as used by itself or as part of another group refers to an aralkyl group attached to a terminal oxygen atom. A non-limiting exemplary aralkyloxy group is PhCH₂O-.

For the purpose of the present disclosure, the term "heteroaryl" or "heteroaromatic" refers to monocyclic and bicyclic aromatic ring systems having 5 to 14 ring atoms (*i.e.*, C₅-C₁₄ heteroaryl), wherein at least one carbon atom of one of the rings is replaced with a heteroatom independently selected from the group consisting of oxygen, nitrogen and sulfur. In one embodiment, the heteroaryl contains 1, 2, 3, or 4 heteroatoms independently selected from the group consisting of oxygen, nitrogen and sulfur. In one embodiment, the heteroaryl has three heteroatoms. In another embodiment, the heteroaryl has two heteroatoms. In another embodiment, the heteroaryl has one heteroatom. Non-limiting exemplary heteroaryl groups include thienyl, benzo[b]thienyl, naphtho[2,3-b]thienyl, thianthrenyl, furyl, benzofuryl, pyranlyl, isobenzofuranyl, benzooxazolyl, chromenyl, xanthenyl, 2*H*-pyrrolyl, pyrrolyl, imidazolyl, pyrazolyl, pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, isoindolyl, 3*H*-

indolyl, indolyl, indazolyl, purinyl, isoquinolyl, quinolyl, phthalazinyl, naphthyridinyl, cinnolinyl, quinazolinyl, pteridinyl, 4aH-carbazolyl, carbazolyl, β -carbolinyl, phenanthridinyl, acridinyl, pyrimidinyl, phenanthrolinyl, phenazinyl, thiazolyl, isothiazolyl, phenothiazolyl, isoxazolyl, furazanyl, and phenoxazinyl. In one embodiment, the heteroaryl is chosen from thienyl (*e.g.*, thien-2-yl and thien-3-yl), furyl (*e.g.*, 2-furyl and 3-furyl), pyrrolyl (*e.g.*, 1H-pyrrol-2-yl and 1H-pyrrol-3-yl), imidazolyl (*e.g.*, 2H-imidazol-2-yl and 2H-imidazol-4-yl), pyrazolyl (*e.g.*, 1H-pyrazol-3-yl, 1H-pyrazol-4-yl, and 1H-pyrazol-5-yl), pyridyl (*e.g.*, pyridin-2-yl, pyridin-3-yl, and pyridin-4-yl), pyrimidinyl (*e.g.*, pyrimidin-2-yl, pyrimidin-4-yl, and pyrimidin-5-yl), thiazolyl (*e.g.*, thiazol-2-yl, thiazol-4-yl, and thiazol-5-yl), isothiazolyl (*e.g.*, isothiazol-3-yl, isothiazol-4-yl, and isothiazol-5-yl), oxazolyl (*e.g.*, oxazol-2-yl, oxazol-4-yl, and oxazol-5-yl) and isoxazolyl (*e.g.*, isoxazol-3-yl, isoxazol-4-yl, and isoxazol-5-yl). The term "heteroaryl" is also meant to include possible N-oxides. Exemplary N-oxides include pyridyl N-oxide and the like.

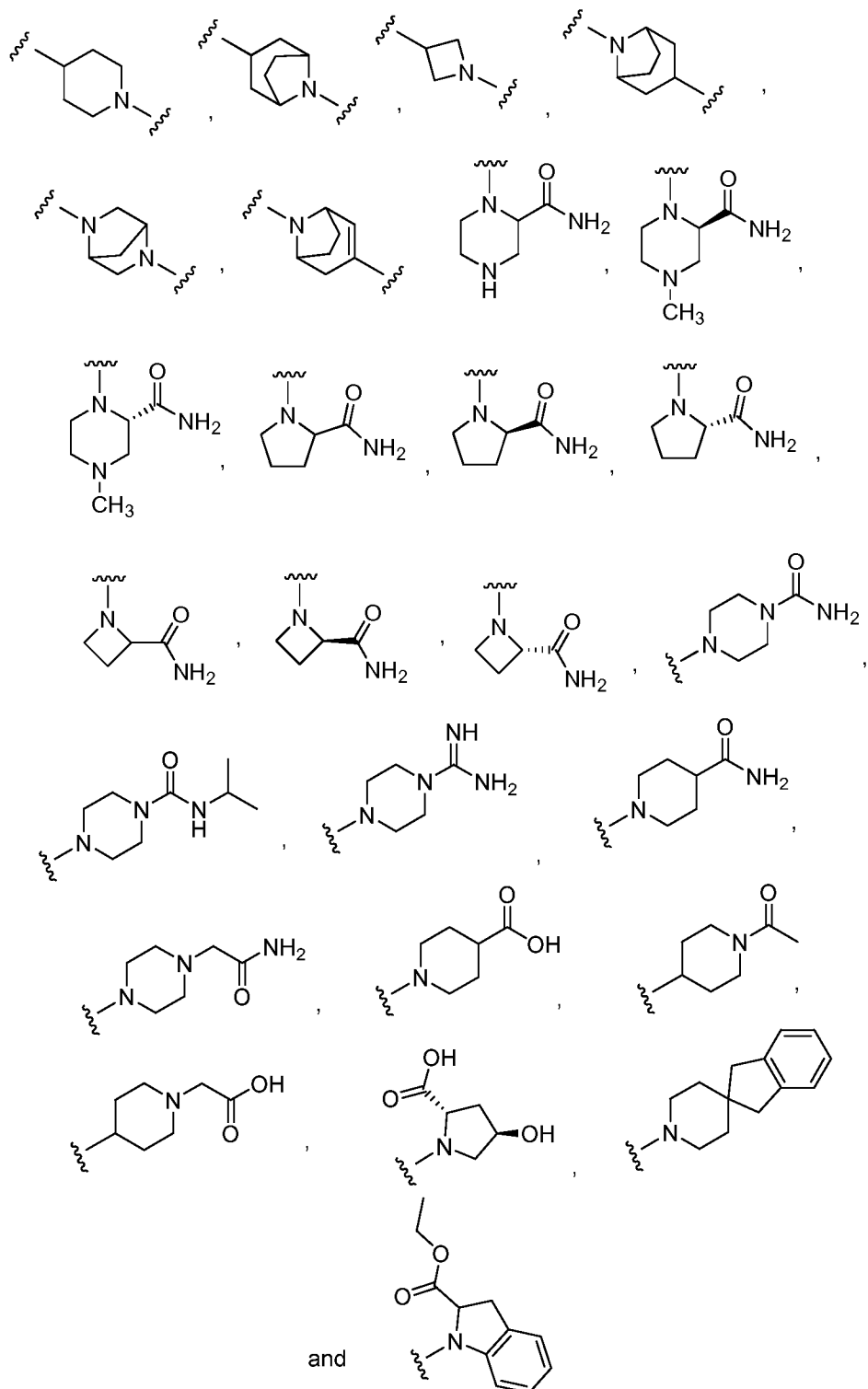
In one embodiment, the heteroaryl is a 5- or 6-membered heteroaryl. In one embodiment, the heteroaryl is a 5-membered heteroaryl, *i.e.*, the heteroaryl is a monocyclic aromatic ring system having 5 ring atoms wherein at least one carbon atom of the ring is replaced with a heteroatom independently selected from nitrogen, oxygen, and sulfur. Non-limiting exemplary 5-membered heteroaryl groups include thienyl, furyl, imidazolyl, thiazolyl, isothiazolyl, and isoxazolyl. In another embodiment, the heteroaryl is a 6-membered heteroaryl, *e.g.*, the heteroaryl is a monocyclic aromatic ring system having 6 ring atoms wherein at least one carbon atom of the ring is replaced with a nitrogen atom. Non-limiting exemplary 6-membered heteroaryl groups include pyridyl, pyrazinyl, pyrimidinyl, and pyridazinyl.

For the purpose of the present disclosure, the term "optionally substituted heteroaryl" as used by itself or as part of another group means that the heteroaryl as defined above is either unsubstituted or substituted with one to four substituents, *e.g.*, one or two substituents, independently chosen from halo, nitro, cyano, hydroxy, amino, alkylamino, dialkylamino, haloalkyl, hydroxyalkyl, alkoxy, haloalkoxy, aryloxy, aralkyloxy, alkylthio, carboxamido, sulfonamido, alkylcarbonyl, arylcarbonyl, alkylsulfonyl, arylsulfonyl, ureido, guanidino, carboxy, carboxyalkyl, alkyl, cycloalkyl, alkenyl, alkynyl, aryl, heteroaryl, heterocyclo, alkoxyalkyl, (amino)alkyl, hydroxyalkylamino, (alkylamino)alkyl, (dialkylamino)alkyl, (cyano)alkyl, (carboxamido)alkyl, mercaptoalkyl, (heterocyclo)alkyl, and (heteroaryl)alkyl.

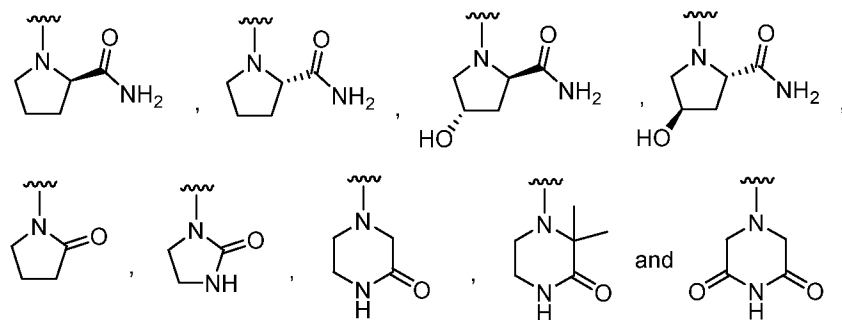
In one embodiment, the optionally substituted heteroaryl has one substituent. In one embodiment, the optionally substituted is an optionally substituted pyridyl, *i.e.*, 2-, 3-, or 4-pyridyl. Any available carbon or nitrogen atom can be substituted. In another embodiment, the optionally substituted heteroaryl is an optionally substituted indole.

5 For the purpose of the present disclosure, the term "heterocycle" or "heterocyclo" as used by itself or as part of another group refers to saturated and partially unsaturated (*e.g.*, containing one or two double bonds) cyclic groups containing one, two, or three rings having from three to fourteen ring members (*i.e.*, a 3- to 14-membered heterocyclo) wherein at least one carbon atom of one of the rings is replaced with a heteroatom. Each heteroatom is
10 independently selected from the group consisting of oxygen, sulfur, including sulfoxide and sulfone, and/or nitrogen atoms, which can be oxidized or quaternized. The term "heterocyclo" is meant to include groups wherein a ring -CH₂- is replaced with a -C(=O)-, for example, cyclic ureido groups such as 2-imidazolidinone and cyclic amide groups such as β-lactam, γ-lactam, δ-lactam, ε-lactam, and piperazin-2-one. The term "heterocyclo" is also
15 meant to include groups having fused optionally substituted aryl groups, *e.g.*, indoliny. In one embodiment, the heterocyclo group is chosen from a 5- or 6-membered cyclic group containing one ring and one or two oxygen and/or nitrogen atoms. The heterocyclo can be optionally linked to the rest of the molecule through a carbon or nitrogen atom. Non-limiting exemplary heterocyclo groups include 2-oxopyrrolidin-3-yl, piperazin-2-one, piperazine-2,6-
20 dione, 2-imidazolidinone, piperidinyl, morpholinyl, piperazinyl, pyrrolidinyl, and indolinyl.

For the purpose of the present disclosure, the term "optionally substituted heterocyclo" as used herein by itself or part of another group means the heterocyclo as defined above is either unsubstituted or substituted with one to four substituents independently selected from halo, nitro, cyano, hydroxy, amino, alkylamino, dialkylamino,
25 haloalkyl, hydroxyalkyl, alkoxy, haloalkoxy, aryloxy, aralkyloxy, alkylthio, carboxamido, sulfonamido, alkylcarbonyl, arylcarbonyl, alkylsulfonyl, arylsulfonyl, ureido, guanidino, carboxy, carboxyalkyl, alkyl, cycloalkyl, alkenyl, alkynyl, aryl, heteroaryl, heterocyclo, alkoxyalkyl, (amino)alkyl, hydroxyalkylamino, (alkylamino)alkyl, (dialkylamino)alkyl, (cyano)alkyl, (carboxamido)alkyl, mercaptoalkyl, (heterocyclo)alkyl, (heteroaryl)alkyl, and
30 the like. Substitution may occur on any available carbon or nitrogen atom, and may form a spirocycle. Non-limiting exemplary optionally substituted heterocyclo groups include:



In one embodiment, the optionally substituted heterocyclo is a 5- or 6-membered optionally substituted heterocyclo. Non-limiting exemplary 5- or 6-membered optionally substituted heterocyclo groups include:



For the purpose of the present disclosure, the term "amino" as used by itself or as part of another group refers to -NH_2 .

For the purpose of the present disclosure, the term "alkylamino" as used by itself or as part of another group refers to -NHR^{15} , wherein R^{15} is alkyl.

For the purpose of the present disclosure, the term "dialkylamino" as used by itself or as part of another group refers to $\text{-NR}^{16a}\text{R}^{16b}$, wherein R^{16a} and R^{16b} are each independently alkyl or R^{16a} and R^{16b} are taken together to form a 3- to 8-membered optionally substituted heterocycle.

For the purpose of the present disclosure, the term "hydroxyalkylamino" as used by itself or as part of another group refers to -NHR^{17} , wherein R^{17} is hydroxyalkyl.

For the purpose of the present disclosure, the term "cycloalkylamino" as used by itself or as part of another group refers to $\text{-NR}^{19a}\text{R}^{19b}$, wherein R^{19a} is optionally substituted cycloalkyl and R^{19b} is hydrogen or alkyl.

For the purpose of the present disclosure, the term "(amino)alkyl" as used by itself or as part of another group refers to an alkyl group substituted with an amino group. Non-limiting exemplary amino alkyl groups include $\text{-CH}_2\text{CH}_2\text{NH}_2$, $\text{-CH}_2\text{CH}_2\text{CH}_2\text{NH}_2$, $\text{-CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{NH}_2$ and the like.

For the purpose of the present disclosure, the term "(alkylamino)alkyl" as used by itself or as part of another group refers to an alkyl group substituted with an alkylamino group. A non-limiting exemplary (alkylamino)alkyl group is $\text{-CH}_2\text{CH}_2\text{N(H)CH}_3$.

For the purpose of the present disclosure, the term "(dialkylamino)alkyl" as used by itself or as part of another group refers to an alkyl group substituted by a dialkylamino group. A non-limiting exemplary (dialkylamino)alkyl group is $\text{-CH}_2\text{CH}_2\text{N(CH}_3)_2$.

For the purpose of the present disclosure, the term "(cycloalkylamino)alkyl" as used by itself or as part of another group refers to an alkyl group substituted by a cycloalkylamino

group. Non-limiting exemplary (cycloalkylamino)alkyl groups include -CH₂N(H)cyclopropyl, -CH₂N(H)cyclobutyl, and -CH₂N(H)cyclohexyl.

For the purpose of the present disclosure, the term "(halo(C₁-C₄)alkoxy)alkyl" as used by itself or as part of another group refers to an alkyl group substituted by a C₁-C₄ haloalkoxy group. Non-limiting exemplary (halo(C₁-C₄)alkoxy)alkyl groups include -CH₂OCH₂CF₃ and -CH₂OCF₃.

For the purpose of the present disclosure, the term "(cyano)alkyl" as used by itself or as part of another group refers to an alkyl group substituted with one or more cyano, *e.g.*, -CN, groups. Non-limiting exemplary (cyano)alkyl groups include -CH₂CH₂CN, -CH₂CH₂CH₂CN, and -CH₂CH₂CH₂CH₂CN.

For the purpose of the present disclosure, the term "carboxamido" as used by itself or as part of another group refers to a radical of formula -C(=O)NR^{24a}R^{24b}, wherein R^{24a} and R^{24b} are each independently hydrogen, optionally substituted alkyl, optionally substituted aryl, or optionally substituted heteroaryl, or R^{24a} and R^{24b} taken together with the nitrogen to which they are attached from a 3- to 8-membered heterocyclo group. In one embodiment, R^{24a} and R^{24b} are each independently hydrogen or optionally substituted alkyl. Non-limiting exemplary carboxamido groups include -CONH₂, -CON(H)CH₃, CON(CH₃)₂, and CON(H)Ph.

For the purpose of the present disclosure, the term "sulfonamido" as used by itself or as part of another group refers to a radical of the formula -SO₂NR^{23a}R^{23b}, wherein R^{23a} and R^{23b} are each independently hydrogen, optionally substituted alkyl, or optionally substituted aryl, or R^{23a} and R^{23b} taken together with the nitrogen to which they are attached from a 3- to 8-membered heterocyclo group. Non-limiting exemplary sulfonamido groups include -SO₂NH₂, -SO₂N(H)CH₃, and -SO₂N(H)Ph.

For the purpose of the present disclosure, the term "alkylcarbonyl" as used by itself or as part of another group refers to a carbonyl group, *i.e.*, -C(=O)-, substituted by an alkyl group. A non-limiting exemplary alkylcarbonyl group is -COCH₃.

For the purpose of the present disclosure, the term "arylcarbonyl" as used by itself or as part of another group refers to a carbonyl group, *i.e.*, -C(=O)-, substituted by an optionally substituted aryl group. A non-limiting exemplary arylcarbonyl group is -COPh.

For the purpose of the present disclosure, the term "alkylsulfonyl" as used by itself or as part of another group refers to a sulfonyl group, *i.e.*, -SO₂-, substituted by any of the

above-mentioned optionally substituted alkyl groups. A non-limiting exemplary alkylsulfonyl group is $-\text{SO}_2\text{CH}_3$.

For the purpose of the present disclosure, the term "arylsulfonyl" as used by itself or as part of another group refers to a sulfonyl group, *i.e.*, $-\text{SO}_2-$, substituted by any of the above-mentioned optionally substituted aryl groups. A non-limiting exemplary arylsulfonyl group is $-\text{SO}_2\text{Ph}$.

For the purpose of the present disclosure, the term "mercaptoalkyl" as used by itself or as part of another group refers to any of the above-mentioned alkyl groups substituted by a $-\text{SH}$ group.

For the purpose of the present disclosure, the term "carboxy" as used by itself or as part of another group refers to a radical of the formula $-\text{COOH}$.

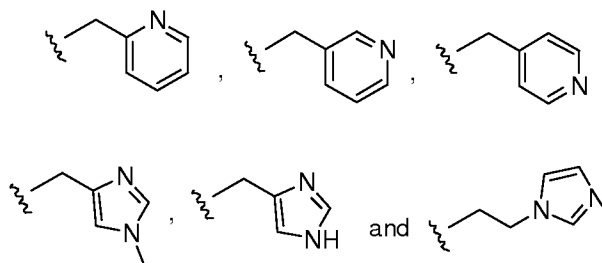
For the purpose of the present disclosure, the term "carboxyalkyl" as used by itself or as part of another group refers to any of the above-mentioned alkyl groups substituted with a $-\text{COOH}$. A non-limiting exemplary carboxyalkyl group is $-\text{CH}_2\text{CO}_2\text{H}$.

For the purpose of the present disclosure, the term "aralkyl" or "arylalkyl" as used by itself or as part of another group refers to an alkyl group substituted with one, two, or three optionally substituted aryl groups. In one embodiment, the aralkyl group is a C_{1-4} alkyl substituted with one optionally substituted aryl group. Non-limiting exemplary aralkyl groups include benzyl, phenethyl, $-\text{CHPh}_2$, $-\text{CH}_2(4\text{-F-Ph})$, and $-\text{CH}(4\text{-F-Ph})_2$.

For the purpose of the present disclosure, the term "ureido" as used by itself or as part of another group refers to a radical of the formula $-\text{NR}^{22a}-\text{C}(=\text{O})-\text{NR}^{22b}\text{R}^{22c}$, wherein R^{22a} is hydrogen, alkyl, or optionally substituted aryl, and R^{22b} and R^{22c} are each independently hydrogen, alkyl, or optionally substituted aryl, or R^{22b} and R^{22c} taken together with the nitrogen to which they are attached form a 4- to 8-membered heterocyclo group. Non-limiting exemplary ureido groups include $-\text{NH}-\text{C}(=\text{O})-\text{NH}_2$ and $-\text{NH}-\text{C}(=\text{O})-\text{NHCH}_3$.

For the purpose of the present disclosure, the term "guanidino" as used by itself or as part of another group refers to a radical of the formula $-\text{NR}^{25a}-\text{C}(=\text{NR}^{26})-\text{NR}^{25b}\text{R}^{25c}$, wherein R^{25a} , R^{25b} , and R^{25c} are each independently hydrogen, alkyl, or optionally substituted aryl, and R^{26} is hydrogen, alkyl, cyano, alkylsulfonyl, alkylcarbonyl, carboxamido, or sulfonamido. Non-limiting exemplary guanidino groups include $-\text{NH}-\text{C}(=\text{NH})-\text{NH}_2$, $-\text{NH}-\text{C}(=\text{NCN})-\text{NH}_2$, $-\text{NH}-\text{C}(=\text{NH})-\text{NHCH}_3$ and the like.

For the purpose of the present disclosure, the term "(heteroaryl)alkyl" as used by itself or as part of another group refers to an alkyl group substituted with one, two, or three optionally substituted heteroaryl groups. In one embodiment, the (heteroaryl)alkyl group is a C₁₋₄ alkyl substituted with one optionally substituted heteroaryl group. Non-limiting exemplary (heteroaryl)alkyl groups include:



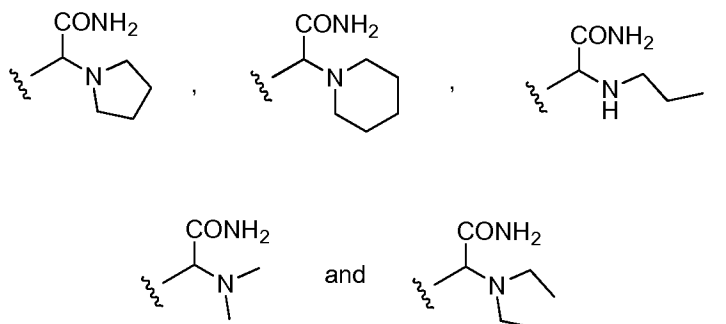
For the purpose of the present disclosure, the term "heteroalkyl" as used by itself or part of another group refers to a stable straight or branched chain hydrocarbon radical containing 1 to 10 carbon atoms and at least two heteroatoms, which can be the same or different, selected from O, N, or S, wherein: 1) the nitrogen atom(s) and sulfur atom(s) can optionally be oxidized; and/or 2) the nitrogen atom(s) can optionally be quaternized. The heteroatoms can be placed at any interior position or terminal position of the heteroalkyl group, or at a position at which the heteroalkyl group is attached to the remainder of the molecule. In one embodiment, the heteroalkyl group contains two oxygen atoms. In another embodiment, the heteroalkyl group contains two nitrogen atoms. In other embodiment, the heteroalkyl group contains one nitrogen atom and one oxygen atom. Non-limiting exemplary heteroalkyl groups include:

-CH₂N(H)CH₂CH₂N(CH₃)₂; -CH₂N(CH₃)CH₂CH₂N(CH₃)₂;
 -CH₂N(H)CH₂CH₂CH₂N(CH₃)₂; -CH₂N(H)CH₂CH₂OH; -CH₂N(CH₃)CH₂CH₂OH;
 -CH₂OCH₂CH₂OCH₃, -OCH₂CH₂OCH₂CH₂OCH₃; -CH₂NHCH₂CH₂OCH₂; -OCH₂CH₂NH₂;
 and -NHCH₂CH₂N(H)CH₃.

For the purpose of the present disclosure, the term "(heterocyclo)alkyl" as used by itself or as part of another group refers to an alkyl group substituted with one optionally substituted heterocyclo group, and optionally one hydroxy group. In one embodiment, the (heterocyclo)alkyl is a C₁₋₄ alkyl substituted with one optionally substituted heterocyclo group and one hydroxy group. In another embodiment, the (heterocyclo)alkyl is a C₁₋₄ alkyl substituted with one optionally substituted heterocyclo group. Non-limiting exemplary (heterocyclo)alkyl groups include:



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The present disclosure encompasses any of the Compounds of the Disclosure being isotopically-labelled (*i.e.*, radiolabeled) by having one or more atoms replaced by an atom having a different atomic mass or mass number. Examples of isotopes that can be incorporated into the disclosed compounds include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorous, fluorine and chlorine, such as ²H, ³H, ¹¹C, ¹³C, ¹⁴C, ¹⁵N, ¹⁸O, ¹⁷O, ³¹P, ³²P, ³⁵S, ¹⁸F, and ³⁶Cl, respectively, *e.g.*, ³H, ¹¹C, and ¹⁴C. Isotopically-labeled Compounds of the Disclosure can be prepared by methods known in the art.

The present disclosure encompasses ³H, ¹¹C, or ¹⁴C radiolabeled Compounds of the Disclosure and the use of any such compounds as radioligands for their ability to bind to the sodium channel. For example, one use of the labeled compounds of the present disclosure is the characterization of specific receptor binding. Another use of a labeled Compound of the Disclosure is an alternative to animal testing for the evaluation of structure-activity relationships. For example, the receptor assay can be performed at a fixed concentration of a labeled Compound of the Disclosure and at increasing concentrations of a test compound in a competition assay. For example, a tritiated Compound of the Disclosure can be prepared by introducing tritium into the particular compound, for example, by catalytic dehalogenation with tritium. This method may include reacting a suitably halogen-substituted precursor of the compound with tritium gas in the presence of a suitable catalyst, for example, Pd/C, in the presence or absence of a base. Other suitable methods for preparing tritiated compounds can be found in Filer, *Isotopes in the Physical and Biomedical Sciences, Vol. 1, Labeled Compounds (Part A)*, Chapter 6 (1987). ¹⁴C-labeled compounds can be prepared by employing starting materials having a ¹⁴C carbon.

Compounds of the Disclosure may contain one or more asymmetric centers and may thus give rise to enantiomers, diastereomers, and other stereoisomeric forms. The present disclosure is meant to encompass the use of all such possible forms, as well as their racemic

and resolved forms and mixtures thereof. The individual enantiomers can be separated according to methods known in the art in view of the present disclosure. When the compounds described herein contain olefinic double bonds or other centers of geometric asymmetry, and unless specified otherwise, it is intended that they include both E and Z
5 geometric isomers. All tautomers are intended to be encompassed by the present disclosure as well.

As used herein, the term "stereoisomers" is a general term for all isomers of individual molecules that differ only in the orientation of their atoms in space. It includes enantiomers and isomers of compounds with more than one chiral center that are not mirror images of one
10 another (diastereomers).

The term "chiral center" refers to a carbon atom to which four different groups are attached.

The terms "enantiomer" and "enantiomeric" refer to a molecule that cannot be superimposed on its mirror image and hence is optically active wherein the enantiomer
15 rotates the plane of polarized light in one direction and its mirror image compound rotates the plane of polarized light in the opposite direction.

The term "racemic" refers to a mixture of equal parts of enantiomers and which mixture is optically inactive.

The term "resolution" refers to the separation or concentration or depletion of one of
20 the two enantiomeric forms of a molecule.

The terms "a" and "an" refer to one or more.

The term "treat," "treating" or "treatment" is meant to encompass administering to a subject a compound of the present disclosure for the purposes of amelioration or cure, including preemptive and palliative treatment. In one embodiment, the term "treat,"
25 "treating" or "treatment" is meant to encompass administering to a subject a compound of the present disclosure for the purposes of amelioration or cure.

The term "about," as used herein in connection with a measured quantity, refers to the normal variations in that measured quantity, as expected by the skilled artisan making the measurement and exercising a level of care commensurate with the objective of measurement
30 and the precision of the measuring equipment.

The present disclosure encompasses the preparation and use of salts of the Compounds of the Disclosure, including non-toxic pharmaceutically acceptable salts.

Examples of pharmaceutically acceptable addition salts include inorganic and organic acid addition salts and basic salts. The pharmaceutically acceptable salts include, but are not limited to, metal salts such as sodium salt, potassium salt, cesium salt and the like; alkaline earth metals such as calcium salt, magnesium salt and the like; organic amine salts such as triethylamine salt, pyridine salt, picoline salt, ethanolamine salt, triethanolamine salt, dicyclohexylamine salt, N,N'-dibenzylethylenediamine salt and the like; inorganic acid salts such as hydrochloride, hydrobromide, phosphate, sulphate and the like; organic acid salts such as citrate, lactate, tartrate, maleate, fumarate, mandelate, acetate, dichloroacetate, trifluoroacetate, oxalate, formate and the like; sulfonates such as methanesulfonate, benzenesulfonate, p-toluenesulfonate and the like; and amino acid salts such as arginate, aspartate, glutamate and the like.

Acid addition salts can be formed by mixing a solution of the particular Compound of the Disclosure with a solution of a pharmaceutically acceptable non-toxic acid such as hydrochloric acid, fumaric acid, maleic acid, succinic acid, acetic acid, citric acid, tartaric acid, carbonic acid, phosphoric acid, oxalic acid, dichloroacetic acid, or the like. Basic salts can be formed by mixing a solution of the compound of the present disclosure with a solution of a pharmaceutically acceptable non-toxic base such as sodium hydroxide, potassium hydroxide, choline hydroxide, sodium carbonate and the like.

The present disclosure encompasses the preparation and use of solvates of Compounds of the Disclosure. Solvates typically do not significantly alter the physiological activity or toxicity of the compounds, and as such may function as pharmacological equivalents. The term "solvate" as used herein is a combination, physical association and/or solvation of a compound of the present disclosure with a solvent molecule such as, *e.g.* a disolvate, monosolvate or hemisolvate, where the ratio of solvent molecule to compound of the present disclosure is about 2:1, about 1:1 or about 1:2, respectively. This physical association involves varying degrees of ionic and covalent bonding, including hydrogen bonding. In certain instances, the solvate can be isolated, such as when one or more solvent molecules are incorporated into the crystal lattice of a crystalline solid. Thus, "solvate" encompasses both solution-phase and isolatable solvates. Compounds of the Disclosure can be present as solvated forms with a pharmaceutically acceptable solvent, such as water, methanol, ethanol, and the like, and it is intended that the disclosure includes both solvated and unsolvated forms of Compounds of the Disclosure. One type of solvate is a hydrate. A

"hydrate" relates to a particular subgroup of solvates where the solvent molecule is water. Solvates typically can function as pharmacological equivalents. Preparation of solvates is known in the art. See, for example, M. Caira *et al*, *J. Pharmaceut. Sci.*, 93(3):601-611 (2004), which describes the preparation of solvates of fluconazole with ethyl acetate and with water. Similar preparation of solvates, hemisolvates, hydrates, and the like are described by E.C. van Tonder *et al.*, *AAPS Pharm. Sci. Tech.*, 5(1):Article 12 (2004), and A.L. Bingham *et al.*, *Chem. Commun.* 603-604 (2001). A typical, non-limiting, process of preparing a solvate would involve dissolving a Compound of the Disclosure in a desired solvent (organic, water, or a mixture thereof) at temperatures above 20°C to about 25°C, then cooling the solution at a rate sufficient to form crystals, and isolating the crystals by known methods, *e.g.*, filtration. Analytical techniques such as infrared spectroscopy can be used to confirm the presence of the solvent in a crystal of the solvate.

Since Compounds of the Disclosure are blockers of sodium (Na⁺) channels, a number of diseases and conditions mediated by sodium ion influx can be treated by employing these compounds. The present disclosure is thus directed generally to a method for treating a disorder responsive to the blockade of sodium channels in an animal suffering from, or at risk of suffering from, said disorder, said method comprising administering to the animal an effective amount of one or more Compounds of the Disclosure.

The present disclosure is further directed to a method of modulating sodium channels in an animal in need thereof, said method comprising administering to the animal a modulating-effective amount of at least one Compound of the Disclosure.

More specifically, the present disclosure provides a method of treating stroke, neuronal damage resulting from head trauma, epilepsy, neuronal loss following global and focal ischemia, pain (*e.g.*, acute pain, chronic pain, which includes but is not limited to neuropathic pain, postoperative pain, and inflammatory pain, or surgical pain), a neurodegenerative disorder (*e.g.*, Alzheimer's disease, amyotrophic lateral sclerosis (ALS), or Parkinson's disease), migraine, manic depression, tinnitus, myotonia, a movement disorder, or cardiac arrhythmia, or providing local anesthesia. In one embodiment, the disclosure provides a method of treating pain. In another embodiment, the type of pain is chronic pain. In another embodiment, the type of pain is neuropathic pain. In another embodiment, the type of pain is postoperative pain. In another embodiment, the type of pain is inflammatory pain. In another embodiment, the type of pain is surgical pain. In another embodiment, the

type of pain is acute pain. In another embodiment, the treatment of pain (*e.g.*, chronic pain, such as neuropathic pain, postoperative pain, or inflammatory pain, acute pain or surgical pain) is preemptive. In another embodiment, the treatment of pain is palliative. In each instance, such method of treatment requires administering to an animal in need of such treatment an amount of a Compound of the Disclosure that is therapeutically effective in achieving said treatment. In one embodiment, the amount of such compound is the amount that is effective to block sodium channels *in vitro*. In one embodiment, the amount of such compound is the amount that is effective to block sodium channels *in vivo*.

Chronic pain includes, but is not limited to, inflammatory pain, postoperative pain, cancer pain, osteoarthritis pain associated with metastatic cancer, trigeminal neuralgia, acute herpetic and postherpetic neuralgia, diabetic neuropathy, causalgia, brachial plexus avulsion, occipital neuralgia, reflex sympathetic dystrophy, fibromyalgia, gout, phantom limb pain, burn pain, and other forms of neuralgia, neuropathic, and idiopathic pain syndromes.

Chronic somatic pain generally results from inflammatory responses to tissue injury such as nerve entrapment, surgical procedures, cancer or arthritis (Brower, *Nature Biotechnology* 18:387-391 (2000)).

The inflammatory process is a complex series of biochemical and cellular events activated in response to tissue injury or the presence of foreign substances (Levine, *Inflammatory Pain, In: Textbook of Pain*, Wall and Melzack eds., 3rd ed., 1994). Inflammation often occurs at the site of injured tissue, or foreign material, and contributes to the process of tissue repair and healing. The cardinal signs of inflammation include erythema (redness), heat, edema (swelling), pain and loss of function (*ibid.*). The majority of patients with inflammatory pain do not experience pain continually, but rather experience enhanced pain when the inflamed site is moved or touched. Inflammatory pain includes, but is not limited to, that associated with osteoarthritis and rheumatoid arthritis.

Chronic neuropathic pain is a heterogeneous disease state with an unclear etiology. In chronic neuropathic pain, the pain can be mediated by multiple mechanisms. This type of pain generally arises from injury to the peripheral or central nervous tissue. The syndromes include pain associated with spinal cord injury, multiple sclerosis, post-herpetic neuralgia, trigeminal neuralgia, phantom pain, causalgia, and reflex sympathetic dystrophy and lower back pain. Chronic pain is different from acute pain in that patients suffer the abnormal pain sensations that can be described as spontaneous pain, continuous superficial burning and/or

deep aching pain. The pain can be evoked by heat-, cold-, and mechano-hyperalgesia or by heat-, cold-, or mechano-allodynia.

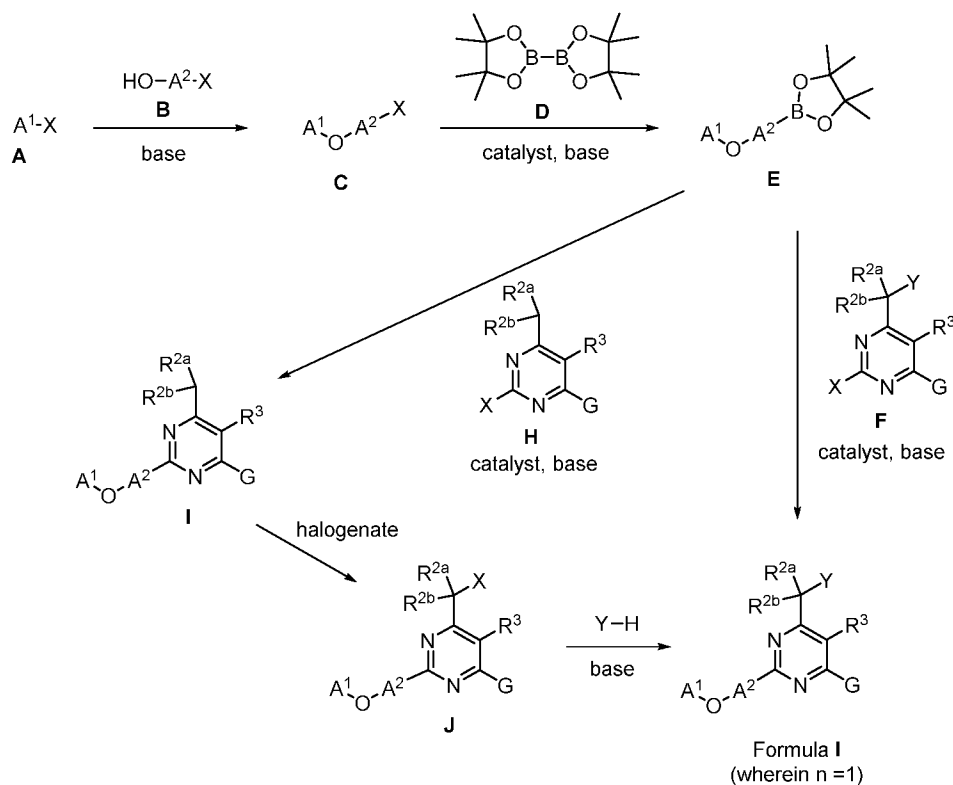
Neuropathic pain can be caused by injury or infection of peripheral sensory nerves. It includes, but is not limited to, pain from peripheral nerve trauma, herpes virus infection, 5 diabetes mellitus, causalgia, plexus avulsion, neuroma, limb amputation, and vasculitis. Neuropathic pain is also caused by nerve damage from chronic alcoholism, human immunodeficiency virus infection, hypothyroidism, uremia, or vitamin deficiencies. Stroke (spinal or brain) and spinal cord injury can also induce neuropathic pain. Cancer-related neuropathic pain results from tumor growth compression of adjacent nerves, brain, or spinal 10 cord. In addition, cancer treatments, including chemotherapy and radiation therapy, can also cause nerve injury. Neuropathic pain includes but is not limited to pain caused by nerve injury, such as the pain from which diabetics suffer.

The present disclosure is also directed to the use of a Compound of the Disclosure in the manufacture of a medicament for treating a disorder responsive to the blockade of sodium 15 channels (*e.g.*, any of the disorders listed above) in an animal suffering from said disorder.

General Synthesis of Compounds

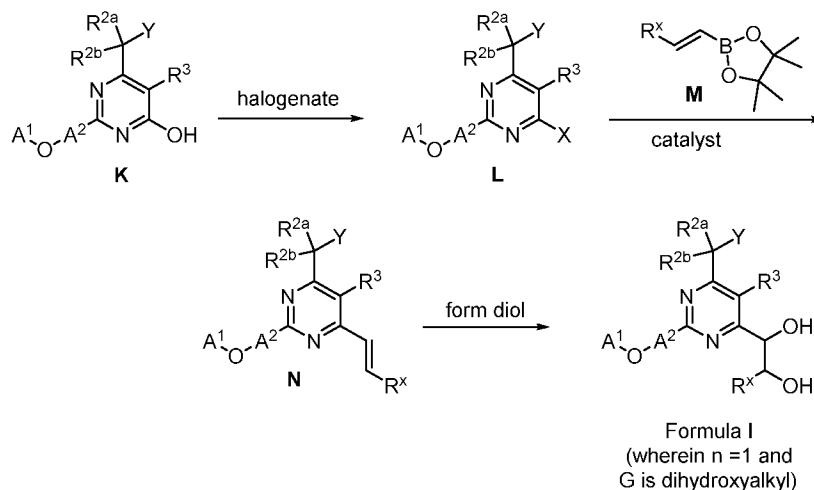
Compounds of Formula **I** can be prepared using conventional organic synthetic 20 methods in view of this disclosure, or by the illustrative methods shown in General Schemes 1-3.

General Scheme 1



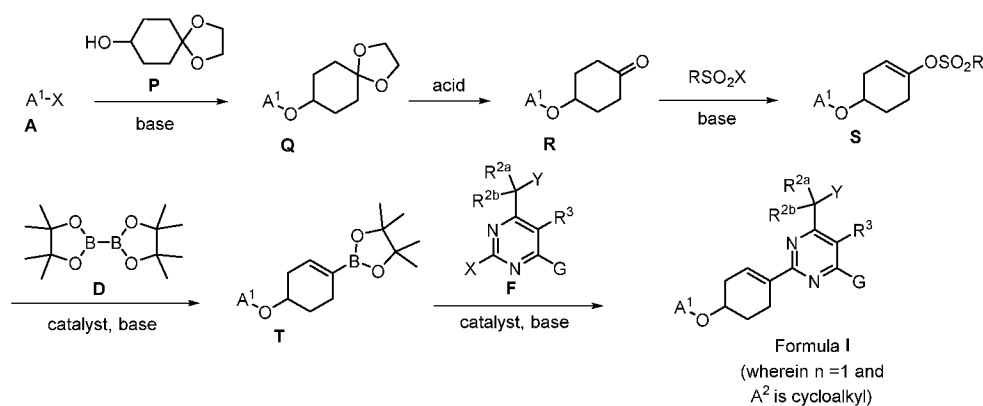
Compound **A** can be converted to Compound **C** by reaction with Compound **B** in the presence of a suitable base such as Cs_2CO_3 in a suitable solvent such as NMP. Compound **C** can be converted to Compound **E** by reaction with Compound **D** in the presence of a suitable base such as KOAc in the presence of a suitable catalyst such as $Pd(dppf)Cl_2$ in a suitable solvent such as DMF. Compound **E** can be converted to a compound of Formula I (wherein n is 1) by several approaches. Reaction of Compound **E** with Compound **F** in the presence of a suitable base such as Cs_2CO_3 in the presence of a suitable catalyst such as $Pd(PPh_3)_2Cl_2$ in a suitable solvent such as DME/aq. EtOH gives a compound having Formula I wherein n is 1 directly. Reaction of Compound **E** with Compound **H** in the presence of a suitable base such as Cs_2CO_3 in the presence of a suitable catalyst such as $Pd(PPh_3)_2Cl_2$ in a suitable solvent such as DME/aq. EtOH gives Compound **I**. Halogenation of Compound **I** with a suitable reagent such as NBS in the presence of a free radical initiator such as AIBN in a suitable solvent such as CCl_4 gives Compound **J**. Compound **J** can be converted to Formula I wherein n is 1 by reaction with a suitable nucleophile $Y-H$ in the presence of a suitable base such as DIPEA in a suitable solvent such as ACN.

General Scheme 2



Compound **K** (prepared in a manner similar to that described in General Scheme 1) can be converted to Compound **L** by reaction with a suitable reagent such as oxalyl chloride in a suitable solvent such as THF. Reaction of Compound **L** with Compound **M** (wherein R^x is, e.g., hydrogen or alkyl) in the presence of a suitable catalyst such as $Pd(dppf)Cl_2$ in a suitable solvent such as toluene gives Compound **N**. Compound **N** can be converted to a compound of Formula I (wherein n is 1 and G is dihydroxyalkyl) by reaction with a suitable reagent such as OsO_4 in a suitable solvent such as aq. acetone, or with a suitable chiral reagent such as AD-mix alpha or beta in a suitable solvent such as aq. t-BuOH.

General Scheme 3



Compound **A** can be reacted with Compound **P** to give Compound **Q** by reaction in the presence of a suitable base such as NaH in a suitable solvent such as DMF. Hydrolysis of

the ketal in Compound **Q** to give Compound **R** is accomplished by treatment with a suitable acid such as aq. HCl. Compound **R** can be converted to Compound **S** by treatment with a suitable base such as LiHMDS and a suitable sulfonyl halide in a suitable solvent such as THF. Compound **S** can be converted to Compound **T** by reaction with Compound **D** in the presence of a suitable base such as KOAc and a suitable catalyst such as Pd(dppf)Cl₂ in a suitable solvent such as dioxane. Compound **T** can be converted to a compound of Formula 1 (wherein n is 1 and A² is cycloalkyl) by reaction with Compound **F** in the presence of a suitable base such as KOAc in the presence of a suitable catalyst such as Pd(dppf)Cl₂ in a suitable solvent such as aq. dioxane.

Testing of Compounds

Compounds of the Disclosure were assessed by sodium mobilization and/or electrophysiological assays for sodium channel blocker activity. One aspect of the present disclosure is based on the use of the Compounds of the Disclosure as sodium channel blockers. Based upon this property, Compounds of the Disclosure are considered useful in treating a condition or disorder responsive to the blockade of sodium ion channels, *e.g.*, stroke, neuronal damage resulting from head trauma, epilepsy, seizures, general epilepsy with febrile seizures, severe myoclonic epilepsy in infancy, neuronal loss following global and focal ischemia, migraine, familial primary erythromelalgia, paroxysmal extreme pain disorder, cerebellar atrophy, ataxia, dystonia, tremor, mental retardation, autism, a neurodegenerative disorder (*e.g.*, Alzheimer's disease, amyotrophic lateral sclerosis (ALS), or Parkinson's disease), manic depression, tinnitus, myotonia, a movement disorder, cardiac arrhythmia, or providing local anesthesia. Compounds of the Disclosure are also expected to be effective in treating pain, *e.g.*, acute pain, chronic pain, which includes but is not limited to, neuropathic pain, postoperative pain, and inflammatory pain, or surgical pain.

More specifically, the present disclosure is directed to Compounds of the Disclosure that are blockers of sodium channels. According to the present disclosure, those compounds having useful sodium channel blocking properties exhibit an IC₅₀ for Na_v1.1, Na_v1.2, Na_v1.3, Na_v1.4, Na_v1.5, Na_v1.6, Na_v1.7, Na_v1.8, and/or Na_v1.9 of about 100 μM or less, *e.g.*, about 50 μM or less, about 25 μM or less, about 10 μM or less, about 5 μM or less, or about 1 μM or less, in sodium mobilization and/or electrophysiological assays. In certain embodiments, Compounds of the Disclosure exhibit an IC₅₀ for Na_v1.7 of 100 μM or less, about 50 μM or

less, about 25 μM or less, about 10 μM or less, about 5 μM or less, about 1 μM or less, about 0.5 μM or less, about 0.1 μM or less, about 0.05 μM or less, or about 0.01 μM or less. Compounds of the Disclosure can be tested for their Na^+ channel blocking activity using methods known in the art and by the following fluorescence imaging and electrophysiological *in vitro* assays and/or *in vivo* assays.

In one embodiment, Compounds of the Disclosure demonstrate substantially no penetration across the CNS blood-brain barrier in a mammal. Such compounds are referred to as "peripherally restricted" as a means to designate their PNS versus CNS tissue selectivity.

In one embodiment, the PNS:CNS concentration ratio of a peripherally restricted Compound of the Disclosure is about 5:1, about 10:1, about 20:1, about 30:1; about 50:1; about 100:1, about 250:1, about 500:1, about 1000:1, about 5,000:1, about 10,000:1, or more. Compounds of the Disclosure can be tested for their ability to penetrate the central nervous system using *in vitro* and *in vivo* methods known in the art.

***In Vitro* Assay Protocols**

FLIPR[®] Assays

Recombinant $\text{Na}_v1.7$ Cell Line: *In vitro* assays were performed in a recombinant cell line expressing cDNA encoding the alpha subunit ($\text{Na}_v1.7$, SCN9a, PN1, NE) of human $\text{Na}_v1.7$ (Accession No. NM_002977). The cell line was provided by investigators at Yale University (Cummins *et al*, *J. Neurosci.* 18(23): 9607-9619 (1998)). For dominant selection of the $\text{Na}_v1.7$ -expressing clones, the expression plasmid co-expressed the neomycin resistance gene. The cell line was constructed in the human embryonic kidney cell line, HEK293, under the influence of the CMV major late promoter, and stable clones were selected using limiting dilution cloning and antibiotic selection using the neomycin analogue, G418. Recombinant beta and gamma subunits were not introduced into this cell line. Additional cell lines expressing recombinant $\text{Na}_v1.7$ cloned from other species can also be used, alone or in combination with various beta subunits, gamma subunits or chaperones.

Non-recombinant Cell Lines Expressing Native $\text{Na}_v1.7$: Alternatively, *in vitro* assays can be performed in a cell line expressing native, non-recombinant $\text{Na}_v1.7$, such as the ND7 mouse neuroblastoma X rat dorsal root ganglion (DRG) hybrid cell line ND7/23, available from the European Cell Culture Collection (Cat. No. 92090903, Salisbury, Wiltshire, United

Kingdom). The assays can also be performed in other cell lines expressing native, non-recombinant $\text{Na}_v1.7$, from various species, or in cultures of fresh or preserved sensory neurons, such as dorsal root ganglion (DRG) cells, isolated from various species. Primary screens or counter-screens of other voltage-gated sodium channels can also be performed, and the cell lines can be constructed using methods known in the art, purchased from collaborators or commercial establishments, and they can express either recombinant or native channels. The primary counter-screen is for one of the central neuronal sodium channels, $\text{Na}_v1.2$ (rBIIa), expressed in HEK293 host cells (Ilyin *et al.*, *Br. J. Pharmacol.* 144:801-812 (2005)). Pharmacological profiling for these counter-screens is carried out under conditions similar to the primary or alternative $\text{Na}_v1.7$ assays described below.

Cell maintenance: Unless otherwise noted, cell culture reagents were purchased from Mediatech of Herndon, VA. The recombinant $\text{Na}_v1.7$ /HEK293 cells were routinely cultured in growth medium consisting of Dulbecco's minimum essential medium containing 10% fetal bovine serum (FBS, Hyclone, Thermo Fisher Scientific, Logan, UT), 100 U/mL penicillin, 100 $\mu\text{g/mL}$ streptomycin, 2-4 mM L-glutamine, and 500 mg/mL G418. For natural, non-recombinant cell lines, the selective antibiotic was omitted, and additional media formulations can be applied as needed.

Assay Buffer: The assay buffer was formulated by removing 120 mL from a 1 L bottle of fresh, sterile dH_2O (Mediatech, Herndon, VA) and adding 100 mL of 10X HBSS that does not contain Ca^{++} or Mg^{++} (Gibco, Invitrogen, Grand Island, NY) followed by 20 mL of 1.0 M Hepes, pH 7.3 (Fisher Scientific, BP299-100). The final buffer consisted of 20 mM Hepes, pH 7.3, 1.261 mM CaCl_2 , 0.493 mM MgCl_2 , 0.407 mM $\text{Mg}(\text{SO})_4$, 5.33 mM KCl, 0.441 mM KH_2PO_4 , 137 mM NaCl, 0.336 mM Na_2HPO_4 and 0.556 mM D-glucose (Hanks *et al.*, *Proc. Soc. Exp. Biol. Med.* 71:196 (1949)), and the simple formulation was typically the basic buffer throughout the assay (*i.e.*, all wash and addition steps).

CoroNaTM Green AM Na^+ Dye for Primary Fluorescence Assay: The fluorescence indicator used in the primary fluorescence assay was the cell permeant version of CoroNaTM Green (Invitrogen, Molecular Probes, Eugene, OR), a dye that emits light in the fluorescence range (Harootunian *et al.*, *J. Biol. Chem.* 264(32):19458-19467 (1989)). The intensity of this emission, but not the wavelength range, is increased when the dye is exposed to Na^+ ions, which it can bind with partial selectivity. Cells expressing $\text{Na}_v1.7$ or other sodium channels were loaded with the CoroNaTM Green dye immediately in advance of the fluorescence assay,

and then, after agonist stimulation, the mobilization of Na⁺ ions was detected as the Na⁺ ions flowed from the extracellular fluid into the cytoplasm through the activated sodium channel pores. The dye was stored in the dark as a lyophilized powder, and then an aliquot was dissolved immediately before the cell loading procedure, according to the instructions of the manufacturer, to a stock concentration of 10 mM in DMSO. It was then diluted in the assay buffer to a 4X concentrated working solution, so that the final concentration of dye in the cell loading buffer was 5 μM.

Membrane Potential Dye for Alternative Fluorescence Assays: A fluorescence indicator that can be used in alternative fluorescence assays is the blue version membrane potential dye (MDS, Molecular Devices, Sunnyvale, CA), a dye that detects changes in molecules following a change in membrane potential. An increase in fluorescence is expected if agonist stimulation provokes a change in membrane potential. Cells expressing Na_v1.7 or other sodium channels are incubated with the membrane potential dye 30-60 minutes before the fluorescence assay. In the case of the KCl pre-stimulation version of the assay, the dye and all other components are washed out immediately before the assay, and the dye is then replaced. In the version lacking KCl pre-stimulation, the dye remains on the cells and is not washed out or replaced. The dye is stored in the dark as a lyophilized powder, and then an aliquot dissolved in assay buffer to form a 20X-concentrated stock solution that can be used for several weeks.

Agonists: In the fluorescence assays, two agonists were used in combination, namely 1) veratridine; and 2) the venom from the yellow scorpion, *Leiurus quinquestriatus hebraeus*. Veratridine is an alkaloid small molecule that facilitates the capture of channel openings by inhibiting inactivation, and the scorpion venom is a natural preparation that includes peptide toxins selective for different subsets of voltage-gated sodium channels. These scorpion toxins inhibit the fast inactivation of their cognate target channels. Stock solutions of the agonists were prepared to 40 mM in DMSO (veratridine) and 1 mg/mL in dH₂O (scorpion venom), and then diluted to make a 4X or 2X stock (depending on the particular assay) in assay buffer, the final concentration being 100 μM (veratridine) and 10 μg/mL (scorpion venom). Both of the agonists were purchased from Sigma Aldrich, St. Louis, MO.

Test Compounds: Test compounds were dissolved in DMSO to yield 10 mM stock solutions. The stock solutions were further diluted using DMSO in 1:3 serial dilution steps with 10 points (10,000 μM, 3,333 μM, 1,111 μM, 370 μM, 123 μM, 41 μM, 14 μM, 4.6 μM,

1.5 μM and 0.5 μM). The stock solutions were further diluted in assay buffer (1:125) as 4X stock serial dilutions with a DMSO concentration of 0.8% (final [DMSO], in the assay, from the compounds component = 0.2%), so that the compounds' final concentrations in the assay were 20 μM , 6.7 μM , 2.2 μM , 0.74 μM , 0.25 μM and 0.08 μM , 0.03 μM , 0.01 μM , 0.003 μM and 0.001 μM . If a particular test article appeared to be especially potent, then the concentration curve was adjusted, *e.g.*, to 10-fold lower concentrations, in order to perform the dose-response in a more relevant concentration range. Compound dilutions were added during the dye-loading and pre-stimulation step, and then again during the fluorescence assay, early in the kinetic read. Compound dilutions were added in duplicate rows across the middle 80 wells of the 96-well plate, whereas the fully stimulated and the fully inhibited controls (positive and negative) were located in the top 4 side wells and the bottom 4 side wells, respectively, on the left and right sides of the assay plate.

Data Analysis: The data were analyzed according to methods known to those skilled in the art or using the GraphPad[®] Prism Program, version 4.0 or higher (available from GraphPad Software, San Diego, CA) to determine the IC_{50} value for the test article. At least one standard reference compound was evaluated during each experiment.

FLIPR[®] or FLIPR^{TETRA}[®] sodium dye assay with KCl and test article pre-incubation: Cells were prepared by plating the recombinant HEK293 cells or other host cells expressing either recombinant or non-recombinant, native, $\text{Na}_v1.7$ alpha subunit, alone or in combination with various beta and gamma subunits at a density of ~40,000 cells/well into a 96-well black, clear-bottom, PDL-coated plate. The assay can be adapted to 384-well or 1,536-well format, if desired, using proportionately fewer cells and less media. The plate was then incubated in growth media, with or without selective antibiotic, overnight at 37°C at 5% CO_2 , 95% humidity, in preparation for the assay. For counter-screens of other voltage-gated sodium channels, the procedure was very similar, though optimal densities of cells, media and subsequent assay components can be fine-tuned for the particular cell line or isoform.

The next day, at the start of the assay, the media was flicked from the cells and the wells were washed once with 50 μl /well assay buffer (1X Hank's balanced salt solution without sodium bicarbonate or phenol red, 20 mM Hepes, pH 7.3) and then pre-incubated with the test articles, CoroNaTM Green AM sodium dye (for cell loading) and KCl for repolarization and synchronization of the channels in the entire population of cells. For this dye-loading and pre-stimulation step, the components were added as follows, immediately

after the wash step: 1) first, the compound dilutions and controls were added as 4X concentrates in assay buffer at 50 μ L/well; 2) CoroNaTM Green AM dye was diluted from the stock solution to 20 μ M in assay buffer (4X concentrate) and added to the plate at 50 μ L/well; and 3) finally, a solution of 180 mM KCl (2X) was prepared by diluting a 2M stock solution into assay buffer and the solution was added to the cells at 100 μ L/well. The cells were incubated at 25°C in the dark for 30 min. before their fluorescence was measured.

The plates containing dye-loaded cells were then flicked to remove the pre-incubation components and washed once with 100 μ L/well assay buffer. A 100 μ L/well aliquot of assay buffer was added back to the plate, and the real-time assay was commenced. The fluorescence of cells was measured using a fluorescence plate reader (FLIPR^{TETRA}[®] or FLIPR384[®], MDS, Molecular Devices, Sunnyvale, CA) Samples were excited by either a laser or a PMT light source (Excitation wavelength = 470-495 nm) and the emissions are filtered (Emission wavelength = 515-575 nm). The additions of compound and the channel activators in this cell-based, medium-to-high throughput assay were performed on the fluorescence plate reader and the results (expressed as relative fluorescence units) were captured by means of camera shots every 1-3 sec., then displayed in real-time and stored. Generally, there was a 15 sec. base line, with camera shots taken every 1.5 sec., then the test compounds were added, then another 120 sec. baseline was conducted, with camera shots taken every 3 sec.; and finally, the agonist solution (containing veratridine and scorpion venom) was added. The amplitude of fluorescence increase, resulting from the binding of Na⁺ ions to the CoroNaTM Green dye, was captured for ~180 sec. thereafter. Results were expressed in relative fluorescence units (RFU) and can be determined by using the maximum signal during the latter part of the stimulation; or the maximum minus the minimum during the whole agonist stimulation period; or by taking the area under the curve for the whole stimulation period.

The assay can be performed as a screening assay as well with the test articles present in standard amounts (*e.g.*, 10 μ M) in only one or two wells of a multi-well plate during the primary screen. Hits in this screen were typically profiled more exhaustively (multiple times), subjected to dose-response or competition assays and tested in counter screens against other voltage-gated sodium channels or other biologically relevant target molecules.

FLIPR[®] or FLIPR^{TETRA}[®] membrane potential assay with KCl and test article pre-incubation: Cells are prepared by plating the recombinant HEK293 cells or other host cells

expressing either recombinant or non-recombinant, native, Na_v1.7 alpha subunit, alone or in combination with various beta and gamma subunits at a density of ~40,000 cells/well into a 96-well black, clear-bottom, PDL-coated plate. The assay can be adapted to 384-well or 1,536-well format, if desired, using proportionately less cells and media. The plate is then
5 incubated in growth media, with or without selective antibiotic, overnight at 37°C at 5% CO₂, 95% humidity, in preparation for the assay (see, *e.g.*, Benjamin *et. al.*, *J. Biomol. Screen* 10(4):365-373 (2005)). For screens and counter-screens of other voltage-gated sodium channels, the assay protocol is similar, though optimal densities of cells, media and subsequent assay components can be fine-tuned for the particular cell line or sodium channel
10 isoform being tested.

The next day, at the start of the assay, the media is flicked from the cells and the wells are washed once with 50 µL/well assay buffer (1X Hank's balanced salt solution without sodium bicarbonate or phenol red, 20 mM Hepes, pH 7.3) and then pre-incubated with the test articles, the membrane potential dye (for cell loading), and the KCl for re-polarization
15 and synchronization of the channels in the entire population of cells. For this dye-loading and pre-stimulation step, the components are added as follows, immediately after the wash step: 1) first, the compound dilutions and controls are added as 4X concentrates in assay buffer at 50 µL/well; 2) membrane potential dye is diluted from the stock solution in assay buffer (4X concentrate) and added to the plate at 50 µL/well; and 3) finally, a solution of 180
20 mM KCl (2X) is prepared by diluting a 2M stock solution into assay buffer and the solution added to the cells at 100 µL/well. The cells are incubated at 37°C in the dark for 30-60 min. before their fluorescence is measured.

The plates containing dye-loaded cells are then flicked to remove the pre-incubation components and washed once with 50 µL/well assay buffer. A 50 µL/well aliquot of
25 membrane potential dye is added back to the plate, and the real-time assay is commenced. The fluorescence of cells is measured using a fluorescence plate reader (FLIPR^{TETRA}® or FLIPR384®, MDS, Molecular Devices, Sunnyvale, CA). Samples are excited by either a laser or a PMT light source (Excitation wavelength = 510-545 nm) and the emissions are filtered (Emission wavelength = 565-625 nm). The additions of the compounds (first) and
30 then the channel activators (later) in this are performed on the fluorescence plate reader and the results, expressed as relative fluorescence units (RFU), are captured by means of camera shots every 1-3 sec., then displayed in real-time and stored. Generally, there is a 15 sec. base

line, with camera shots taken every 1.5 sec., then the test compounds are added, then another 120 sec. baseline is conducted, with camera shots taken every 3 sec.; and finally, the agonist solution (containing veratridine and scorpion venom) is added. The amplitude of fluorescence increase, resulting from the detection of membrane potential change, is captured for ~120 sec. thereafter. Results are expressed in relative fluorescence units (RFU) and can be determined by using the maximum signal during the latter part of the stimulation; or the maximum minus the minimum during the whole stimulation period; or by taking the area under the curve for the whole stimulation period.

The assay can be performed as a screening assay as well with the test articles present in standard amounts (*e.g.*, 10 μ M) in only one or two wells of a multi-well plate during the primary screen. Hits in this screen are typically profiled more exhaustively (multiple times), subjected to dose-response or competition assays and tested in counter screens against other voltage-gate sodium channels or other biologically relevant target molecules.

FLIPR[®] or FLIPR^{TETRA}[®] sodium dye assay without KCl and test article pre-incubation: Cells are prepared by plating the recombinant HEK293 cells or other host cells expressing either recombinant or non-recombinant, native, Na_v1.7 alpha subunit, alone or in combination with various beta and gamma subunits at a density of ~40,000 cells/well into a 96-well black, clear-bottom, PDL-coated plate. The assay can be adapted to 384-well or 1,536-well format, if desired, using proportionately less cells and media. The plate is then incubated in growth media, with or without selective antibiotic, overnight at 37°C at 5% CO₂, 95% humidity, in preparation for the assay. For counter-screens of other voltage-gated sodium channels, the procedure is very similar, though optimal densities of cells, media and subsequent assay components can be fine-tuned for the particular cell line or isoform.

The next day, at the start of the assay, the media is flicked from the cells and the wells washed once with 50 μ L/well assay buffer (1X Hank's balanced salt solution without sodium bicarbonate or phenol red, 20 mM Hepes, pH 7.3). Membrane potential dye is then added to each well of the 96-well plate (50 μ L/well), from a freshly diluted sample of the stock (now at 4X concentration) in the assay buffer. The cells are incubated at 37°C in the dark for 30-60 min. before their fluorescence is measured.

In this standard membrane potential assay, the 96-well plate containing dye-loaded cells is then loaded directly onto the plate reader without aspirating the dye solution and without any further washing of the cells. The fluorescence of cells is measured using a

fluorescence plate reader (FLIPR^{TETRA}® or FLIPR384®, MDS, Molecular Devices, Sunnyvale, CA). Samples are excited by either a laser or a PMT light source (Excitation wavelength = 510-545 nm) and the emissions are filtered (Emission wavelength = 565-625 nm). The additions of the compounds (first, 50 µL/well from a 4X stock plate) and then the channel activators (later, 100 µL/well from a 2X stock solution) in this kinetic assay are performed on the fluorescence plate reader and the results, expressed as relative fluorescence units (RFU), are captured by means of camera shots every 1-3 sec., then displayed in real-time and stored. Generally, there is a 15 sec. base line, with camera shots taken every 1.5 sec., then the test compounds are added, then another 120 sec. baseline is conducted, with camera shots taken every 3 sec.; and finally, the agonist solution (containing veratridine and scorpion venom) is added. The amplitude of fluorescence increase, resulting from the detection of membrane potential change, is captured for ~120 sec. thereafter. Results are expressed in relative fluorescence units (RFU) and can be determined by using the maximum signal during the latter part of the stimulation; or the maximum minus the minimum during the whole stimulation period; or by taking the area under the curve for the whole stimulation period.

The assay can be performed as a screening assay as well, with the test articles present in standard amounts (*e.g.* 10 µM) in only one or two wells of a multi-well plate during the primary screen. Hits in this screen are typically profiled more exhaustively (multiple times), subjected to dose-response or competition assays and tested in counter screens against other voltage-gate sodium channels or other biologically relevant target molecules.

Electrophysiology Assay

Cells Manual Electrophysiology: The hNa_v1.7 expressing HEK-293 cells are plated on 35 mm culture dishes pre-coated with poly-D-lysine in standard DMEM culture media (Mediatech, Inc., Herndon, VA) and incubated in a 5% CO₂ incubator at 37 °C. Cultured cells are used approximately 12 - 48 hours after plating.

Cells Automated Electrophysiology: The hNa_v1.7 expressing HEK-293 cells are plated on tissue culture flasks in standard DMEM culture media (Mediatech, Inc.) and incubated in a 5% CO₂ incubator at 37 °C. Cultured cells are used approximately 12 - 48 hours after plating.

Manual Electrophysiology: On the day of experimentation, the 35 mm dish is placed on the stage of an inverted microscope equipped with a perfusion system that continuously perfuses the culture dish with fresh recording media. A gravity driven superfusion system is used to apply test solutions directly to the cell under evaluation. This “shooter” system consists of an array of glass pipettes connected to a motorized horizontal translator. The outlet of the shooter is positioned approximately 100 μm from the cell of interest.

Whole cell currents are recorded using the whole-cell patch clamp configuration using an Axopatch 200B amplifier (Axon Instruments, Foster City CA), 1322A A/D converter (Axon Instruments) and pClamp software (v. 8; Axon Instruments) and stored on a personal computer. Gigaseals are formed and the whole-cell configuration is established in voltage clamp mode, and membrane currents generated by $\text{hNa}_v1.7$ channels are recorded. Borosilicate glass pipettes with resistance values between 1.5 and 2.0 $\text{M}\Omega$ when filled with pipette solution are used and series resistance ($< 5 \text{ M}\Omega$) is compensated by 75 – 80%. Signals are sampled at 50 kHz and low pass filtered at 3 kHz.

Automated Electrophysiology: On the day of experimentation, cells are prepared by removing media and digesting with appropriate enzymes to suspend cells in external solution.

Whole cell currents are recorded using the whole-cell patch clamp configuration using an Patchliner (Nanion Technologies, Munich Germany), EPC 10 quadro amplifiers (HEKA, Bellmore, New York) and PatchControl HT 10905 (Nanion Technologies) and PatchMaster v2x73 software (HEKA) and stored on a personal computer. Gigaseals are formed and the whole-cell configuration is established in voltage clamp mode, and membrane currents generated by $\text{hNa}_v1.7$ are recorded. NPC-16 chips have resistance values between 1.0 and 2.0 $\text{M}\Omega$ when filled with pipette solution and series resistance ($< 5 \text{ M}\Omega$). Signals are sampled at 25 kHz and low pass filtered at 3 kHz.

Voltage protocols Manual Electrophysiology: After establishing the whole-cell configuration in voltage clamp mode, voltage protocols are run to establish the 1) test potential (V_{max}), 2) holding potential (V_h), and 3) the conditioning potential for each cell.

After establishing the whole-cell configuration in voltage clamp mode, a standard I-V protocol is run to determine the potential at which the maximal current (I_{max}) is elicited. This potential is the test potential (V_t). To determine a conditioning potential at which 100% of channels are in the inactivated state, a standard steady-state inactivation (SSIN) protocol is run using a series of fifteen 100 ms-long depolarizing prepulses, incrementing in 10 mV

steps, immediately followed by a 5 ms testing pulse to $V_{\max}$. This protocol also permits determination of the holding potential at which all channels are in the resting state.

For compounds causing significant retardation of recovery from inactivation, an estimate of the affinity for the inactivated state of the channel (K_i) is generated using the following protocol. From the negative, no residual inactivation, holding potential, the cell is depolarized to the conditioning voltage for 2-5 seconds, returned to the negative holding potential for 10 -20 ms to relieve fast inactivation and then depolarized to the test potential for ~15 ms. This voltage protocol is repeated every 10-15 seconds, first to establish a baseline in the absence of the test compound, then in the presence of the test compound.

After a stable baseline is established, the test compound is applied and block of the current elicited by the test pulse assessed. In some cases, multiple cumulative concentrations are applied to identify a concentration that blocked between 40-60 % of this current. Washout of the compound is attempted by superfusing with control solution once steady-state block is observed. An estimate of the K_i is calculated as follows:

$$K_i = [\text{drug}] * \{FR/(1-FR)\}, \quad \text{Eq. 1}$$

where [drug] is the concentration of a drug, and

$$FR = I(\text{after drug})/I(\text{control}), \quad \text{Eq. 2}$$

where I is the peak current amplitude. If multiple concentrations were used, K_i is determined from the fit of a logistic equation to FRs plotted against corresponding drug concentrations.

In the alternative, the voltage clamp protocol to examine $hNa_v1.7$ currents is as follows. After establishing the whole-cell configuration in voltage clamp mode, two voltage protocols were run to establish: 1) the holding potential; and 2) the test potential for each cell.

Resting block: To determine a membrane potential at which the majority of channels are in the resting state, a standard steady-state inactivation (SSIN) protocol is run using 100 ms prepulses x 10 mV depolarizing steps. The holding potential for testing resting block (V_{h1}) is typically 20 mV more hyperpolarized than the first potential where inactivation is observed with the inactivation protocol.

From this holding potential a standard I-V protocol is run to determine the potential at which the maximal current is elicited ($V_{\max}$). This potential is the test potential (V_t).

The compound testing protocol is a series of 10 ms depolarizations from the V_{h1} (determined from the SSIN) to the V_t (determined from the I-V protocol) repeated every 10-

15 seconds. After a stable baseline is established, a high concentration of a test compound (highest concentration solubility permits or that which provides ~50% block) is applied and block of the current assessed. Washout of the compound is attempted by superfusing with control solution once steady-state block was observed. The affinity for the resting state of the channels is calculated as follows:

$$K_r = [\text{drug}] * \{FR/(1-FR)\}, \quad \text{Eq. 3}$$

where [drug] is the concentration of a drug, and

$$FR = I(\text{after drug})/I(\text{control}), \quad \text{Eq. 2}$$

where I is the peak current amplitude and was used for estimating resting block dissociation constant, K_r .

Block of inactivated channels: To assess the block of inactivated channels the holding potential is depolarized such that 20-50% of the current amplitude is reduced when pulsed to the same V_t as above. This is the second holding potential (V_{h2}). The magnitude of this depolarization depends upon the initial current amplitude and the rate of current loss due to slow inactivation. The current reduction is recorded to determine the fraction of available channels at this potential (h).

$$h = I @ V_{h2} / I_{\max}. \quad \text{Eq. 4}$$

At this membrane voltage a proportion of channels are in the inactivated state, and thus inhibition by a blocker includes interaction with both resting and inactivated channels.

To determine the potency of the test compound on inactivated channels, a series of currents are elicited by 10 ms voltage steps from V_{h2} to V_t every 10-15 seconds. After establishing a stable baseline, the low concentration of the compound is applied. In some cases, multiple cumulative concentrations will have to be applied to identify a concentration that blocks between 40-60 % of the current. Washout is attempted to re-establish baseline.

Fractional responses are measured with respect to a projected baseline to determine K_{app} .

$$K_{app} = [\text{drug}] * \{FR/(1-FR)\}, \quad \text{Eq. 5}$$

where [drug] is the concentration of a drug.

This K_{app} value, along with the calculated K_r and h values, are used to calculate the affinity of the compound for the inactivated channels (K_i) using the following equation:

$$K_i = (1-h) / ((1/K_{app}) - (h/K_r)). \quad \text{Eq. 6}$$

Voltage protocols Automated Electrophysiology: Similar voltage protocols are used as described above, however the test potential (V_t) is set to a predetermined voltage. K_{app} is determined as described above.

Solutions and chemicals: For electrophysiological recordings the external solution is either standard, HBSS supplemented with 10 mM HEPES (pH adjusted to 7.34 with NaOH and the osmolarity adjusted to 320) or Tyrodes salt solution (Sigma, USA) supplemented with 10 mM HEPES (pH adjusted to 7.4 with NaOH; osmolarity = 320). The internal pipette solution contains (in mM): NaCl (10), CsF (140), CaCl₂ (1), MgCl₂ (5), EGTA (11), HEPES (10; pH 7.4, 305 mOsm). Compounds are prepared first as series of stock solutions in DMSO and then dissolved in external solution; DMSO content in final dilutions did not exceed 0.3%. At this concentration, DMSO does not affect sodium currents. Vehicle solution used to establish base line also contains 0.3% DMSO.

Data analysis Manual Electrophysiology: Data is analyzed off-line using Clampfit software (pClamp, v.8; Axon Instruments) and graphed using GraphPad Prism (v. 4.0) software.

Data analysis Automated Electrophysiology: Data is analyzed off-line using Igor Pro (v 6.2.2.2; Wave Metrics, Inc., Lake Oswego, OR) and Microsoft XL (Microsoft Office 2010, v14x, Microsoft, Renton WA).

20 ***In Vivo* Assay for Pain**

Compounds of the Disclosure can be tested for their antinociceptive activity in the formalin model as described in Hunskaar *et al.*, *J. Neurosci. Methods* 14: 69-76 (1985). Male Swiss Webster NIH mice (20-30 g; Harlan, San Diego, CA) can be used in all experiments. Food is withdrawn on the day of the experiment. Mice are placed in Plexiglass jars for at least 1 hour to acclimate to the environment. Following the acclimation period, mice are weighed and given either the compound of interest administered i.p. or p.o., or the appropriate volume of vehicle (for example, 10 % Tween-80 or 0.9 % saline, and other pharmaceutically acceptable vehicles) as control. Fifteen minutes after the i.p. dosing, and 30 minutes after the p.o. dosing mice are injected with formalin (20 μ L of 5% formaldehyde solution in saline) into the dorsal surface of the right hind paw. Mice are transferred to the Plexiglass jars and monitored for the amount of time spent licking or biting the injected paw. Periods of licking and biting are recorded in 5-minute intervals for 1 hour after the formalin

injection. All experiments are done in a blinded manner during the light cycle. The early phase of the formalin response is measured as licking / biting between 0-5 minutes, and the late phase is measured from 15-50 minutes. Differences between vehicle and drug treated groups can be analyzed by one-way analysis of variance (ANOVA). A P value <0.05 is considered significant. Compounds are considered to be efficacious for treating acute and chronic pain if they have activity in blocking both the early and second phase of formalin-induced paw-licking activity.

In Vivo Assays for Inflammatory or Neuropathic Pain

Test Animals: Each experiment uses rats weighing between 200-260 g at the start of the experiment. The rats are group-housed and have free access to food and water at all times, except prior to oral administration of a test compound when food is removed for 16 h before dosing. A control group acts as a comparison to rats treated with a Compound of the Disclosure. The control group is administered the carrier as used for the test compound. The volume of carrier administered to the control group is the same as the volume of carrier and test compound administered to the test group.

Inflammatory Pain: To assess the actions of Compounds of the Disclosure on the treatment of inflammatory pain, the Freund's complete adjuvant ("FCA") model of inflammatory pain is used. FCA-induced inflammation of the rat hind paw is associated with the development of persistent inflammatory mechanical and thermal hyperalgesia and provides reliable prediction of the anti-hyperalgesic action of clinically useful analgesic drugs (Bartho *et al.*, *Naunyn-Schmiedeberg's Archives of Pharmacol.* 342:666-670 (1990)). Prior to the injury, the animal is assessed for response to noxious mechanical stimuli by determining the paw withdrawal threshold (PWT), or to noxious thermal stimuli by determining paw withdrawal latency (PWL), as described below (baseline PWT or PWL). Then, the left hind paw of each animal is administered a 50 μ L intraplantar injection of 50% FCA. 24 hour post injection, the PWT or PWL is again assessed (pre-administration PWT or PWL). Rats are then administered a single injection of either a test compound or 30 mg/Kg of a positive control compound (*e.g.*, indomethacin). Responses to noxious mechanical or thermal stimuli are then determined 1, 3, 5 and 24 hours post administration (post-administration PWT or PWL). Percentage reversal of hyperalgesia for each animal is defined as:

$$\% \text{ reversal} = \frac{[(\text{post administration PWT or PWL}) - (\text{pre-administration PWT or PWL})]}{[(\text{baseline PWT or PWL}) - (\text{pre-administration PWT or PWL})]} \times 100$$

5 *Neuropathic Pain:* To assess the actions of the test compounds for the treatment of neuropathic pain the Seltzer model or the Chung model can be used.

In the Seltzer model, the partial sciatic nerve ligation model of neuropathic pain is used to produce neuropathic hyperalgesia in rats (Seltzer *et al.*, *Pain* 43:205-218 (1990)). Partial ligation of the left sciatic nerve is performed under isoflurane/O₂ inhalation
 10 anesthesia. Following induction of anesthesia, the left thigh of the rat is shaved and the sciatic nerve exposed at high thigh level through a small incision and is carefully cleared of surrounding connective tissues at a site near the trochanter just distal to the point at which the posterior biceps semitendinosus nerve branches off of the common sciatic nerve. A 7-0 silk suture is inserted into the nerve with a 3/8 curved, reversed-cutting mini-needle and tightly
 15 ligated so that the dorsal 1/3 to 1/2 of the nerve thickness is held within the ligature. The wound is closed with a single muscle suture (4-0 nylon (Vicryl)) and vetbond tissue glue. Following surgery, the wound area is dusted with antibiotic powder. Sham-treated rats undergo an identical surgical procedure except that the sciatic nerve is not manipulated. Following surgery, animals are weighed and placed on a warm pad until they recover from
 20 anesthesia. Animals are then returned to their home cages until behavioral testing begins. The animals are assessed for response to noxious mechanical stimuli by determining PWT, as described below, prior to surgery (baseline), then immediately prior to and 1, 3, and 5 hours after administration of either drug or vehicle, for the ipsilateral (injured side) rear paw of the animal. Percentage reversal of neuropathic hyperalgesia is defined as:

$$\% \text{ reversal} = \frac{[(\text{post administration PWT}) - (\text{pre-administration PWT})]}{[(\text{baseline PWT}) - (\text{pre-administration PWT})]} \times 100$$

30 In the Chung model, the spinal nerve ligation (SNL) model of neuropathic pain is used to produce mechanical hyperalgesia, thermal hyperalgesia, and tactile allodynia in rats. Surgery is performed under isoflurane/O₂ inhalation anesthesia. Following induction of

anesthesia a 3 cm incision is made and the left paraspinal muscles are separated from the spinous process at the L₄ - S₂ levels. The L₆ transverse process is carefully removed with a pair of small rongeurs to identify visually the L₄ - L₆ spinal nerves. The left L₅ (or L₅ and L₆) spinal nerve(s) is (are) isolated and tightly ligated with silk thread. A complete hemostasis is confirmed and the wound is sutured using non-absorbable sutures, such as nylon sutures or stainless steel staples. Sham-treated rats undergo an identical surgical procedure except that the spinal nerve(s) is (are) not manipulated. Following surgery animals are weighed, administered a subcutaneous (s.c.) injection of saline or ringers lactate, the wound area is dusted with antibiotic powder and they are kept on a warm pad until they recover from the anesthesia. Animals are then returned to their home cages until behavioral testing begins. The animals are assessed for response to noxious mechanical stimuli by determining PWT, as described below, prior to surgery (baseline), then immediately prior to and 1, 3, and 5 hours after being administered a Compound of the Disclosure or vehicle, for the left rear paw of the animal. The animals can also be assessed for response to noxious thermal stimuli or for tactile allodynia, as described below. The Chung model for neuropathic pain is described in Kim *et al.*, *Pain* 50(3):355-363 (1992).

Tactile Allodynia: Sensitivity to non-noxious mechanical stimuli can be measured in animals to assess tactile allodynia. Rats are transferred to an elevated testing cage with a wire mesh floor and allowed to acclimate for five to ten minutes. A series of von Frey monofilaments are applied to the plantar surface of the hindpaw to determine the animal's withdrawal threshold. The first filament used possesses a buckling weight of 9.1 gms (.96 log value) and is applied up to five times to see if it elicits a withdrawal response. If the animal has a withdrawal response, then the next lightest filament in the series would be applied up to five times to determine if it also could elicit a response. This procedure is repeated with subsequent lesser filaments until there is no response and the identity of the lightest filament that elicits a response is recorded. If the animal does not have a withdrawal response from the initial 9.1 gms filament, then subsequent filaments of increased weight are applied until a filament elicits a response and the identity of this filament is recorded. For each animal, three measurements are made at every time point to produce an average withdrawal threshold determination. Tests can be performed prior to, and at 1, 2, 4 and 24 hours post drug administration.

Mechanical Hyperalgesia: Representative Compounds of the Disclosure can be tested in the SNL-induced mechanical hyperalgesia model in rats. Sensitivity to noxious mechanical stimuli are measured in animals using the paw pressure test to assess mechanical hyperalgesia. In rats, hind paw withdrawal thresholds ("PWT"), measured in grams, in response to a noxious mechanical stimulus are determined using an analgesymeter (Model 7200, commercially available from Ugo Basile of Italy), as described in Stein (*Biochemistry & Behavior* 31: 451-455 (1988)). The rat's paw is placed on a small platform, and a punctate weight was applied in a graded manner up to a maximum of 250 grams. The endpoint is taken as the weight at which the paw is completely withdrawn. PWT is determined once for each rat at each time point. PWT can be measured only in the injured paw, or in both the injured and non-injured paw. Rats are tested prior to surgery to determine a baseline, or normal, PWT. Rats are tested again 2 to 3 weeks post-surgery, prior to, and at different times after (e.g. 1, 3, 5 and 24 hr) drug administration. An increase in PWT following drug administration indicates that the test compound reduces mechanical hyperalgesia.

***In Vivo* Assay for Anticonvulsant Activity**

Compounds of the Disclosure can be tested for *in vivo* anticonvulsant activity after i.v., p.o., or i.p. injection using any of a number of anticonvulsant tests in mice or rats, including the maximum electroshock seizure test (MES). Maximum electroshock seizures are induced in male NSA mice weighing between 15-20 g and in male Sprague-Dawley rats weighing between 200-225 g by application of current (for mice: 50 mA, 60 pulses/sec, 0.8 msec pulse width, 1 sec duration, D.C.; for rats: 99 mA, 125 pulses/sec, 0.8 msec pulse width, 2 sec duration, D.C.) using a Ugo Basile ECT device (Model 7801). Mice are restrained by gripping the loose skin on their dorsal surface and saline-coated corneal electrodes are held lightly against the two corneae. Rats are allowed free movement on the bench top and ear-clip electrodes are used. Current is applied and animals are observed for a period of up to 30 seconds for the occurrence of a tonic hindlimb extensor response. A tonic seizure is defined as a hindlimb extension in excess of 90 degrees from the plane of the body. Results can be treated in a quantal manner.

Pharmaceutical Compositions

Compounds of the Disclosure can be administered to a mammal in the form of a raw chemical without any other components present. Compounds of the Disclosure can also be administered to a mammal as part of a pharmaceutical composition containing the compound
5 combined with a suitable pharmaceutically acceptable carrier. Such a carrier can be selected from pharmaceutically acceptable excipients and auxiliaries.

Pharmaceutical compositions within the scope of the present disclosure include all compositions where a Compound of the Disclosure is combined with one or more pharmaceutically acceptable carriers. In one embodiment, the Compound of the Disclosure is
10 present in the composition in an amount that is effective to achieve its intended therapeutic purpose. While individual needs may vary, a determination of optimal ranges of effective amounts of each compound is within the skill of the art. Typically, a Compound of the Disclosure can be administered to a mammal, *e.g.*, a human, orally at a dose of from about 0.0025 to about 1500 mg per kg body weight of the mammal, or an equivalent amount of a
15 pharmaceutically acceptable salt or solvate thereof, per day to treat the particular disorder. A useful oral dose of a Compound of the Disclosure administered to a mammal is from about 0.0025 to about 50 mg per kg body weight of the mammal, or an equivalent amount of the pharmaceutically acceptable salt or solvate thereof. For intramuscular injection, the dose is typically about one-half of the oral dose.

A unit oral dose may comprise from about 0.01 mg to about 1 g of the Compound of the Disclosure, *e.g.*, about 0.01 mg to about 500 mg, about 0.01 mg to about 250 mg, about 0.01 mg to about 100 mg, 0.01 mg to about 50 mg, *e.g.*, about 0.1 mg to about 10 mg, of the compound. The unit dose can be administered one or more times daily, *e.g.*, as one or more tablets or capsules, each containing from about 0.01 mg to about 1 g of the compound, or an
25 equivalent amount of a pharmaceutically acceptable salt or solvate thereof.

A pharmaceutical composition of the present disclosure can be administered to any animal that may experience the beneficial effects of a Compound of the Disclosure. Foremost among such animals are mammals, *e.g.*, humans and companion animals, although the disclosure is not intended to be so limited.

A pharmaceutical composition of the present disclosure can be administered by any
30 means that achieves its intended purpose. For example, administration can be by the oral, parenteral, subcutaneous, intravenous, intramuscular, intraperitoneal, transdermal, intranasal,

transmucosal, rectal, intravaginal or buccal route, or by inhalation. The dosage administered and route of administration will vary, depending upon the circumstances of the particular subject, and taking into account such factors as age, gender, health, and weight of the recipient, condition or disorder to be treated, kind of concurrent treatment, if any, frequency
5 of treatment, and the nature of the effect desired.

In one embodiment, a pharmaceutical composition of the present disclosure can be administered orally and is formulated into tablets, dragees, capsules or an oral liquid preparation. In one embodiment, the oral formulation comprises extruded multiparticulates comprising the Compound of the Disclosure.

10 Alternatively, a pharmaceutical composition of the present disclosure can be administered rectally, and is formulated in suppositories.

Alternatively, a pharmaceutical composition of the present disclosure can be administered by injection.

Alternatively, a pharmaceutical composition of the present disclosure can be
15 administered transdermally.

Alternatively, a pharmaceutical composition of the present disclosure can be administered by inhalation or by intranasal or transmucosal administration.

Alternatively, a pharmaceutical composition of the present disclosure can be administered by the intravaginal route.

20 A pharmaceutical composition of the present disclosure can contain from about 0.01 to 99 percent by weight, and preferably from about 0.25 to 75 percent by weight, of active compound(s).

A method of the present disclosure, such as a method for treating a disorder responsive to the blockade of sodium channels in an animal in need thereof, can further
25 comprise administering a second therapeutic agent to the animal in combination with a Compound of the Disclosure. In one embodiment, the other therapeutic agent is administered in an effective amount.

Effective amounts of the other therapeutic agents are known to those skilled in the art. However, it is well within the skilled artisan's purview to determine the other therapeutic
30 agent's optimal effective-amount range.

Compounds of the Disclosure (*i.e.*, the first therapeutic agent) and the second therapeutic agent can act additively or, in one embodiment, synergistically. Alternatively, the

second therapeutic agent can be used to treat a disorder or condition that is different from the disorder or condition for which the first therapeutic agent is being administered, and which disorder or condition may or may not be a condition or disorder as defined herein. In one embodiment, a Compound of the Disclosure is administered concurrently with a second therapeutic agent; for example, a single composition comprising both an effective amount of a Compound of the Disclosure and an effective amount of the second therapeutic agent can be administered. Accordingly, the present disclosure further provides a pharmaceutical composition comprising a combination of a Compound of the Disclosure, the second therapeutic agent, and a pharmaceutically acceptable carrier. Alternatively, a first pharmaceutical composition comprising an effective amount of a Compound of the Disclosure and a second pharmaceutical composition comprising an effective amount of the second therapeutic agent can be concurrently administered. In another embodiment, an effective amount of a Compound of the Disclosure is administered prior or subsequent to administration of an effective amount of the second therapeutic agent. In this embodiment, the Compound of the Disclosure is administered while the second therapeutic agent exerts its therapeutic effect, or the second therapeutic agent is administered while the Compound of the Disclosure exerts its therapeutic effect for treating a disorder or condition.

The second therapeutic agent can be an opioid agonist, a non-opioid analgesic, a non-steroidal anti-inflammatory agent, an antimigraine agent, a Cox-II inhibitor, a β -adrenergic blocker, an anticonvulsant, an antidepressant, an anticancer agent, an agent for treating addictive disorder, an agent for treating Parkinson's disease and parkinsonism, an agent for treating anxiety, an agent for treating epilepsy, an agent for treating a seizure, an agent for treating a stroke, an agent for treating a pruritic condition, an agent for treating psychosis, an agent for treating ALS, an agent for treating a cognitive disorder, an agent for treating a migraine, an agent for treating vomiting, an agent for treating dyskinesia, or an agent for treating depression, or a mixture thereof.

A pharmaceutical composition of the present disclosure is manufactured in a manner which itself will be known in view of the instant disclosure, for example, by means of conventional mixing, granulating, dragee-making, dissolving, extrusion, or lyophilizing processes. Thus, pharmaceutical compositions for oral use can be obtained by combining the active compound with solid excipients, optionally grinding the resulting mixture and

processing the mixture of granules, after adding suitable auxiliaries, if desired or necessary, to obtain tablets or dragee cores.

Suitable excipients include fillers such as saccharides (for example, lactose, sucrose, mannitol or sorbitol), cellulose preparations, calcium phosphates (for example, tricalcium phosphate or calcium hydrogen phosphate), as well as binders such as starch paste (using, for example, maize starch, wheat starch, rice starch, or potato starch), gelatin, tragacanth, methyl cellulose, hydroxypropylmethylcellulose, sodium carboxymethylcellulose, and/or polyvinyl pyrrolidone. If desired, one or more disintegrating agents can be added, such as the above-mentioned starches and also carboxymethyl-starch, cross-linked polyvinyl pyrrolidone, agar, or alginic acid or a salt thereof, such as sodium alginate.

Auxiliaries are typically flow-regulating agents and lubricants such as, for example, silica, talc, stearic acid or salts thereof (*e.g.*, magnesium stearate or calcium stearate), and polyethylene glycol. Dragee cores are provided with suitable coatings that are resistant to gastric juices. For this purpose, concentrated saccharide solutions can be used, which may optionally contain gum arabic, talc, polyvinyl pyrrolidone, polyethylene glycol and/or titanium dioxide, lacquer solutions and suitable organic solvents or solvent mixtures. In order to produce coatings resistant to gastric juices, solutions of suitable cellulose preparations such as acetylcellulose phthalate or hydroxypropylmethyl-cellulose phthalate can be used. Dye stuffs or pigments can be added to the tablets or dragee coatings, for example, for identification or in order to characterize combinations of active compound doses.

Examples of other pharmaceutical preparations that can be used orally include push-fit capsules made of gelatin, or soft, sealed capsules made of gelatin and a plasticizer such as glycerol or sorbitol. The push-fit capsules can contain a compound in the form of granules, which can be mixed with fillers such as lactose, binders such as starches, and/or lubricants such as talc or magnesium stearate and, optionally, stabilizers, or in the form of extruded multiparticulates. In soft capsules, the active compounds are preferably dissolved or suspended in suitable liquids, such as fatty oils or liquid paraffin. In addition, stabilizers can be added.

Possible pharmaceutical preparations for rectal administration include, for example, suppositories, which consist of a combination of one or more active compounds with a suppository base. Suitable suppository bases include natural and synthetic triglycerides, and

paraffin hydrocarbons, among others. It is also possible to use gelatin rectal capsules consisting of a combination of active compound with a base material such as, for example, a liquid triglyceride, polyethylene glycol, or paraffin hydrocarbon.

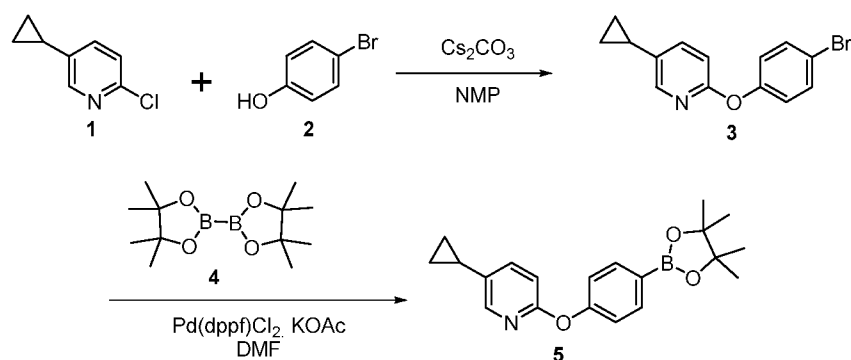
Suitable formulations for parenteral administration include aqueous solutions of the active compound in a water-soluble form such as, for example, a water-soluble salt, alkaline solution, or acidic solution. Alternatively, a suspension of the active compound can be prepared as an oily suspension. Suitable lipophilic solvents or vehicles for such as suspension may include fatty oils (for example, sesame oil), synthetic fatty acid esters (for example, ethyl oleate), triglycerides, or a polyethylene glycol such as polyethylene glycol-400 (PEG-400). An aqueous suspension may contain one or more substances to increase the viscosity of the suspension, including, for example, sodium carboxymethyl cellulose, sorbitol, and/or dextran. The suspension may optionally contain stabilizers.

The following examples are illustrative, but not limiting, of the compounds, compositions, and methods of the present disclosure. Suitable modifications and adaptations of the variety of conditions and parameters normally encountered in clinical therapy and which are obvious to those skilled in the art in view of this disclosure are within the spirit and scope of the disclosure.

EXAMPLES

EXAMPLE 1

Synthesis of 5-cyclopropyl-2-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenoxy)pyridine (Compound **5**)

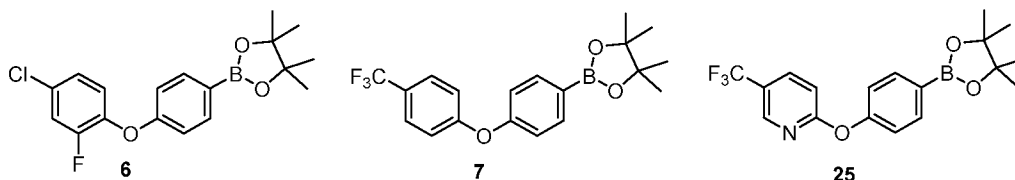


A sealed pressure glass vessel containing a mixture of 2-chloro-5-cyclopropylpyridine (Compound **1**) (10 g, 65 mmol) (J&W Pharmed), 4-bromophenol (Compound **2**) (13.5 g, 78 mmol), and Cs_2CO_3 (25 g, 78 mmol) in NMP (150 mL) was heated at 190 °C for 24 h. After

cooling to RT, the mixture was diluted with brine (1400 mL) and extracted with EtOAc (2 x 500 mL). The combined organic layers were dried over Na₂SO₄, filtered, and concentrated. The residue was purified by flash chromatography (SiO₂, 0-20% EtOAc/hexanes) to give Compound **3** as a white solid (13 g). Yield 68%. LC/MS: m/z = 291 [M+H]⁺ (Calc: 290).

5 A mixture of Compound **3** (402 mg, 1.385 mmol), pinacol diborane (Compound **4**) (387 mg, 1.524 mmol), KOAc (408 mg, 4.16 mmol) and Pd(dppf)Cl₂ (101 mg, 0.11 mmol) in DMF (6 mL) was purged with argon for 2 min. The mixture was heated under argon for 2 h, cooled to RT, adsorbed onto SiO₂ and purified by flash chromatography (SiO₂, 0-40% EtOAc/hexanes) to give Compound **5** as a white solid (266 mg). Yield 57% LC/MS: m/z =
10 338 [M+H]⁺ (Calc: 337).

In a similar manner the following compounds were prepared:



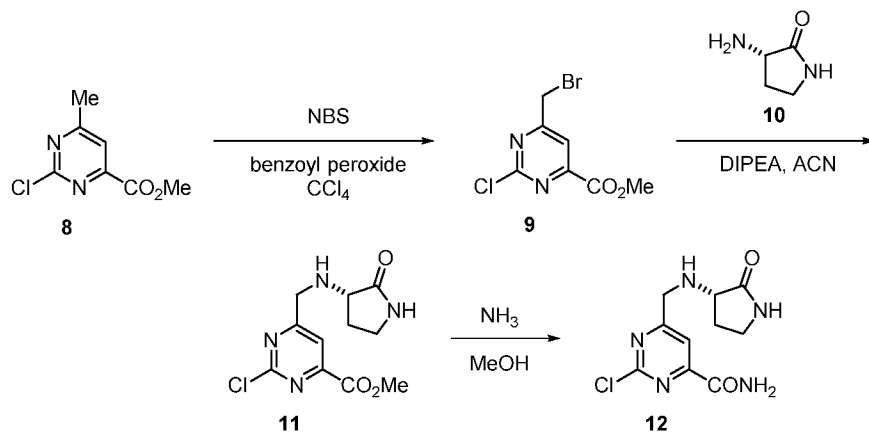
Compound **6**: LC/MS: m/z = 349 [M+H]⁺ (Calc: 348).

15 Compound **7**: LC/MS: m/z = 365 [M+H]⁺ (Calc: 364).

Compound **25**: LC/MS: m/z = 366 [M+H]⁺ (Calc: 365).

EXAMPLE 2

Synthesis of (S)-2-chloro-6-(((2-oxopyrrolidin-3-yl)amino)methyl)pyrimidine-4-carboxamide
(Compound **12**)

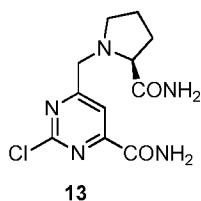


A mixture of Compound **8** (1.536 g, 8.23 mmol) (Sigma-Aldrich), NBS (1.757 g, 9.87 mmol) and benzoyl peroxide (199 mg, 0.823 mmol) in CCl₄ (43 mL) was purged with argon for 2 min. The mixture was heated at 80 °C under argon for 24 h. Additional NBS (1.757 g, 9.87 mmol) and benzoyl peroxide (199 mg, 0.823 mmol) were added and the mixture heated at 80 °C for an additional 24 h. After cooling to RT, the mixture was filtered and the filtrate concentrated. The residue was adsorbed onto SiO₂ and purified by flash chromatography (SiO₂, 0-40% EtOAc/hexanes) to give Compound **9** as a brown liquid (440 mg). Yield 20%. LC/MS: m/z = 266 [M+H]⁺ (Calc: 265).

To a solution of Compound **9** (125 mg, 1.249 mmol) in ACN (6 mL) and DIPEA (121 mg, 1.249 mmol) was added a solution of Compound **10** (331 mg, 1.249 mmol) at RT dropwise. The resulting solution was stirred at RT for 2 h and concentrated to dryness to give crude Compound **11** which was used directly in the next step. LC/MS: m/z = 285 [M+H]⁺ (Calc: 284)

To a 20 mL vial containing the crude Compound **11** from the previous step was added 7N NH₃ in MeOH (12 mL) at RT. The resulting solution was stirred at RT for 1 h and concentrated to dryness to give crude Compound **12** which was used in subsequent steps without purification. LC/MS: m/z = 270 [M+H]⁺ (Calc: 269).

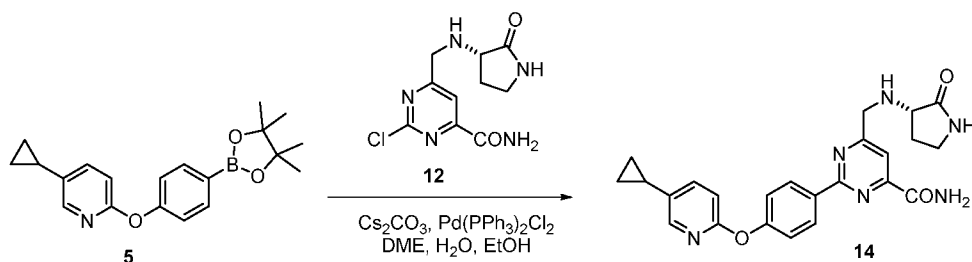
In a similar manner, the Compound **13** was prepared:



Compound **13**: LC/MS: m/z = 284 [M+H]⁺ (Calc: 283).

EXAMPLE 3

Synthesis of (S)-2-(4-((5-cyclopropylpyridin-2-yl)oxy)phenyl)-6-(((2-oxopyrrolidin-3-yl)amino)methyl)pyrimidine-4-carboxamide (Compound **14**)



A mixture of Compound **5** (125 mg, 0.371 mmol), Compound **12** (100 mg, 0.371 mmol), Cs₂CO₃ (242 mg, 0.742 mmol), Pd(PPh₃)₂Cl₂ (20.82 mg, 0.080 mmol), DME (1 mL), water (1 mL) and EtOH (0.5 mL) was purged with argon, sealed and heated at 80 °C for 1 h. After cooling to RT, the mixture was concentrated to dryness and the residue purified by reverse-phase chromatography (C18, 0-60% ACN/H₂O) to give Compound **14** as a white solid (11 mg, yield 6%): ¹H NMR (400 MHz, MeOH-d₄): δ 8.64 (d, J= 8.5 Hz, 2H), 7.91 (dd, J=2.6 Hz, 1H), 7.90 (s, 1H), 7.47 (dd, J=2.6, 8 Hz, 1H), 7.12 (d, J=8.5 Hz, 2H), 6.89 (d, J=8.5 Hz, 1H), 4.77 (d, J=16 Hz, 1H), 4.64 (d, J=16 Hz, 1H), 4.22 (dd, J=9.7, 11 Hz, 1H), 3.39 (m, 2H), 2.60 (m, 1H), 2.21 (m, 1H), 1.87 (m, 1H), 0.94 (m, 2H), 0.63 (m, 2H). LC/MS: *m/z*= 445 [M+H]⁺ (Calc: 444)..

In a similar manner, the following compounds were prepared:

(S)-2-(4-(4-chloro-2-fluorophenoxy)phenyl)-6-(((2-oxopyrrolidin-3-yl)amino)methyl)pyrimidine-4-carboxamide (Compound **15**): ¹H NMR (400 MHz, MeOH-d₄): δ 8.61 (d, J=10 Hz, 2H), 7.89 (s, 1H), 7.33 (dd, J=2.1, 10 Hz, 1H), 7.20 (dd, J=2.1, 10 Hz, 1H), 7.16 (d, J=8.7 Hz, 1H), 7.00 (d, J=8.7 Hz, 2H), 4.74 (d, J=16 Hz, 1H), 4.62 (d, J=16 Hz, 1H), 4.20 (dd, J=8.5, 12 Hz, 1H), 3.37 (m, 2H), 2.59 (m, 1H), 2.19 (m, 1H). LC/MS: *m/z*= 456 [M+H]⁺ (Calc: 455);

(S)-6-((2-carbamoylpyrrolidin-1-yl)methyl)-2-(4-(4-(trifluoromethyl)phenoxy)phenyl)pyrimidine-4-carboxamide (Compound **16**): ¹H NMR (400 MHz, MeOH-d₄): δ 8.61 (d, J= 10 Hz, 2H), 7.89 (s, 1H), 7.63 (d, 2H), 7.13 (m, 4H), 4.80 (d, J=16 Hz, 1H), 4.68 (d, J= 16 Hz, 1H), 4.34 (dd, J= 5.0, 8.5 Hz, 1H), 3.88 (m, 1H), 3.38 (m, 1H), 2.52 (m, 1H), 2.22-2.00 (m, 3H). LC/MS: *m/z*= 486 [M+H]⁺ (Calc: 485);

(S)-6-(((2-oxopyrrolidin-3-yl)amino)methyl)-2-(4-((5-(trifluoromethyl)pyridin-2-yl)oxy)phenyl)pyrimidine-4-carboxamide (Compound **26**): ¹H NMR (400 MHz, MeOH-d₄):

δ 8.66-8.74 (m, 2H), 8.37 (d, $J=0.9$ Hz, 1H), 8.06 (dd, $J=8.7, 2.5$ Hz, 1H), 7.93 (s, 1H), 7.22-7.30 (m, 2H), 7.15 (d, $J=8.6$ Hz, 1H), 4.79 (br. s., 1H), 4.60-4.68 (m, 1H), 4.21 (dd, $J=10.6, 8.6$ Hz, 1H), 3.31-3.46 (m, 2H), 2.60 (s, 1H), 2.12-2.27 (m, 1H). LC/MS: $m/z=473$ $[M+H]^+$ (Calc: 472);

5 6-((3-oxopiperazin-1-yl)methyl)-2-(4-(4-(trifluoromethyl)phenoxy)phenyl)pyrimidine-4-carboxamide (Compound **27**): ^1H NMR (400 MHz, DMSO- d_6): δ 8.70 (d, $J=8.8$ Hz, 2H), 8.64 (s, 1H), 8.01 (s, 1H), 7.95 (s, 1H), 7.84 (s, 1H), 7.79 (d, $J=8.6$ Hz, 2H), 7.27 (dd, $J=8.7, 4.7$ Hz, 4H), 3.87 (s, 2H), 3.21 (br. s., 2H), 3.10 (s, 2H), 2.72 (t, $J=5.4$ Hz, 2H). LC/MS: $m/z=472$ $[M+H]^+$ (Calc: 471);

10 6-((3-oxopiperazin-1-yl)methyl)-2-(4-((5-(trifluoromethyl)pyridin-2-yl)oxy)-phenyl)pyrimidine-4-carboxamide (Compound **28**): ^1H NMR (400 MHz, MeOH- d_4): δ 8.59-8.66 (m, 2H), 8.33-8.41 (m, 1H), 8.05 (dd, $J=8.8, 2.4$ Hz, 1H), 7.96 (s, 1H), 7.21-7.29 (m, 2H), 7.14 (d, $J=8.8$ Hz, 1H), 4.46 (s, 2H), 3.77 (s, 2H), 3.48-3.54 (m, 2H), 3.31-3.39 (m, 2H). LC/MS: $m/z=473$ $[M+H]^+$ (Calc: 472);

15 6-((2,2-dimethyl-3-oxopiperazin-1-yl)methyl)-2-(4-((5-(trifluoromethyl)pyridin-2-yl)oxy)phenyl)pyrimidine-4-carboxamide (Compound **60**): ^1H NMR (400 MHz, DMSO- d_6): δ 8.63 (d, $J=8.8$ Hz, 2H), 8.51-8.59 (m, 2H), 8.22 (dd, $J=8.7, 2.5$ Hz, 1H), 7.97 (s, 1H), 7.94 (s, 1H), 7.62 (s, 1H), 7.30 (d, $J=9.0$ Hz, 2H), 7.26 (d, $J=8.6$ Hz, 1H), 3.83 (s, 2H), 3.04 (br. s., 2H), 2.63 (t, $J=5.2$ Hz, 2H), 1.25 (s, 6H). LC/MS: $m/z=501$ $[M+H]^+$ (Calc: 500);

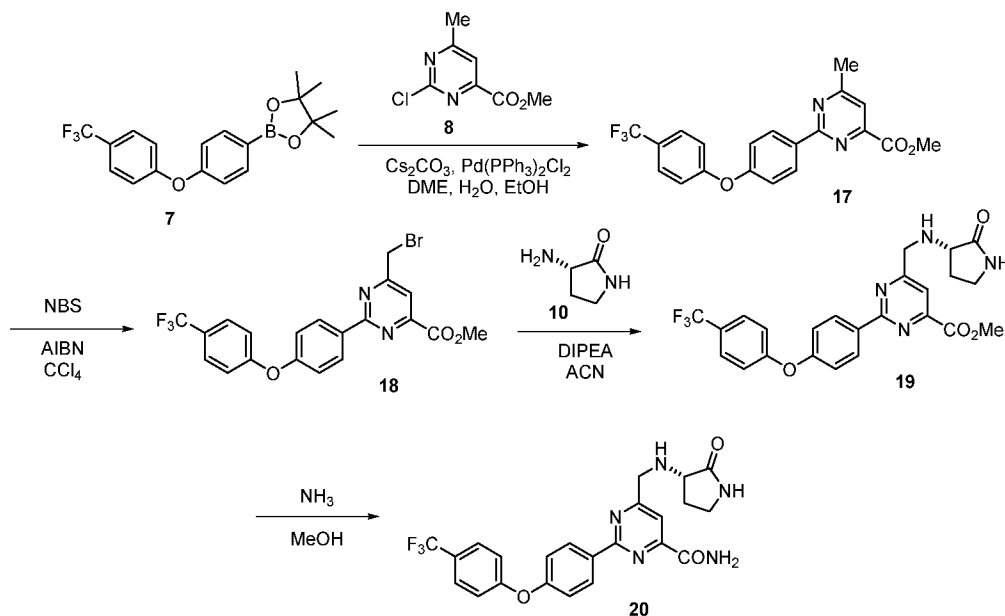
20 6-((2,2-dimethyl-3-oxopiperazin-1-yl)methyl)-2-(4-(4-(trifluoromethyl)phenoxy)phenyl)pyrimidine-4-carboxamide (Compound **61**): ^1H NMR (400 MHz, DMSO- d_6): δ 8.70 (d, $J=8.8$ Hz, 2H), 8.62 (s, 1H), 8.03 (s, 1H), 8.00 (s, 1H), 7.79 (d, $J=8.6$ Hz, 2H), 7.69 (s, 1H), 7.26 (d, $J=8.8$ Hz, 4H), 3.89 (s, 2H), 3.10 (br. s., 2H), 2.69 (dd, $J=9.6, 4.5$ Hz, 3H), 1.32 (s, 6H). LC/MS: $m/z=500$ $[M+H]^+$ (Calc: 499); and

25 6-((3,5-dioxopiperazin-1-yl)methyl)-2-(4-(4-(trifluoromethyl)phenoxy)phenyl)pyrimidine-4-carboxamide (Compound **62**): ^1H NMR (400 MHz, MeOH- d_4): δ 8.56 (d, $J=8.8$ Hz, 2H), 7.94 (s, 1H), 7.61 (d, $J=8.8$ Hz, 2H), 7.07-7.15 (m, 5H), 3.93 (s, 2H), 3.48 (s, 5H). LC/MS: $m/z=486$ $[M+H]^+$ (Calc: 485).

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EXAMPLE 4

Synthesis of (S)-6-(((2-oxopyrrolidin-3-yl)amino)methyl)-2-(4-(4-(trifluoromethyl)phenoxy)phenyl)pyrimidine-4-carboxamide (Compound **20**)



A mixture of Compound **7** (9.76 g, 26.8 mmol), Compound **8** (5 g, 26.8 mmol), Cs₂CO₃ (17.46 g, 53.6 mmol), Pd(PPh₃)₂Cl₂ (1.5 g, 2.14 mmol) in DME (50 mL), H₂O (50 mL) and EtOH (25 mL) was purged with argon and heated at 85 °C for 3h. After cooling to
 5 RT the mixture was diluted with EtOAc (200 mL) and brine (100 mL). 1M aq. HCl (20 mL) was used to adjust the pH to 6. The aq. layer was extracted with additional EtOAc (100 mL) and the combined EtOAc portions were dried over Na₂SO₄, filtered and concentrated. The crude material was dissolved in MeOH, 4N HCl in dioxane (10 mL) was added and the mixture stirred at RT overnight. The mixture was concentrated, adsorbed onto SiO₂ and
 10 purified by flash chromatography (SiO₂, 0-15% EtOAc/hexanes) to give Compound **17** as a white solid (3.2 g, yield 30%): LC/MS: *m/z*= 389 [M+H]⁺ (Calc: 388).

A mixture of Compound **17** (3.6 g, 9.27 mmol), AIBN (316 mg, 1.924 mmol), NBS (1.65 g, 9.27 mmol) in CCl₄ (80 mL) was purged with argon for 1 min, sealed and heated at 80 °C for 4 days. After cooling to RT the mixture was concentrated, adsorbed onto SiO₂ and
 15 purified by flash chromatography (SiO₂, 0-40% EtOAc/hexanes) to give Compound **18** still contaminated with some of Compound **17**. This material was used in the next step without further purification. Compound **18**: LC/MS: *m/z*= 468 [M+H]⁺ (Calc: 467).

A mixture of Compound **18** (78 mg, 0.167 mmol), DIPEA (29 µL, 0.167 mmol) and Compound **10** (16.71 mg, 0.167 mmol) in ACN (1.5 mL) was shaken at RT for 2 h. The
 20 mixture was adsorbed onto SiO₂ and purified by flash chromatography (SiO₂, 0-20% MeOH/DCM) to give Compound **19** as brown solid (35 mg, yield 43%): ¹H NMR (400

MHz, MeOH- d_4): δ 8.52 (d, $J=10$ Hz, 2H), 7.86 (s, 1H), 7.60 (d, $J=10$ Hz, 2H), 7.11 (d, $J=8$ Hz, 2H), 7.07 (d, $J=10$ Hz, 2H), 4.08 (s, 2H), 3.94 (s, 3H), 3.48 (dd, $J=8, 9$ Hz, 1H), 3.30 (dt, $J=2.2, 10$ Hz, 1H), 3.22 (m, 2H), 2.38 (m, 1H), 1.90 (m, 1H). LC/MS: $m/z=487$ [M+H] $^+$ (Calc: 486).

- 5 A solution of Compound **19** (35 mg, 0.072 mmol) in 7N NH_3 in MeOH (2 mL) was shaken at RT for 3 h. After concentration the residue was adsorbed onto SiO_2 and purified by flash chromatography (SiO_2 , 0-80% MeOH/DCM) to give Compound **20** as white solid (15 mg, Yield 44%): 1H NMR (400 MHz, MeOH- d_4): δ 8.72 (d, $J=10$ Hz, 2H), 8.00 (s, 1H), 7.73 (d, $J=10$ Hz, 2H), 7.24 (d, $J=10$ Hz, 2H), 7.21 (m, 2H), 4.20 (s, 2H), 3.58 (dd, $J=8.2, 9.3$ Hz, 1H), 3.41 (dt, $J=2.2, 10$ Hz, 1H), 3.33 (m, 1H), 2.49 (m, 1H), 2.01 (m, 1H). LC/MS: $m/z=472$ [M+H] $^+$ (Calc: 471).

In a similar manner, the following compounds were prepared:

- (S)-6-(((1-amino-1-oxopropan-2-yl)amino)methyl)-2-(4-(4-(trifluoromethyl) phenoxy)phenyl)pyrimidine-4-carboxamide (Compound **21**): 1H NMR (400 MHz, MeOH- d_4): δ 8.69 (d, $J=10$ Hz, 2H), 8.02 (s, 1H), 7.73 (d, $J=10$ Hz, 2H), 7.22 (m, 4H), 4.07 (d, $J=16$ Hz, 1H), 3.99 (d, $J=16$ Hz, 1H), 3.37 (q, $J=7.1$ Hz, 1H), 1.39 (d, $J=7.1$ Hz, 3H). LC/MS: $m/z=460$ [M+H] $^+$ (Calc: 459);

- (S)-6-(((1-amino-3-methyl-1-oxobutan-2-yl)amino)methyl)-2-(4-(4-(trifluoromethyl) phenoxy)phenyl)pyrimidine-4-carboxamide (Compound **22**): 1H NMR (400 MHz, MeOH- d_4): δ 8.63 (d, $J=10$ Hz, 2H), 7.92 (s, 1H), 7.63 (d, $J=10$ Hz, 2H), 7.14 (m, 4H), 4.54 (d, $J=16$ Hz, 1H), 4.42 (d, $J=16$ Hz, 1H), 3.81 (d, $J=5.5$ Hz, 1H), 2.27 (m, 1H), 1.09 (d, $J=7.7$ Hz, 3H), 1.05 (d, $J=7.7$ Hz, 3H). LC/MS: $m/z=488$ [M+H] $^+$ (Calc: 487);

- (S)-6-(((1-amino-3-hydroxy-1-oxopropan-2-yl)amino)methyl)-2-(4-(4-(trifluoromethyl)phenoxy)phenyl)pyrimidine-4-carboxamide (Compound **23**): 1H NMR (400 MHz, MeOH- d_4): δ 8.66 (d, $J=10$ Hz, 2H), 7.90 (s, 1H), 7.63 (d, $J=10$ Hz, 2H), 7.13 (m, 4H), 4.59 (s, 2H), 4.15 (dd, $J=3.9, 6.0$ Hz, 1H), 4.05 (dd, $J=3.9, 6.0$ Hz, 1H), 4.05 (dd, $J=3.9, 12$ Hz, 1H), 3.94 (dd, $J=6.4, 12$ Hz, 1H). LC/MS: $m/z=476$ [M+H] $^+$ (Calc: 475); and

- 6-(((2S,4R)-2-carbamoyl-4-hydroxypyrrolidin-1-yl)methyl)-2-(4-(4-(trifluoromethyl)phenoxy)phenyl)pyrimidine-4-carboxamide (Compound **24**): 1H NMR (400 MHz, MeOH- d_4): δ 8.63 (d, $J=10$ Hz, 2H), 7.91 (s, 1H), 7.63 (d, $J=10$ Hz, 2H), 7.13 (m, 4H),

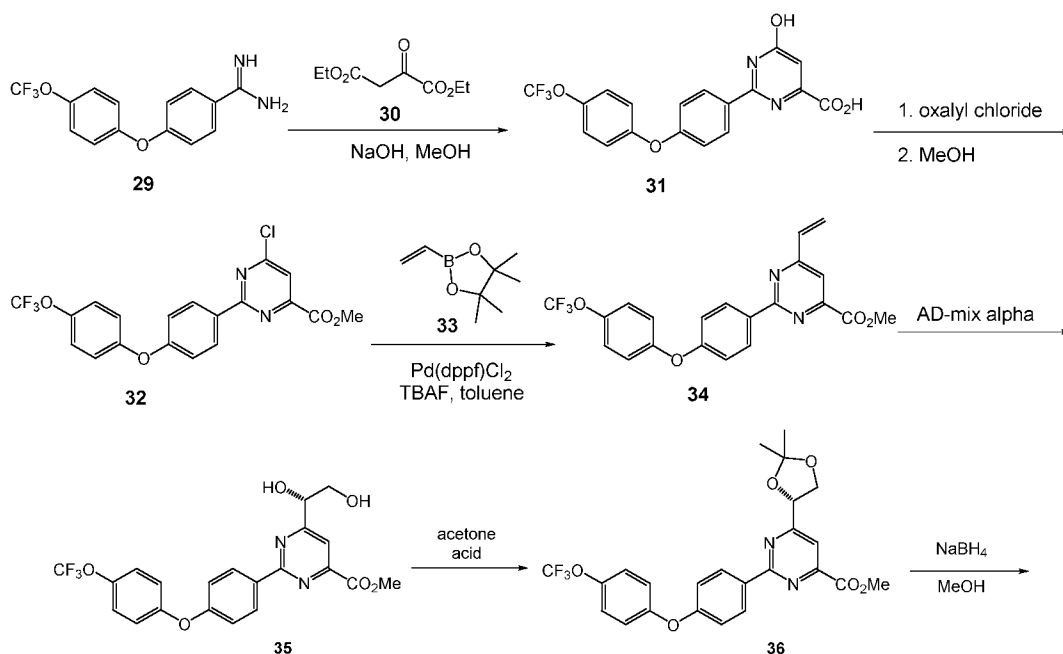
4.96 (brs, 1H), 4.71 (brs, 1H), 4.57 (bs, 1H), 4.48 (brs, 1H), 3.85 (m, 1H), 3.38 (m, 1H), 2.50 (m, 1H), 2.19 (m, 1H). LC/MS: m/z = 502 $[M+H]^+$ (Calc: 501)

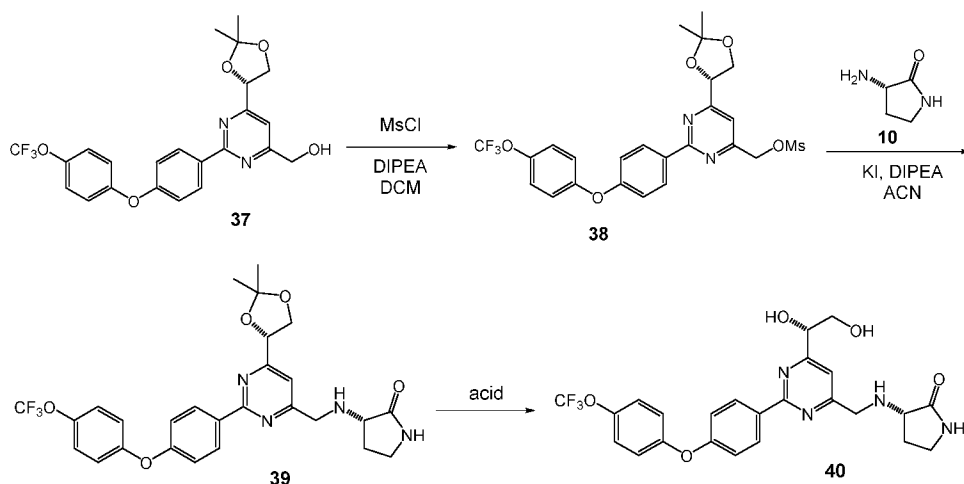
6-(((2*S*,3*R*)-2-carbamoyl-3-hydroxypyrrolidin-1-yl)methyl)-2-(4-(4-(trifluoromethyl)phenoxy)phenyl)pyrimidine-4-carboxamide (Compound **65**): ^1H NMR (Chloroform-*d*): δ 8.38 (d, J =8.9 Hz, 2H), 7.94 (s, 1H), 7.83 (br. s., 1H), 7.72 (br. s., 1H), 7.57 (d, J =8.6 Hz, 2H), 7.05-7.13 (m, 4H), 5.72 (br. s., 1H), 5.55 (br. s., 1H), 4.60 (dd, J =6.9, 3.5 Hz, 1H), 4.09 (d, J =15.0 Hz, 1H), 3.79 (d, J =15.0 Hz, 1H), 3.49 (d, J =7.3 Hz, 1H), 3.20 (ddd, J =9.8, 7.1, 3.9 Hz, 1H), 2.72 (d, J =3.4 Hz, 1H), 2.50 (td, J =9.2, 7.1 Hz, 1H), 2.21 (td, J =6.5, 3.8 Hz, 1H), 1.74-1.91 (m, 1H). LC/MS: m/z = 502 $[M+H]^+$ (Calc: 501).

6-(((2*S*,3*R*)-1-amino-3-hydroxy-1-oxobutan-2-yl)amino)methyl)-2-(4-(4-(trifluoromethyl)phenoxy)phenyl)pyrimidine-4-carboxamide (Compound **66**): ^1H NMR (400 MHz, MeOD): δ 8.58 (d, J =8.9 Hz, 2H), 7.87-7.97 (m, 1H), 7.61 (d, J =8.6 Hz, 2H), 7.01-7.16 (m, 5H), 3.85-4.05 (m, 3H), 3.82 (t, J =6.3 Hz, 1H), 2.98 (d, J =6.3 Hz, 1H), 1.16 (d, J =6.4 Hz, 4H); LC/MS: m/z = 490 $[M+H]^+$ (Calc: 491).

EXAMPLE 5

Synthesis of (S)-3-(((6-((S)-1,2-dihydroxyethyl)-2-(4-(4-(trifluoromethoxy)phenoxy)phenyl)pyrimidin-4-yl)methyl)amino)pyrrolidin-2-one (Compound **40**)





Compound **30** (18.95 g, 90 mmol) and NaOH (4.33 g, 108 mmol) were dissolved in a mixture of water (200 mL) and EtOH (30 mL). A slurry of Compound **29** (30 g, 90 mmol) (prepared as in U.S. Patent 7,229,993) in a mixture of water (90 mL) and EtOH (20 mL) was added in one portion. The mixture was stirred at RT and the pH maintained at *ca* 11.5 by the addition of 2 M aq. NaOH. The mixture was then heated at 70 °C for 4 h. After the mixture was cooled to RT, i-PrOAc (300 mL) and water (50 mL) were added. The aqueous layer was separated and washed with i-PrOAc. The aqueous layer (pH 10.8) was added into a solution of conc. HCl (39 mL) and water (117 mL) at RT to pH 1.7 over 30 min with vigorous stirring. Additional conc. HCl was added as needed to adjust the pH to 1.5. The mixture was stirred at RT for 1 h and the resulting solids were filtered and washed with water (300 mL). The material obtained was dried in vacuum at 40-50 °C to give 26.9 g (76%) of Compound **31** as a tan solid: LC/MS: m/z = 393 [M+H]⁺ (Calc: 392).

To a suspension of Compound **31** (10 g, 25.5 mmol) in THF (60 mL) and DMF (0.19 mL) at 0 °C was added oxalyl chloride (11.3 g, 89 mmol) dropwise. After the addition was complete, the mixture was stirred at 0 °C for 15 min and at RT for 3 h. The reaction was cooled back to 0 °C and MeOH (20 mL) was added slowly. After the addition was complete, the mixture was stirred at RT for 30 min. The volatiles were removed in vacuum to give 10.0 g (92%) of Compound **32** as a light brown solid: LC/MS: m/z = 425 [M+H]⁺ (Calc: 424).

A mixture of Compound **32** (10.0 g, 23.54 mmol), TBAF (18.5 g, 70.6 mmol), Pd(dppf)Cl₂ (1.71 g, 1.883 mmol) and Compound **33** (4.35 g, 28.3 mmol) in toluene (100 mL) was heated for 1.5 h. The mixture was concentrated and the residue purified by flash chromatography (SiO₂, 0-30% EtOAc/hexanes) to give 8.7 g (88%) of Compound **34**: LC/MS: m/z = 417 [M+H]⁺ (Calc: 416).

AD-mix alpha (25.0 g, 1.3 g/mmol of vinyl substrate) (Sigma-Aldrich) was added to a suspension of Compound **34** (8.0 g, 19.21 mmol) in a mixture of t-BuOH (100 mL) and water (100 mL) at 0 °C. The mixture was vigorously stirred at RT for 12 h. After cooling to 0 °C, solid Na₂S₂O₃ was added to the mixture until gas evolution ceased and the color turned from brownish yellow to light grey (pH=7). The mixture was poured to a separatory funnel, the flask was rinsed with EtOAc (200 mL) and poured into the funnel. The layers were separated without shaking. The organic layer was dried over Na₂SO₄, filtered and concentrated. The residue was purified by flash chromatography (SiO₂, 0-100% MeOH/DCM) to give 2.2 g (25%) of Compound **35** as a viscous liquid: LC/MS: m/z = 451 [M+H]⁺ (Calc: 450).

To a solution of Compound **35** (2.2 g, 4.88 mmol) in acetone (200 mL) was added 4 N HCl in dioxane (1 mL) at RT. The resulting mixture was stirred at RT for 12 h. After concentration, the residue was purified by flash chromatography (SiO₂, 0-20% EtOAc/hexanes) to give 1.00 g (42%) of Compound **36**: LC/MS: m/z = 491 [M+H]⁺ (Calc: 490).

To a solution of Compound **36** (1.00 g, 2.04 mmol) in MeOH (10 mL) at 0 °C was added solid NaBH₄ (excess). After gas evolution ceased the reaction mixture was concentrated and the residue purified by flash chromatography (SiO₂, 0-50% EtOAc/hexanes) to give 550 mg (58%) of Compound **37**: LC/MS: m/z = 463 [M+H]⁺ (Calc: 462).

To a solution of Compound **37** (550 mg, 1.189 mmol) and MsCl (150 mg, 1.31 mmol) in DCM at 0 °C was added DIPEA (231 mg, 1.784 mmol) dropwise. After the addition was complete the mixture was allowed to warm to RT and stirred for 12 h. The reaction mixture was concentrated and the residue purified by flash chromatography (SiO₂, 0-100% EtOAc/hexanes) to give 100 mg (31%) of Compound **38**: LC/MS: m/z = 541 [M+H]⁺ (Calc: 540).

To a solution of Compound **10** (37 mg, 0.37 mmol) in ACN (1 mL) at RT was added DIPEA (23.9 mg, 0.185 mmol) and a solution of Compound **38** (100 mg, 0.185 mmol) in ACN (1 mL). A catalytic amount of KI was added. The mixture was then heated at 40 °C for 2 h. The mixture was then concentrated and the residue purified by flash chromatography (SiO₂, 0-100% EtOAc/hexanes followed by 0-20% MeOH/DCM) to give 91 mg (90%) of Compound **39** as a white solid. LC/MS: m/z = 545 [M+H]⁺ (Calc: 544).

To a solution of Compound **39** (91 mg, 0.167 mmol) in THF (3 mL) at RT was added 10 drops of 1N aq. HCl and the resulting mixture was stirred at RT for 12 h. After cooling to

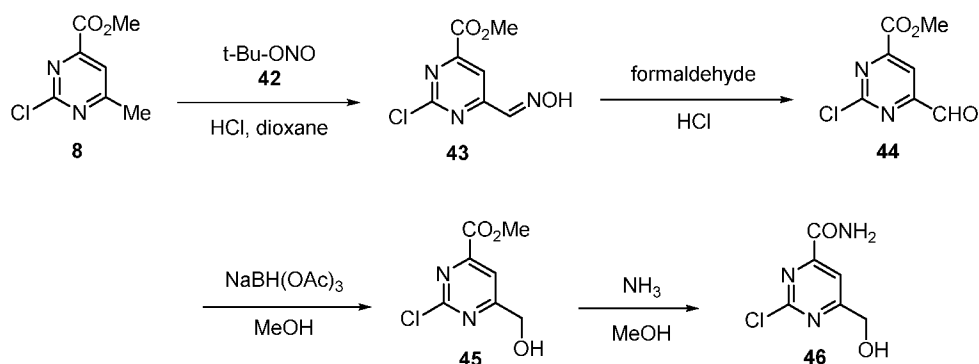
0 °C, solid NaHCO₃ was added until gas evolution ceased. The mixture was concentrated to *ca* 1/2 the volume and then extracted with EtOAc. The organic extracts were dried over K₂CO₃, filtered and concentrated. The residue was purified by flash chromatography (SiO₂, 0-100% EtOAc/hexanes followed by 0-20% MeOH/DCM) to give 44 mg (52%) of Compound **40** as a light grey solid. ¹H NMR (400 MHz, CDCl₃): δ 8.48 (d, J=8.8 Hz, 2H), 7.39 (s, 1H), 7.24 (d, J=8.6 Hz, 2H), 7.06-7.14 (m, 4H), 5.66 (br. s., 1H), 4.85 (t, J=4.5 Hz, 1H), 4.11 (d, J=4.0 Hz, 2H), 4.00-4.08 (m, 1H), 3.90 (dd, J=11.3, 5.2 Hz, 1H), 3.52 (t, J=8.7 Hz, 1H), 3.39-3.47 (m, 1H), 3.29-3.38 (m, 1H), 2.41-2.51 (m, 1H), 1.97-2.11 (m, 2H). LC/MS: *m/z* = 505 [M+H]⁺ (Calc: 504).

In a similar manner, Compound **41** was prepared:

(S)-4-(((6-(1,2-dihydroxyethyl)-2-(4-(4-(trifluoromethoxy)phenoxy)phenyl)pyrimidin-4-yl)methyl)piperazin-2-one (Compound **41**): ¹H NMR (400 MHz, MeOH-d₄): δ 8.48-8.53 (m, 2H), 7.65 (s, 1H), 7.34 (d, J=8.4 Hz, 2H), 7.14-7.20 (m, 2H), 7.09-7.14 (m, 2H), 4.79 (d, J=2.0 Hz, 1H), 3.99 (d, J=3.7 Hz, 1H), 3.82-3.88 (m, 3H), 3.40 (t, J=5.4 Hz, 2H), 3.30 (s, 2H), 2.80-2.88 (m, 2H). LC/MS: *m/z* = 505 [M+H]⁺ (Calc: 504).

EXAMPLE 6

Synthesis of 2-chloro-6-(hydroxymethyl)pyrimidine-4-carboxamide (Compound **46**)



Compound **8** (3.5 g, 18.76 mmol) was dissolved in 4M HCl in dioxanes (10 mL) and cooled to 0 °C. Tert-butyl nitrite (Compound **42**) (2.23 mL, 18.76 mmol) was added dropwise with vigorous stirring. After the addition was complete, the reaction mixture was stirred at 0 °C for 9 h. Solid Na₂S₂O₃ (*ca* 5 g) was added and the reaction mixture stirred for additional 15 min, then basified with satd. aq. NaHCO₃ and extracted with EtOAc. The organic extracts were dried over Na₂SO₄ and concentrated to give 3.0 g (74%) of Compound

43 as a yellow solid which was taken directly to the next step. LC/MS: m/z = 216 $[M+H]^+$ (Calc: 215).

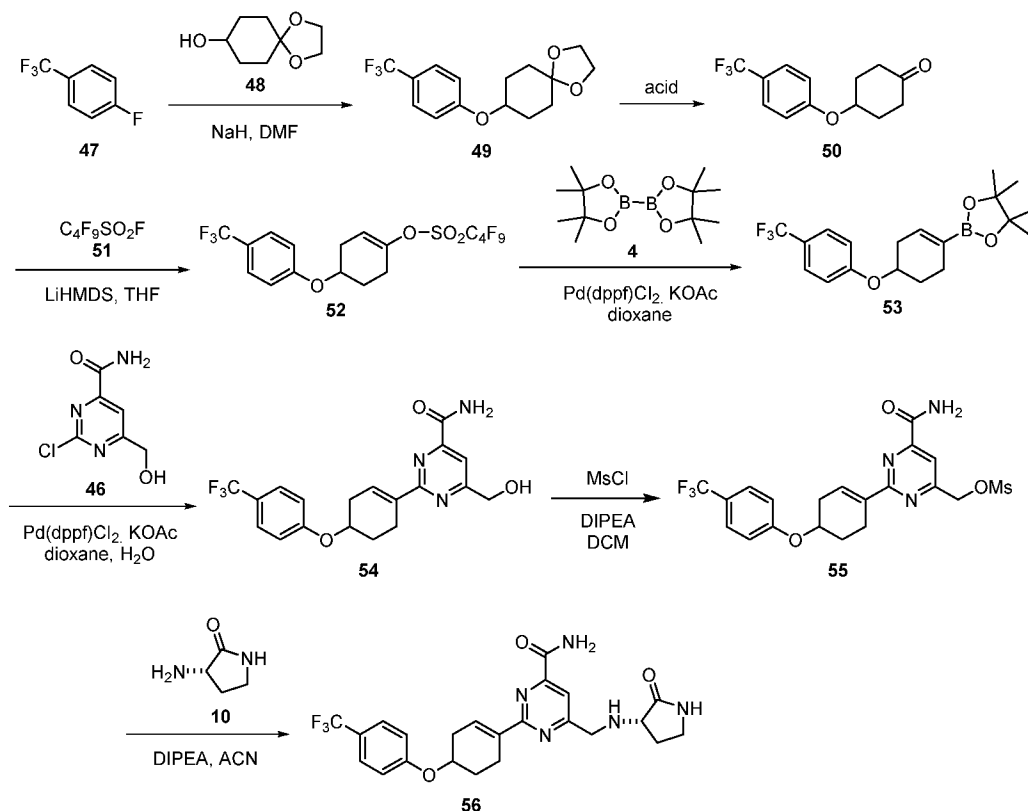
Compound **43** (1.0 g, 4.64 mmol) was suspended in formaldehyde solution (10 mL, 37%) and cooled to 0 °C. To this mixture, was added 6N aq. HCl (2 mL) and the resulting mixture was stirred at 0 °C for 20 min and RT for 1h. The reaction mixture was cooled to 0 °C and carefully neutralized with solid NaHCO₃ to pH=8 and extracted with EtOAc. The organic extracts were dried over Na₂SO₄ and concentrated to give 0.70 g (75%) of Compound **44** which was taken directly to the next step. LC/MS: m/z = 201 $[M+H]^+$ (Calc: 200).

Compound **44** (0.60 g, 2.99 mmol) was dissolved in MeOH (10 mL) and cooled to 0 °C. To the mixture was added NaBH(OAc)₃ (0.76g, 3.59 mmol) portionwise with vigorous stirring. After 1 h the mixture was concentrated. The residue was suspended in water and extracted with EtOAc. The organic extracts were dried over Na₂SO₄, concentrated and the residue purified by flash chromatography (SiO₂, 0-100% EtOAc/hexanes) to give 0.50 g (83%) of Compound **45** as an off-white solid. LC/MS: m/z = 203 $[M+H]^+$ (Calc: 202).

Compound **45** (1.0 g, 4.94 mmol) was dissolved in 7N NH₃ in MeOH (10 mL) and the mixture was stirred at RT for 1 h. The mixture was concentrated to give 0.90 g (97%) of Compound **46** which was used in subsequent steps without further purification. LC/MS: m/z = 188 $[M+H]^+$ (Calc: 187).

EXAMPLE 7

Synthesis of 6-(hydroxymethyl)-2-(4-(4-(trifluoromethyl)phenoxy)cyclohex-1-en-1-yl)pyrimidine-4-carboxamide (Compound **54**) and 6-(((R)-2-oxopyrrolidin-3-yl)amino)methyl)-2-(4-(4-(trifluoromethyl)phenoxy)cyclohex-1-en-1-yl)pyrimidine-4-carboxamide (Compound **56**)



To a solution of Compound **48** (4.82 g, 30.5 mmol) in DMF (10 mL) at 0 °C was slowly added NaH (0.73 g, 30.5 mmol). After the addition was finished, the mixture was stirred at RT for 30 min and then Compound **47** (5.0 g, 30.5 mmol) was added via syringe. The resulting mixture was stirred at RT overnight, quenched with water and extracted with EtOAc. The organic extracts were dried over MgSO₄ and concentrated. The crude Compound **49** was taken directly to the next step.

Crude Compound **49** (7.0 g, 23.16 mmol) was dissolved in MeOH (10 mL) and a mixture of 6 N aq. HCl (10 mL) and water (5 mL) was added. The mixture was stirred at RT for 1 hr and then carefully neutralized with sat. aq. NaHCO₃. The mixture was extracted with EtOAc. The organic extracts were dried over MgSO₄ and concentrated. The residue was purified by flash chromatography (SiO₂, 0-50% EtOAc/hexanes) to give 5.0 g (64% for 2 steps) of Compound **50** as a white solid. LC/MS: *m/z* = 259 [M+H]⁺ (Calc: 258).

To a -78 °C solution of LiHMDS in THF (19.5 mL) was added Compound **50** (5.0 g, 19.35 mmol) in THF (20 mL) dropwise. The mixture was stirred at -78 °C for 3 h. 1,1,2,2,3,3,4,4,4-Nonafluorobutane-1-sulfonyl fluoride (Compound **51**) (5.89 g, 19.35 mmol) was added dropwise via syringe and the resulting mixture was slowly warmed to RT

overnight. The reaction mixture was quenched with water and extracted with EtOAc. The organic extracts were dried over MgSO_4 and concentrated. The crude Compound **52** was taken directly to the next step.

A mixture of Compound **52** (4.0 g, 7.40 mmol), Compound **4** (1.88 g, 7.40 mmol),
5 KOAc (1.09 g, 11.1 mmol) and Pd(dppf)Cl_2 (0.32 g, 0.37 mmol) in dioxane (20 mL) was
purged with argon for 2 min, then heated at 80 °C for 6 h. The mixture was then cooled to
RT, quenched with water and extracted with EtOAc. The organic extracts were dried over
 MgSO_4 and concentrated. The residue was purified by flash chromatography (SiO_2 , 0-50%
EtOAc/hexanes) to give 1.8 g (66% for 2 steps) of Compound **53** as a colorless oil. LC/MS:
10 $m/z = 369$ $[\text{M}+\text{H}]^+$ (Calc: 368).

A mixture of Compound **53** (270 mg, 0.73 mmol), Compound **46** (138 mg, 0.73
mmol), Pd(dppf)Cl_2 (60 mg, 0.073 mmol) and K_2CO_3 (101 mg, 0.73 mmol) in a mixture of
dioxane (2 mL) and water (0.4 mL) was purged with argon for 1 min, then heated at 90 °C for
2 h. The mixture was then cooled to RT, quenched with water and extracted with EtOAc.
15 The organic extracts were dried over MgSO_4 and concentrated. The residue was purified by
flash chromatography (SiO_2 , 0-10% MeOH/DCM) to give 120 mg (42%) of Compound **54** as
an off white solid. ^1H NMR (400 MHz, MeOH-d_4): δ 7.90 (s, 1H), 7.50 (d, $J = 7.2$ Hz, 2H),
7.30 (m, 1H), 6.95 (d, $J = 7.20$ Hz, 2H), 4.75 (m, 1H), 4.60 (s, 2H); 2.60-2.80 (m, 3H), 2.49
(m, 1H), 1.95 -2.15 (m, 2H). LC/MS: $m/z = 394$ $[\text{M}+\text{H}]^+$ (Calc: 393).

20 To a mixture of Compound **54** (0.30 g, 0.763 mmol) and DIPEA (0.265 mL, 1.53
mmol) in DCM (10 mL) at 0 °C was added MsCl (0.059 mL, 0.763 mmol) via syringe. The
mixture was stirred at 0 °C for 30 min quenched with water and extracted with DCM. The
organic extracts were dried over MgSO_4 , passed through a short plug of SiO_2 and
concentrated to give 0.32 g (89%) of Compound **55** as a yellow oil. LC/MS: $m/z = 472$
25 $[\text{M}+\text{H}]^+$ (Calc: 471).

A mixture of Compound **55** (60 mg, 0.127 mmol), Compound **10** (12.7 mg, 0.127
mmol) and DIPEA (0.22 mL, 1.27 mmol) in ACN (5 mL) was stirred at 60 °C for 14 h. The
mixture was concentrated and the residue purified by flash chromatography (SiO_2 , 0-20%
MeOH/DCM) to give 40 mg (66%) of Compound **56** as a white solid. ^1H NMR (400 MHz,
30 MeOH-d_4): δ 7.92 (s, 1H), 7.58 (d, $J = 7.2$ Hz, 2H), 7.53 (m, 1H), 7.10 (d, $J = 7.20$ Hz, 2H),

4.95 (m, 1H), 4.70 (m, 1H), 4.25 (m, 1H), 3.95 (m, 2H), 2.70-3.00 (m, 3H), 2.50-2.70 (m, 2H), 2.05-2.35 (m, 3H). LC/MS: m/z = 476 $[M+H]^+$ (Calc: 475).

In a similar manner the following compounds were prepared:

5 6-((((S)-1-amino-1-oxopropan-2-yl)amino)methyl)-2-(4-(4-(trifluoromethyl)phenoxy)cyclohex-1-en-1-yl)pyrimidine-4-carboxamide (Compound **57**): ^1H NMR (400 MHz, MeOH- d_4): δ 7.92 (s, 1H), 7.58 (d, J = 7.2 Hz, 2H), 7.49 (m, 1H), 7.10 (d, J = 7.20 Hz, 2H), 4.95 (m, 1H), 4.80 (m, 1H), 3.95 (m, 1H), 3.95 (m, 2H), 2.70-3.00 (m, 3H), 2.50-2.70 (m, 1H), 2.00-2.35 (m, 2H). LC/MS, m/z = 464 $[M + H]^+$ (Calc: 463);

10 6-((((S)-1-amino-3-hydroxy-1-oxopropan-2-yl)amino)methyl)-2-(4-(4-(trifluoromethyl)phenoxy)cyclohex-1-en-1-yl)pyrimidine-4-carboxamide (Compound **58**): ^1H NMR (400 MHz, MeOH- d_4): δ 7.92 (s, 1H), 7.60 (d, J = 7.2 Hz, 2H), 7.49 (m, 1H), 7.10 (d, J = 7.20 Hz, 2H), 4.95 (m, 1H), 4.80 (m, 1H), 4.00 (m, 2H), 3.90 (m, 1H), 3.70 (m, 1H), 2.70-3.00 (m, 3H), 2.50-2.70 (m, 1H), 2.00-2.35 (m, 2H), 1.40 (d, J = 7.20, 3H). LC/MS, m/z = 480 $[M + H]^+$ (Calc: 479); and

15 6-(((3-oxopiperazin-1-yl)methyl)-2-(4-(4-(trifluoromethyl)phenoxy)cyclohex-1-en-1-yl)pyrimidine-4-carboxamide (Compound **59**): ^1H NMR (400 MHz, MeOH- d_4): δ 7.98 (s, 1H), 7.60 (d, J = 7.2 Hz, 2H), 7.49 (m, 1H), 7.10 (d, J = 7.20 Hz, 2H), 3.95 (s, 2H), 3.40 (m, 2H); 3.35 (m, 2H), 2.75-3.00 (m, 5H), 2.50-2.65 (m, 1H), 2.00-2.30 (m, 2H). LC/MS, m/z = 476 $[M + H]^+$ (Calc: 475).

Further, Compounds **63** and **64** can be prepared using synthetic methods that are known in the art (see, e.g., WO2007/079239 and WO2011/021645) in view of the General Schemes and Examples of this disclosure.

In the foregoing EXAMPLES, the following abbreviations are used:

ACN	acetonitrile
AIBN	2,2-azobisisobutyronitrile
aq.	aqueous
atm	atmosphere(s)
°C	degrees Celcius
conc.	concentrated

DCM	dichloromethane
DIPEA	diisopropylethylamine
DME	1,2-dimethoxyethane
DMF	dimethylformamide
DMSO	dimethylsulfoxide
Et ₂ O	diethyl ether
EtOAc	ethyl acetate
EtOH	ethanol
h	hour(s)
HPLC	high pressure liquid chromatography
i-PrOAc	<i>iso</i> -propyl acetate
LiHMDS	lithium hexamethyldisilazide
MeOH	methanol
min	minute(s)
Ms	methanesulfonyl
MsCl	methanesulfonyl chloride
NBS	N-bromosuccinimide
NMP	N-methyl-2-pyrrolidone
Pd(dppf)Cl ₂	[1,1'-bis(diphenylphosphino)ferrocene]palladium(II) dichloride
Pd(PPh ₃) ₂ Cl ₂	bis(triphenylphosphine)palladium(II) dichloride
(Ph) ₃ P	triphenylphosphine
RT	room temperature
satd.	saturated
TBAF	tetrabutylammonium fluoride
t-BuOH	<i>tert</i> -butyl alcohol
TFA	trifluoroacetic acid
THF	tetrahydrofuran

EXAMPLE 8

Representative Compounds of the Disclosure have been tested in the FLIPR[®] or FLIPR^{TETRA®} assay and/or EP assays for sodium channel blocking activity, which is described in detail above. Representative values are presented in TABLE 3.

5

TABLE 3

Evaluation of compounds as sodium channel (Na_v) blockers

Compound #	Na _v 1.7 Activity (μM) FLIPR assay IC ₅₀	Na _v 1.7 Activity (μM) EP assay K _i
14	3.386±1.152	1.407±0.231
15	0.065±0.010	0.041±0.006
16	0.085±0.012	
20	0.439±0.023	
21	0.042±0.006	
22	0.200±0.045	0.220±0.034
23	0.200±0.045	0.145±0.044
24	0.583±0.056	0.342±0.095
26	1.745±0.600	0.662±0.130
57	0.557±0.049	0.175±0.039
54	0.242±0.023	
58	1.472±0.091	0.524±0.161
27	0.072±0.008	0.080±0.027
56	0.544±0.062	0.117±0.010
40	1.555±0.215	2.678±0.206
41	1.191±0.110	0.875±0.167
28	2.454±0.133	
59	0.070±0.003	0.059±0.018
60	>20	
61	0.627±0.022	
62	0.205±0.006	
65	0.094±0.008	0.046 ± 0.009

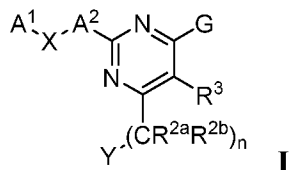
Having now fully described this disclosure, it will be understood by those of ordinary skill in the art that the same can be performed within a wide and equivalent range of conditions, formulations and other parameters without affecting the scope of the disclosure or any embodiment thereof.

5 Other embodiments of the disclosure will be apparent to those skilled in the art from consideration of the specification and practice of the invention disclosed herein. It is intended that the specification and examples be considered as exemplary only, with a true scope and spirit of the invention being indicated by the following claims.

10 All patents and publications cited herein are fully incorporated by reference in their entirety.

What is Claimed Is:

1. A compound having Formula I:



5 or a pharmaceutically acceptable salt or solvate thereof,

wherein:

A¹ is selected from the group consisting of optionally substituted phenyl, optionally substituted 5- or 6-membered heteroaryl, optionally substituted cycloalkyl, optionally substituted heterocyclo, and aralkyl;

X is selected from the group consisting of -O-, -S-, -SO₂-, -CH₂-, -CH(OH)-, -C(=O)-, -C(=O)N(H)-, and -SO₂(H)N-;

A² is selected from the group consisting of optionally substituted aryl, optionally substituted heteroaryl, optionally substituted heterocyclo, and optionally substituted cycloalkyl;

G is selected from the group consisting of dihydroxyalkyl, -CH(OH)CH(OH)C(=O)E, and -C(=O)E;

E is selected from the group consisting of hydroxy, alkoxy, hydroxyalkyl, and -NR^{1a}R^{1b};

R^{1a} is selected from the group consisting of hydrogen, alkyl, aralkyl, (heterocyclo)alkyl, (heteroaryl)alkyl, (amino)alkyl, (alkylamino)alkyl, (dialkylamino)alkyl, (carboxamido)alkyl, (cyano)alkyl, alkoxyalkyl, hydroxyalkyl, and heteroalkyl;

R^{1b} is selected from the group consisting of hydrogen and alkyl; or

R^{1a} and R^{1b} taken together with the nitrogen atom to which they are attached form a 3- to 8-membered optionally substituted heterocycle;

R^{2a} and R^{2b} are independently selected from the group consisting of hydrogen and alkyl;

5

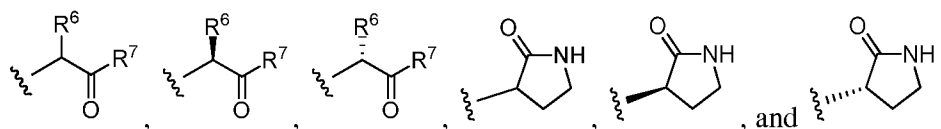
n is 1, 2, or 3;

Y is selected from the group consisting of $-OR^{4a}$ and $-NR^{4b}R^5$;

10 R^3 selected from the group consisting of hydrogen, alkyl, halo, nitro, cyano, hydroxy, amino, alkylamino, dialkylamino, haloalkyl, hydroxyalkyl, alkoxy, haloalkoxy, and alkoxyalkyl;

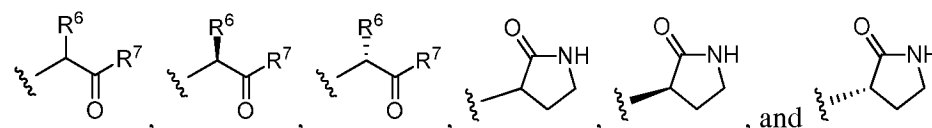
R^{4a} is selected from the group consisting of hydrogen, alkyl, (heterocyclo)alkyl, (heteroaryl)alkyl, (amino)alkyl, (alkylamino)alkyl, (dialkylamino)alkyl, (carboxamido)alkyl, (cyano)alkyl, alkoxyalkyl, hydroxyalkyl, heteroalkyl,

15



R^{4b} is selected from the group consisting of hydrogen, alkyl, (heterocyclo)alkyl, (heteroaryl)alkyl, (amino)alkyl, (alkylamino)alkyl, (dialkylamino)alkyl, (carboxamido)alkyl, (cyano)alkyl, alkoxyalkyl, hydroxyalkyl, heteroalkyl,

20



R^6 is selected from the group consisting of hydrogen, alkyl, and hydroxyalkyl;

25 R^7 is selected from the group consisting of hydroxy, alkoxy, and $-NR^{8a}R^{8b}$;

R^{8a} is selected from the group consisting of hydrogen, alkyl, aralkyl, (heterocyclo)alkyl, (heteroaryl)alkyl, (amino)alkyl, (alkylamino)alkyl, (dialkylamino)alkyl, (carboxamido)alkyl, (cyano)alkyl, alkoxyalkyl, hydroxyalkyl, and heteroalkyl;

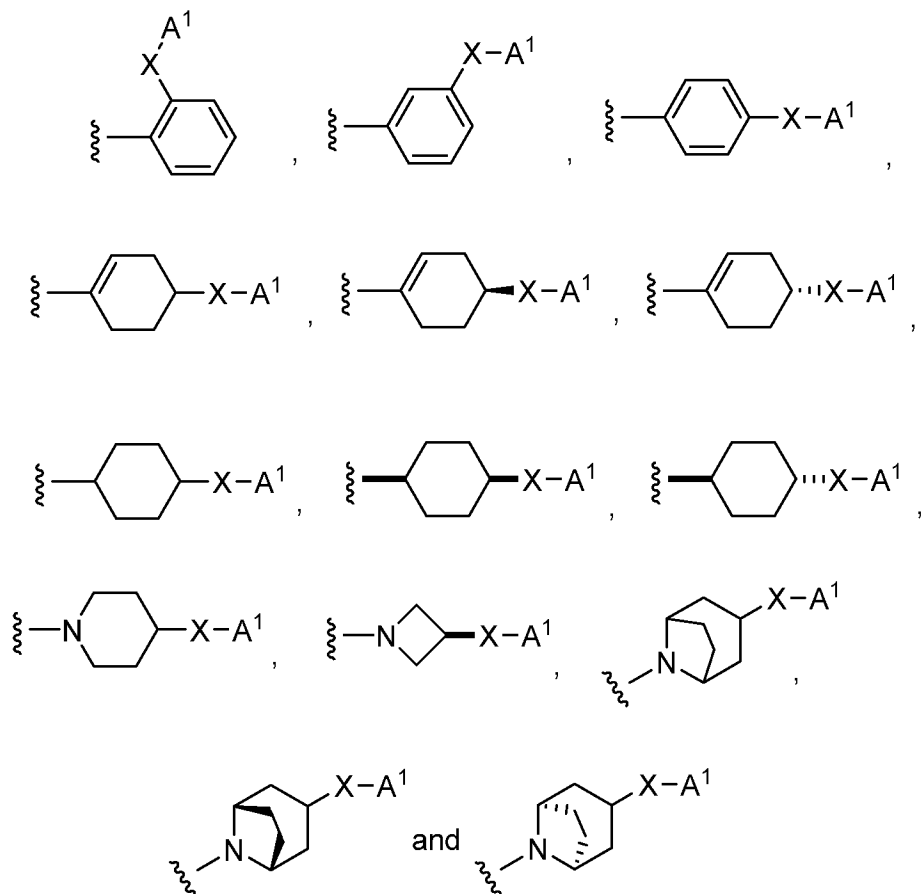
5 R^{8b} is selected from the group consisting of hydrogen and alkyl; or

R^{8a} and R^{8b} taken together with the nitrogen atom to which they are attached form a 3- to 8-membered optionally substituted heterocyclo; and

10 R^5 is selected from the group consisting of hydrogen and alkyl; or

R^{4b} and R^5 taken together with the nitrogen atom to which they are attached form a 3- to 8-membered optionally substituted heterocyclo.

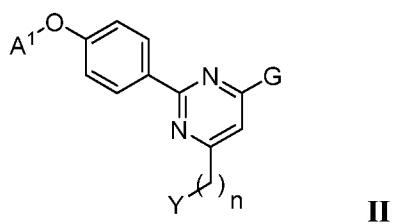
15 2. The compound of claim 1, wherein $-A^2-X-A^1$ is selected from the group consisting of:



and the pharmaceutically acceptable salts and solvates thereof.

3. The compound of claims 1 or 2, wherein X is -O-, and the pharmaceutically
5 acceptable salts and solvates thereof.

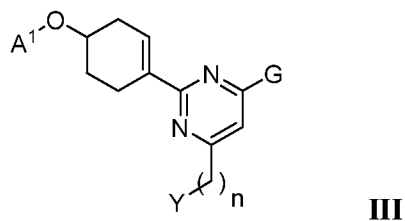
4. The compound of any one of claims 1-3 having Formula II:



or a pharmaceutically acceptable salt or solvate thereof.

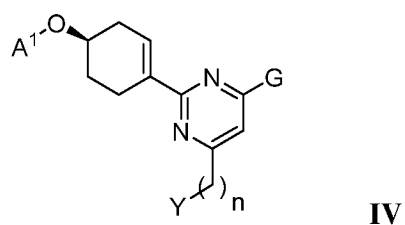
10

5. The compound of any one of claims 1-3 having Formula III:



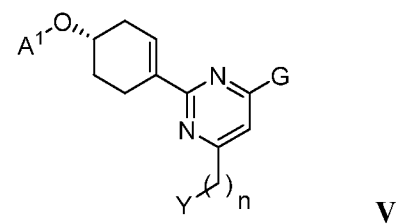
or a pharmaceutically acceptable salt or solvate thereof.

6. The compound of claim 5 having Formula **IV**:



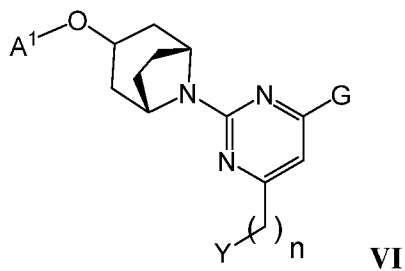
or a pharmaceutically acceptable salt or solvate thereof.

7. The compound of claim 5 having Formula **V**:



or a pharmaceutically acceptable salt or solvate thereof.

8. The compound of any one of claims 1-3 having Formula **VI**:

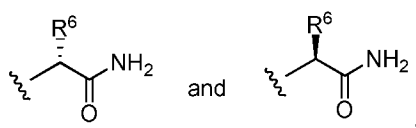


or a pharmaceutically acceptable salt or solvate thereof.

9 The compound of any one of claims 1-8, wherein n is 1, or a pharmaceutically acceptable salt or solvate thereof.

10. The compound of any one of claims 1-9, wherein Y is $-OR^{4a}$, or a pharmaceutically acceptable salt or solvate thereof.

11. The compound of any one of claims 1-10, wherein R^{4a} is selected from the group consisting of:

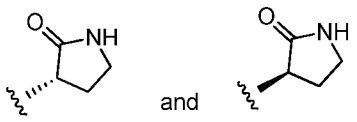


10 or a pharmaceutically acceptable salt or solvate thereof.

12. The compound of claim 11, wherein R^6 is selected from the group consisting of methyl, isopropyl, and hydroxymethyl, or a pharmaceutically acceptable salt or solvate thereof.

15

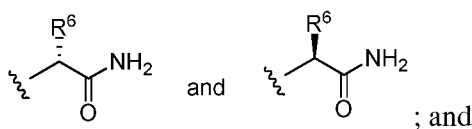
13. The compound of any one of claims 1-10, wherein R^{4a} is:



or a pharmaceutically acceptable salt or solvate thereof.

20 14. The compound of any one of claims 1-9, wherein Y is $-NR^{4b}R^5$, or a pharmaceutically acceptable salt or solvate thereof.

15. The compound of any one of claims 1-9 or 14, wherein R^{4b} is selected from the group consisting of:

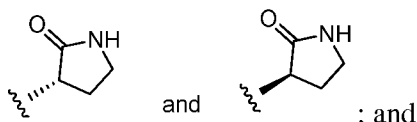


25

R^5 is hydrogen, or a pharmaceutically acceptable salt or solvate thereof.

16. The compound of claim 15, wherein R^6 is selected from the group consisting of methyl, isopropyl, hydroxyethyl, and hydroxymethyl, or a pharmaceutically acceptable salt or solvate thereof.

5 17. The compound of any one of claims 1-9 or 14, wherein R^{4b} is selected from the group consisting of:



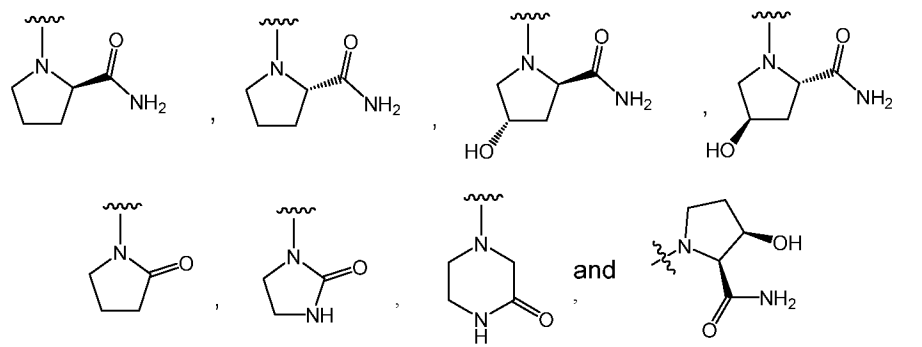
R^5 is hydrogen, or a pharmaceutically acceptable salt or solvate thereof.

10 18. The compound of any one of claims 1-9 or 14, wherein R^{4b} and R^5 taken together with the nitrogen atom to which they are attached form a 3- to 8-membered optionally substituted heterocyclo, or a pharmaceutically acceptable salt or solvate thereof.

15 19. The compound of claim 18, wherein R^{4b} and R^5 taken together with the nitrogen atom to which they are attached form a 5- or 6-membered optionally substituted heterocyclo, or a pharmaceutically acceptable salt or solvate thereof.

20 20. The compound of claim 19, wherein R^{4b} and R^5 taken together with the nitrogen atom to which they are attached form a 5- or 6-membered heterocyclo that is optionally substituted by one to three substituents selected from the group consisting of halo, hydroxy, alkoxy, and carboxamido, or a pharmaceutically acceptable salt or solvate thereof.

25 21. The compound of claim 20, wherein R^{4b} and R^5 taken together with the nitrogen atom to which they are attached form a 5- or 6-membered optionally substituted heterocyclo selected from the group consisting of:

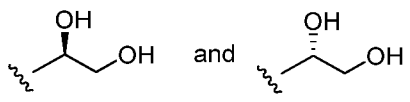


or a pharmaceutically acceptable salt or solvate thereof.

22. The compound of any one of claims 1-10, wherein Y is -OH, or a pharmaceutically acceptable salt or solvate thereof.

23. The compound of any one of claims 1-22, wherein G is dihydroxyalkyl, or a pharmaceutically acceptable salt or solvate thereof.

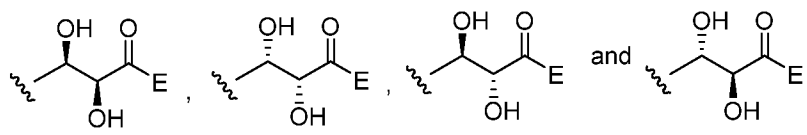
24. The compound of claim 23, wherein G is dihydroxyalkyl selected from the group consisting of:



or a pharmaceutically acceptable salt or solvate thereof.

25. The compound of any one of claims 1-22, wherein G is -CH(OH)CH(OH)C(=O)E, or a pharmaceutically acceptable salt or solvate thereof.

26. The compound of claim 25, wherein G is -CH(OH)CH(OH)C(=O)E selected from the group consisting of:



or a pharmaceutically acceptable salt or solvate thereof.

27. The compound of any one of claims 1-22, wherein G is -C(=O)E, or a pharmaceutically acceptable salt or solvate thereof.

28. The compound of any one of claims 25-27, wherein E is -NR^{1a}R^{1b}, or a pharmaceutically acceptable salt or solvate thereof.

29. The compound of claim 28, wherein R^{1a} and R^{1b} are hydrogen, or a pharmaceutically acceptable salt or solvate thereof.

30. The compound of any one of claims 1-29, wherein A¹ is selected from the group consisting of optionally substituted phenyl and optionally substituted 6-membered heteroaryl, or a pharmaceutically acceptable salt or solvate thereof.

31. The compound of claim 30, wherein A¹ is optionally substituted pyridyl, or a pharmaceutically acceptable salt or solvate thereof.

32. The compound of claim 30, wherein A¹ is optionally substituted phenyl, or a pharmaceutically acceptable salt or solvate thereof.

33. The compound of claims 31 or 32, where the optional substituents are independently selected from the group consisting of halo, cyano, hydroxy, amino, alkylamino, dialkylamino, haloalkyl, hydroxyalkyl, alkoxy, haloalkoxy, alkyl, and cycloalkyl.

34. The compound of claim 1 selected from the group consisting of:

(S)-2-(4-((5-cyclopropylpyridin-2-yl)oxy)phenyl)-6-(((2-oxopyrrolidin-3-yl)amino)methyl)pyrimidine-4-carboxamide;

(S)-2-(4-(4-chloro-2-fluorophenoxy)phenyl)-6-(((2-oxopyrrolidin-3-yl)amino)methyl)pyrimidine-4-carboxamide;

(S)-6-((2-carbamoylpyrrolidin-1-yl)methyl)-2-(4-(4-(trifluoromethyl)phenoxy)phenyl)pyrimidine-4-carboxamide;

methyl (S)-6-(((2-oxopyrrolidin-3-yl)amino)methyl)-2-(4-(4-(trifluoromethyl)phenoxy)phenyl)pyrimidine-4-carboxylate;

(S)-6-(((2-oxopyrrolidin-3-yl)amino)methyl)-2-(4-(4-(trifluoromethyl)phenoxy)phenyl)pyrimidine-4-carboxamide;

(S)-6-(((1-amino-1-oxopropan-2-yl)amino)methyl)-2-(4-(4-(trifluoromethyl)phenoxy)phenyl)pyrimidine-4-carboxamide;

5 (S)-6-(((1-amino-3-methyl-1-oxobutan-2-yl)amino)methyl)-2-(4-(4-(trifluoromethyl)phenoxy)phenyl)pyrimidine-4-carboxamide;

(S)-6-(((1-amino-3-hydroxy-1-oxopropan-2-yl)amino)methyl)-2-(4-(4-(trifluoromethyl)phenoxy)phenyl)pyrimidine-4-carboxamide;

10 6-(((2S,4R)-2-carbamoyl-4-hydroxypyrrolidin-1-yl)methyl)-2-(4-(4-(trifluoromethyl)phenoxy)phenyl)pyrimidine-4-carboxamide;

(S)-6-(((2-oxopyrrolidin-3-yl)amino)methyl)-2-(4-((5-(trifluoromethyl)pyridin-2-yl)oxy)phenyl)pyrimidine-4-carboxamide;

6-((3-oxopiperazin-1-yl)methyl)-2-(4-(4-(trifluoromethyl)phenoxy)phenyl)pyrimidine-4-carboxamide;

15 6-((3-oxopiperazin-1-yl)methyl)-2-(4-((5-(trifluoromethyl)pyridin-2-yl)oxy)phenyl)pyrimidine-4-carboxamide;

(S)-3-(((6-((S)-1,2-dihydroxyethyl)-2-(4-(4-(trifluoromethoxy)phenoxy)phenyl)pyrimidin-4-yl)methyl)amino)pyrrolidin-2-one;

20 (S)-4-((6-(1,2-dihydroxyethyl)-2-(4-(4-(trifluoromethoxy)phenoxy)phenyl)pyrimidin-4-yl)methyl)piperazin-2-one;

6-(hydroxymethyl)-2-(4-(4-(trifluoromethyl)phenoxy)cyclohex-1-en-1-yl)pyrimidine-4-carboxamide;

6-(((R)-2-oxopyrrolidin-3-yl)amino)methyl)-2-(4-(4-(trifluoromethyl)phenoxy)cyclohex-1-en-1-yl)pyrimidine-4-carboxamide;

25 6-(((S)-1-amino-1-oxopropan-2-yl)amino)methyl)-2-(4-(4-(trifluoromethyl)phenoxy)cyclohex-1-en-1-yl)pyrimidine-4-carboxamide;

6-(((S)-1-amino-3-hydroxy-1-oxopropan-2-yl)amino)methyl)-2-(4-(4-(trifluoromethyl)phenoxy)cyclohex-1-en-1-yl)pyrimidine-4-carboxamide;

30 6-((3-oxopiperazin-1-yl)methyl)-2-(4-(4-(trifluoromethyl)phenoxy)cyclohex-1-en-1-yl)pyrimidine-4-carboxamide;

6-((2,2-dimethyl-3-oxopiperazin-1-yl)methyl)-2-(4-((5-(trifluoromethyl)pyridin-2-yl)oxy)phenyl)pyrimidine-4-carboxamide;

6-((2,2-dimethyl-3-oxopiperazin-1-yl)methyl)-2-(4-(4-(trifluoromethyl)phenoxy)phenyl)pyrimidine-4-carboxamide;

6-((3,5-dioxopiperazin-1-yl)methyl)-2-(4-(4-(trifluoromethyl)phenoxy)phenyl)pyrimidine-4-carboxamide;

5 6-((3-oxopiperazin-1-yl)methyl)-2-((1R,5S)-3-(4-(trifluoromethyl)phenoxy)-8-azabicyclo[3.2.1]octan-8-yl)pyrimidine-4-carboxamide;

6-((3-oxopiperazin-1-yl)methyl)-2-((1R,5S)-3-((5-(trifluoromethyl)pyridin-2-yl)oxy)-8-azabicyclo[3.2.1]octan-8-yl)pyrimidine-4-carboxamide;

10 6-(((2S,3R)-2-carbamoyl-3-hydroxypyrrolidin-1-yl)methyl)-2-(4-(4-(trifluoromethyl)phenoxy)phenyl)pyrimidine-4-carboxamide; and

6-(((2S,3R)-1-amino-3-hydroxy-1-oxobutan-2-yl)amino)methyl)-2-(4-(4-(trifluoromethyl)phenoxy)phenyl)pyrimidine-4-carboxamide;

or a pharmaceutically acceptable salt or solvate thereof.

15 35. A pharmaceutical composition comprising the compound of any one of claims 1-34, or a pharmaceutically acceptable salt or solvate thereof, and a pharmaceutically acceptable carrier.

20 36. A method of treating a disorder responsive to blockade of sodium channels in a mammal suffering from said disorder, comprising administering to a mammal in need of such treatment an effective amount of a compound as claimed in any one of claims 1-34, or a pharmaceutically acceptable salt or solvate thereof.

25 37. The method of claim 36, wherein a disorder responsive to blockade of TTX resistant sodium channels is treated.

38. The method of claim 37, wherein a disorder responsive to blockade of TTX sensitive sodium channels is treated.

30 39. The method of claim 36, wherein a disorder responsive to blockade of one or more Nav1.7 sodium channels is treated.

40. A method for treating a condition or disorder in mammal, or providing local anesthesia in a mammal, comprising administering an effective amount of a compound as claimed in any one of claims 1-34, or a pharmaceutically acceptable salt or solvate thereof, to a mammal in need of such treatment, wherein the condition or disorder is stroke, neuronal damage resulting from head trauma, epilepsy, seizures, neuronal loss following global and focal ischemia, pain, migraine, primary erythromelalgia, paroxysmal extreme pain disorder, cerebellar atrophy, ataxia, mental retardation, a neurodegenerative disorder, manic depression, tinnitus, myotonia, a movement disorder, or cardiac arrhythmia.
41. The method of claim 40, wherein said method is for treating pain.
42. The method of claim 41, wherein said method is for preemptive or palliative treatment of pain.
43. The method of claim 41, wherein said pain is selected from the group consisting of chronic pain, inflammatory pain, neuropathic pain, acute pain, and surgical pain.
44. A method of modulating sodium channels in a mammal, comprising administering to the mammal at least one compound as claimed in any one of claims 1-34, or a pharmaceutically acceptable salt or solvate thereof.
45. The method of claim 43, wherein Nav1.7 sodium channel is modulated.
46. A pharmaceutical composition, comprising the compound as claimed in any one of claims 1-34, or a pharmaceutically acceptable salt or solvate thereof, for treating a disorder responsive to the blockade of sodium ion channels.
47. A compound as claimed in any one of claims 1-34, or a pharmaceutically acceptable salt or solvate thereof, for use in treating a disorder responsive to blockade of sodium ion channels.

48. A compound as claimed in any one of claims 1-34, or a pharmaceutically acceptable salt or solvate thereof, wherein the compound is ^3H , ^{11}C , or ^{14}C radiolabeled.

49. A method of preparing a pharmaceutical composition, comprising admixing a
5 therapeutically effective amount of a compound of any one of claims 1-34, or a pharmaceutically acceptable salt or solvate thereof, with a pharmaceutically acceptable carrier.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2014/056601**A. CLASSIFICATION OF SUBJECT MATTER****C07D 403/12(2006.01)i, C07D 239/08(2006.01)i, A61K 31/506(2006.01)i, A61K 31/505(2006.01)i**

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

C07D 403/12; C07D 213/46; none ; C07D 213/30; C07D 239/00; A61K 31/44; C07D 213/65; C07D 239/08; A61K 31/506; A61K 31/505

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Korean utility models and applications for utility models

Japanese utility models and applications for utility models

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

eKOMPASS(KIPO internal) & Keywords:Nav1.7 sodium channel, VGSCs, pyrimidine

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2012-035421 A2 (PURDUE PHARMA L.P.) 22 March 2012 See claims 1-97, examples	1-3,34
X	WO 03-076414 A2 (EURO-CELTIQUE S.A.) 18 September 2003 See claim 1	1-3,34
A	WO 2010-137351 A1 (RAQUALIA PHARMA INC.) 02 December 2010 See the whole document	1-3,34
A	WO 2011-158108 A2 (PURDUE PHARMA L.P.) 22 December 2011 See the whole document	1-3,34



Further documents are listed in the continuation of Box C.



See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

02 January 2015 (02.01.2015)

Date of mailing of the international search report

02 January 2015 (02.01.2015)

Name and mailing address of the ISA/KR

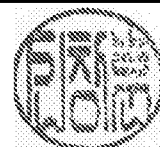
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INTERNATIONAL SEARCH REPORT

International application No.

PCT/US2014/056601**Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)**

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 36-45
because they relate to subject matter not required to be searched by this Authority, namely:
The subject matter of claims 36-45 relates to a method of treatment of the human body, and relates to a subject matter which this International Searching Authority is not required, under PCT Article 17(2)(a)(I) and Rule 39.1(IV), to search.
2. ☒ Claims Nos.: 6,7,12,16,19-21,24,26,29,31,32,37-39,41-43,45
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
Claims 6,7,12,16,19-21,24,26,29,31,32,37-39,41-43,45 are unsearchable because they are worded in reference to multiple dependant claims.
3. ☒ Claims Nos.: 4,5,8-11,13-15,17,18,22,23,25,27,28,30,33,35,36,40,44,46-49
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of any additional fees.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
- ☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.

PCT/US2014/056601

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.

PCT/US2014/056601

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		US 2012-0101105 A1	26/04/2012
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