



(43) International Publication Date
6 February 2014 (06.02.2014)

(10) International Publication Number
WO 2014/022639 A1

- (51) **International Patent Classification:**
C07D 487/22 (2006.01) *A61K 31/499* (2006.01)
A61P 29/00 (2006.01)
- (21) **International Application Number:**
PCT/US2013/053176
- (22) **International Filing Date:**
1 August 2013 (01.08.2013)
- (25) **Filing Language:** English
- (26) **Publication Language:** English
- (30) **Priority Data:**
61/678,270 1 August 2012 (01.08.2012) US
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- (81) **Designated States** (*unless otherwise indicated, for every kind of national protection available*): AE, AG, AL, AM,

AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

- (84) **Designated States** (*unless otherwise indicated, for every kind of regional protection available*): ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:

- *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))*
- *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii))*

Published:

- *with international search report (Art. 21(3))*

(54) **Title:** SOLID FORMS OF (4-ISOPROPOXY-3-METHOXYPHENYL)(2'-METHYL-6'-(TRIFLUOROMETHYL)-3',4'-DIHYDRO-2'H-SPIRO[PIPERIDINE-4,1'-PYRROLO[1,2-A]PYRAZINE]-1-YL)METHANONE

(57) **Abstract:** The invention relates to solid state forms, for example, crystalline forms, of (4-isopropoxy-3-methoxyphenyl)(2'-methyl-6'-(trifluoromethyl)-3',4'- dihydro-2'H-spiro[piperidine-4, 1'-pyrrolo[1,2-a]pyrazine]- 1 -yl)methanone (Compound 1) or pharmaceutically acceptable salts thereof, pharmaceutical compositions thereof, and methods therewith. The present invention also relates to a method of preparing Compound 1 in various solid forms. The invention also provides pharmaceutically acceptable compositions comprising the compounds of the invention and methods of using the compositions in the treatment of various disorders such as pain.



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SOLID FORMS OF (4-ISOPROPOXY-3-METHOXYPHENYL)(2'-METHYL-6'-(TRIFLUOROMETHYL)-3',4'-DIHYDRO-2'H-SPIRO[PIPERIDINE-4,1'-PYRROLO[1,2-A]PYRAZINE]-1-YL)METHANONE

CROSS-REFERENCE TO RELATED APPLICATIONS

[001] This application claims the benefit of U.S. Provisional Patent Application No. 61/678,270, filed August 1, 2012, the entire contents of which are hereby incorporated herein by reference.

TECHNICAL FIELD OF THE INVENTION

[002] The present invention relates to solid state forms, for example, crystalline forms, of (4-isopropoxy-3-methoxyphenyl)(2'-methyl-6'-(trifluoromethyl)-3',4'-dihydro-2'H-spiro[piperidine-4,1'-pyrrolo[1,2-a]pyrazine]-1-yl)methanone (Compound 1) or pharmaceutically acceptable salts thereof, pharmaceutical compositions thereof, and methods therewith. The present invention also relates to a method of preparing Compound 1 Form A.

BACKGROUND OF THE INVENTION

[003] Pain is a protective mechanism that allows healthy animals to avoid tissue damage and to prevent further damage to injured tissue. Nonetheless there are many conditions where pain persists beyond its usefulness, or where patients would benefit from inhibition of pain. Voltage-gated sodium channels are believed to play a critical role in pain signaling. This belief is based on the known roles of these channels in normal physiology, pathological states arising from mutations in sodium channel genes, preclinical work in animal models of disease, and the clinical usefulness of known sodium channel modulating agents (Cummins, T. R., Sheets, P. L., and Waxman, S. G., The roles of sodium channels in nociception: Implications for mechanisms of pain. *Pain* **131** (3), 243 (2007); England, S., Voltage-gated sodium channels: the search for subtype-selective analgesics. *Expert Opin Investig Drugs* **17**

(12), 1849 (2008); Krafte, D. S. and Bannon, A. W., Sodium channels and nociception: recent concepts and therapeutic opportunities. *Curr Opin Pharmacol* 8 (1), 50 (2008)).

[004] Voltage-gated sodium channels (NaV's) are key biological mediators of electrical signaling. NaV's are the primary mediators of the rapid upstroke of the action potential of many excitable cell types (e.g. neurons, skeletal myocytes, cardiac myocytes), and thus are critical for the initiation of signaling in those cells (Hille, Bertil, *Ion Channels of Excitable Membranes*, Third ed. (Sinauer Associates, Inc., Sunderland, MA, 2001)). Because of the role NaV's play in the initiation and propagation of neuronal signals, antagonists that reduce NaV currents can prevent or reduce neural signaling. Thus NaV channels are considered likely targets in pathologic states where reduced excitability is predicted to alleviate the clinical symptoms, such as pain, epilepsy, and some cardiac arrhythmias (Chahine, M., Chatelier, A., Babich, O., and Krupp, J. J., Voltage-gated sodium channels in neurological disorders. *CNS Neurol Disord Drug Targets* 7 (2), 144 (2008)).

[005] The NaV's form a subfamily of the voltage-gated ion channel superfamily and comprises 9 isoforms, designated NaV 1.1 – NaV 1.9. The tissue localizations of the nine isoforms vary greatly. NaV 1.4 is the primary sodium channel of skeletal muscle, and NaV 1.5 is primary sodium channel of cardiac myocytes. NaV's 1.7, 1.8 and 1.9 are primarily localized to the peripheral nervous system, while NaV's 1.1, 1.2, 1.3, and 1.6 are neuronal channels found in both the central and peripheral nervous systems. The functional behaviors of the nine isoforms are similar but distinct in the specifics of their voltage-dependent and kinetic behavior (Catterall, W. A., Goldin, A. L., and Waxman, S. G., International Union of Pharmacology. XLVII. Nomenclature and structure-function relationships of voltage-gated sodium channels. *Pharmacol Rev* 57 (4), 397 (2005)).

[006] NaV channels have been identified as the primary target for some clinically useful pharmaceutical agents that reduce pain (Cummins, T. R., Sheets, P. L., and Waxman, S. G., The roles of sodium channels in nociception: Implications for mechanisms of pain. *Pain* 131 (3), 243 (2007)). The local anesthetic drugs such as lidocaine block pain by inhibiting NaV channels. These compounds provide excellent

local pain reduction but suffer the drawback of abolishing normal acute pain and sensory inputs. Systemic administration of these compounds results in dose limiting side effects that are generally ascribed to block of neural channels in the CNS (nausea, sedation, confusion, ataxia). Cardiac side effects can also occur, and indeed these compounds are also used as class 1 anti-arrhythmics, presumably due to block of NaV1.5 channels in the heart. Other compounds that have proven effective at reducing pain have also been suggested to act by sodium channel blockade including carbamazepine, lamotrigine, and tricyclic antidepressants (Soderpalm, B., Anticonvulsants: aspects of their mechanisms of action. *Eur J Pain* **6 Suppl A**, 3 (2002); Wang, G. K., Mitchell, J., and Wang, S. Y., Block of persistent late Na⁺ currents by antidepressant sertraline and paroxetine. *J Membr Biol* **222** (2), 79 (2008)). These compounds are likewise dose limited by adverse effects similar to those seen with the local anesthetics. Antagonists that specifically block only the isoform(s) critical for nociception are expected to have increased efficacy since the reduction of adverse effects caused by block of off-target channels should enable higher dosing and thus more complete block of target channels isoforms.

[007] Four NaV isoforms, NaV 1.3, 1.7, 1.8, and 1.9, have been specifically indicated as likely pain targets. NaV 1.3 is normally found in the pain sensing neurons of the dorsal root ganglia (DRG) only early in development and is lost soon after birth both in humans and in rodents. Nonetheless, nerve damaging injuries have been found to result in a return of the NaV 1.3 channels to DRG neurons and this may contribute to the abnormal pain signaling in various chronic pain conditions resulting from nerve damage (neuropathic pain). These data have led to the suggestion that pharmaceutical block of NaV 1.3 could be an effective treatment for neuropathic pain. In opposition to this idea, global genetic knockout of NaV 1.3 in mice does not prevent the development of allodynia in mouse models of neuropathic pain (Nassar, M. A. et al., Nerve injury induces robust allodynia and ectopic discharges in NaV 1.3 null mutant mice. *Mol Pain* **2**, 33 (2006)). It remains unknown whether compensatory changes in other channels allow for normal neuropathic pain in NaV 1.3 knockout mice, though it has been reported that knockout of NaV 1.1 results in drastic upregulation of NaV 1.3. The converse effect in NaV 1.3 knockouts might explain these results.

[008] NaV 1.7, 1.8, and 1.9 are highly expressed in DRG neurons, including the neurons whose axons make up the C-fibers and A δ nerve fibers that are believed to carry most pain signals from the nociceptive terminals to the central nervous. Like NaV 1.3, NaV 1.7 expression increases after nerve injury and may contribute to
5 neuropathic pain states. The localization of NaV 1.7, 1.8, and 1.9 in nociceptors led to the hypothesis that reducing the sodium currents through these channels might alleviate pain. Indeed, specific interventions that reduce the levels of these channels have proven effective in animal models of pain.

[009] Specific reduction of NaV 1.7 in rodents by multiple different
10 techniques has resulted in the reduction of observable pain behaviors in model animals. Injection of a viral antisense NaV 1.7 cDNA construct greatly reduces normal pain responses due to inflammation or mechanical injury (Yeomans, D. C. et al., Decrease in inflammatory hyperalgesia by herpes vector-mediated knockdown of NaV 1.7 sodium channels in primary afferents. *Hum Gene Ther* **16** (2), 271 (2005)). Likewise,
15 a genetic knockout of NaV 1.7 in a subset of nociceptor neurons reduced acute and inflammatory pain in mouse models (Nassar, M. A. et al., Nociceptor-specific gene deletion reveals a major role for NaV 1.7 (PN1) in acute and inflammatory pain. *Proc Natl Acad Sci U S A* **101** (34), 12706 (2004)). Global knockouts of NaV 1.7 in mice lead to animals that die on the first day after birth. These mice fail to feed and this is
20 the presumed cause of death.

[0010] Treatments that specifically reduce NaV 1.8 channels in rodent models effectively reduce pain sensitivity. Knockdown of NaV 1.8 in rats by intrathecal injection of antisense oligodeoxynucleotides reduces neuropathic pain behaviors, while leaving acute pain sensation intact (Lai, J. et al., Inhibition of neuropathic pain by
25 decreased expression of the tetrodotoxin-resistant sodium channel, NaV1.8. *Pain* **95** (1-2), 143 (2002); Porreca, F. et al., A comparison of the potential role of the tetrodotoxin-insensitive sodium channels, PN3/SNS and NaN/SNS2, in rat models of chronic pain. *Proc Natl Acad Sci U S A* **96** (14), 7640 (1999)). Global genetic knockout of NaV 1.8 in mice or specific destruction of NaV 1.8 expressing neurons
30 greatly reduces perception of acute mechanical, inflammatory, and visceral pain (Akopian, A. N. et al., The tetrodotoxin-resistant sodium channel SNS has a

- specialized function in pain pathways. *Nat Neurosci* **2** (6), 541 (1999); Abrahamsen, B. et al., The cell and molecular basis of mechanical, cold, and inflammatory pain. *Science* **321** (5889), 702 (2008); Laird, J. M., Souslova, V., Wood, J. N., and Cervero, F., Deficits in visceral pain and referred hyperalgesia in NaV 1.8 (SNS/PN3)-null mice. *J Neurosci* **22** (19), 8352 (2002)). In contrast to the antisense experiments in rats, genetic knockout mice appear to develop neuropathic pain behaviors normally after nerve injury (Lai, J. et al., Inhibition of neuropathic pain by decreased expression of the tetrodotoxin-resistant sodium channel, NaV1.8. *Pain* **95** (1-2), 143 (2002); Akopian, A. N. et al., The tetrodotoxin-resistant sodium channel SNS has a specialized function in pain pathways. *Nat Neurosci* **2** (6), 541 (1999); Abrahamsen, B. et al., The cell and molecular basis of mechanical, cold, and inflammatory pain. *Science* **321** (5889), 702 (2008); Laird, J. M., Souslova, V., Wood, J. N., and Cervero, F., Deficits in visceral pain and referred hyperalgesia in NaV 1.8 (SNS/PN3)-null mice. *J Neurosci* **22** (19), 8352 (2002)).
- 15 **[0011]** NaV 1.9 global knock out mice have decreased sensitivity to inflammation induced pain, despite normal acute, and neuropathic pain behaviors (Amaya, F. et al., The voltage-gated sodium channel Na(v)1.9 is an effector of peripheral inflammatory pain hypersensitivity. *J Neurosci* **26** (50), 12852 (2006); Priest, B. T. et al., Contribution of the tetrodotoxin-resistant voltage-gated sodium channel NaV1.9 to sensory transmission and nociceptive behavior. *Proc Natl Acad Sci U S A* **102** (26), 9382 (2005)). Spinal knockdown of NaV 1.9 had no apparent effect on pain behavior in rats (Porreca, F. et al., A comparison of the potential role of the tetrodotoxin-insensitive sodium channels, PN3/SNS and NaN/SNS2, in rat models of chronic pain. *Proc Natl Acad Sci U S A* **96** (14), 7640 (1999)).
- 25 **[0012]** The understanding of the role of NaV channels in human physiology and pathology has been greatly advanced by the discovery and analysis of naturally occurring human mutations. NaV 1.1 and NaV 1.2 mutations result in various forms of epilepsy (Fujiwara, T., Clinical spectrum of mutations in SCN1A gene: severe myoclonic epilepsy in infancy and related epilepsies. *Epilepsy Res* **70 Suppl 1**, S223 (2006); George, A. L., Jr., Inherited disorders of voltage-gated sodium channels. *J Clin Invest* **115** (8), 1990 (2005); Misra, S. N., Kahlig, K. M., and George, A. L., Jr.,
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Impaired NaV1.2 function and reduced cell surface expression in benign familial neonatal-infantile seizures. *Epilepsia* **49** (9), 1535 (2008)). Mutations of the NaV 1.4 cause muscular disorders like paramyotonia congenital (Vicart, S., Sternberg, D., Fontaine, B., and Meola, G., Human skeletal muscle sodium channelopathies. *Neurol Sci* **26** (4), 194 (2005)). NaV 1.5 mutations result in cardiac abnormalities like Brugada Syndrome and long QT syndrome (Bennett, P. B., Yazawa, K., Makita, N., and George, A. L., Jr., Molecular mechanism for an inherited cardiac arrhythmia. *Nature* **376** (6542), 683 (1995); Darbar, D. et al., Cardiac sodium channel (SCN5A) variants associated with atrial fibrillation. *Circulation* **117** (15), 1927 (2008); Wang, Q. et al., SCN5A mutations associated with an inherited cardiac arrhythmia, long QT syndrome. *Cell* **80** (5), 805 (1995)).

[0013] Recent discoveries have demonstrated that mutations in the gene that encodes the NaV 1.7 channel (SCN9A) can cause both enhanced and reduced pain syndromes. Work by Waxman's group and others have identified at least 15 mutations that result in enhanced current through NaV 1.7 and are linked to dominant congenital pain syndromes. Mutations that lower the threshold for NaV 1.7 activation cause inherited erythromelalgia (IEM). IEM patients exhibit abnormal burning pain in their extremities. Mutations that interfere with the normal inactivation properties of NaV 1.7 lead to prolonged sodium currents and cause paroxysmal extreme pain disorder (PEPD). PEPD patients exhibit periocular, perimandibular, and rectal pain symptoms that progresses throughout life (Drenth, J. P. et al., SCN9A mutations define primary erythromelalgia as a neuropathic disorder of voltage gated sodium channels. *J Invest Dermatol* **124** (6), 1333 (2005); Estacion, M. et al., NaV 1.7 gain-of-function mutations as a continuum: A1632E displays physiological changes associated with erythromelalgia and paroxysmal extreme pain disorder mutations and produces symptoms of both disorders. *J Neurosci* **28** (43), 11079 (2008)).

[0014] NaV 1.7 null mutations in human patients were recently described by several groups (Ahmad, S. et al., A stop codon mutation in SCN9A causes lack of pain sensation. *Hum Mol Genet* **16** (17), 2114 (2007); Cox, J. J. et al., An SCN9A channelopathy causes congenital inability to experience pain. *Nature* **444** (7121), 894 (2006); Goldberg, Y. P. et al., Loss-of-function mutations in the NaV 1.7 gene underlie

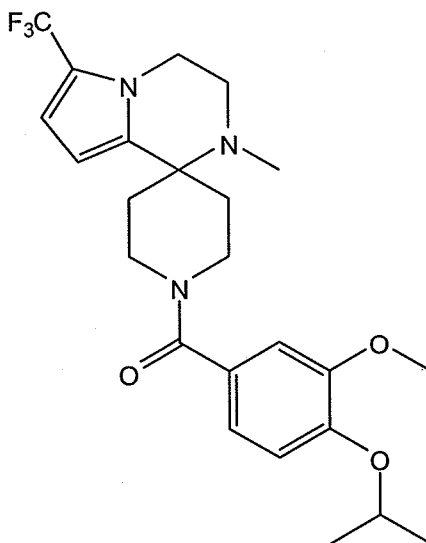
congenital indifference to pain in multiple human populations. *Clin Genet* **71** (4), 311 (2007)). In all cases patients exhibit congenital indifference to pain. These patients report no pain under any circumstances. Many of these patients suffer dire injuries early in childhood since they do not have the protective, normal pain that helps to prevent tissue damage and develop appropriate protective behaviors. Aside from the striking loss of pain sensation and reduced or absent of smell (Goldberg, Y. P. et al., Loss-of-function mutations in the NaV 1.7 gene underlie congenital indifference to pain in multiple human populations. *Clin Genet* **71** (4), 311 (2007)), these patients appear completely normal. Despite the normally high expression of NaV 1.7 in sympathetic neurons (Toledo-Aral, J. J. et al., Identification of PN1, a predominant voltage-dependent sodium channel expressed principally in peripheral neurons. *Proc Natl Acad Sci U S A* **94** (4), 1527 (1997)) and adrenal chromafin cells (Klugbauer, N., Lacinova, L., Flockerzi, V., and Hofmann, F., Structure and functional expression of a new member of the tetrodotoxin-sensitive voltage-activated sodium channel family from human neuroendocrine cells. *EMBO J* **14** (6), 1084 (1995)), these NaV 1.7-null patients show no sign of neuroendocrine or sympathetic nervous dysfunction.

[0015] The gain of NaV 1.7 function mutations that cause pain, coupled with the loss of NaV 1.7 function mutations that abolish pain, provide strong evidence that NaV 1.7 plays an important role in human pain signaling. The relative good health of NaV 1.7-null patients indicates that ablation of NaV 1.7 is well tolerated in these patients.

[0016] Unfortunately, the efficacy of currently used sodium channel blockers for the disease states described above has been to a large extent limited by a number of side effects. These side effects include various CNS disturbances such as blurred vision, dizziness, nausea, and sedation as well more potentially life threatening cardiac arrhythmias and cardiac failure. Accordingly, there remains a need to develop additional Na channel antagonists, preferably those with higher potency and fewer side effects.

[0017] (4-Isopropoxy-3-methoxyphenyl)(2'-methyl-6'-(trifluoromethyl)-3',4'-dihydro-2'H-spiro[piperidine-4,1'-pyrrolo[1,2-a]pyrazin]-1-yl)methanone (Compound 1), has been found to be a useful inhibitor of voltage-gated sodium channels, and is

disclosed in U.S. published patent application US20120196869, filed February 2, 2012; U.S. provisional patent applications 61/438,685, filed February 2, 2011; 61/440,987, filed February 9, 2011; and 61/495,538, filed June 10, 2011 (said applications being incorporated herein by reference in their entirety).



Compound 1

[0018] There remains, however, a need for stable solid forms of Compound 1 that can be used readily in pharmaceutical compositions suitable for use as therapeutics..

SUMMARY OF THE INVENTION

[0019] As described herein, the present invention provides crystalline forms of Compound 1 and salts thereof, useful for treating or lessening the severity of sodium ion channel related conditions, such as the treatment of pain, including, but not limited to, acute, chronic, neuropathic, or inflammatory pain, arthritis, migraine, cluster headaches, trigeminal neuralgia, herpetic neuralgia, general neuralgias, epilepsy or epilepsy conditions, neurodegenerative disorders, psychiatric disorders such as anxiety and depression, myotonia, arrhythmia, movement disorders, neuroendocrine disorders, ataxia, multiple sclerosis, irritable bowel syndrome, incontinence, visceral pain, osteoarthritis pain, postherpetic neuralgia, diabetic neuropathy, radicular pain, sciatica, back pain, head or neck pain, severe or intractable pain, nociceptive pain, breakthrough pain, postsurgical pain, or cancer pain.

BRIEF DESCRIPTION OF THE DRAWINGS

[0020] **Figure 1** depicts an x-ray powder diffraction pattern of Compound 1 Form A.

5 [0021] **Figure 2** depicts a differential scanning calorimetry (DSC) trace of Compound 1 Form A.

[0022] **Figure 3** depicts a thermogravimetric analysis (TGA) trace of Compound 1 Form A.

[0023] **Figure 4** depicts an FTIR spectrum of Compound 1 Form A.

10 [0024] **Figure 5** depicts a conformational picture of Compound 1 Form A based on single crystal x-ray analysis.

[0025] **Figure 6** depicts a conformational picture of Compound 1 Form A based on single crystal X-ray analysis showing interaction between the molecules.

[0026] **Figure 7** depicts an x-ray powder diffraction pattern of Compound 1 HCl Salt Form A.

15 [0027] **Figure 8** depicts a differential scanning calorimetry (DSC) trace of Compound 1 HCl Salt Form A.

[0028] **Figure 9** depicts a thermogravimetric analysis (TGA) trace of Compound 1 HCl Salt Form A.

20 [0029] **Figure 10** depicts an x-ray powder diffraction pattern of Compound 1 HCl Salt Form B.

[0030] **Figure 11** depicts a differential scanning calorimetry (DSC) trace of Compound 1 HCl Salt Form B.

[0031] **Figure 12** depicts a thermogravimetric analysis (TGA) trace of Compound 1 HCl Salt Form B.

25 [0032] **Figure 13** depicts an FTIR spectrum of Compound 1 HCl Salt Form B.

[0033] **Figure 14** depicts a conformational picture of Compound 1 HCl Salt Form B based on single crystal x-ray analysis.

[0034] **Figure 15** depicts an x-ray powder diffraction pattern of Compound 1 Mesylate Salt Form A.

[0035] **Figure 16** depicts a differential scanning calorimetry (DSC) trace of Compound 1 Mesylate Salt Form A.

5 [0036] **Figure 17** depicts a thermogravimetric analysis (TGA) trace of Compound 1 Mesylate Salt Form A.

[0037] **Figure 18** depicts depicts an x-ray powder diffraction pattern of Compound 1 Besylate Salt Form A.

10 [0038] **Figure 19** depicts a differential scanning calorimetry (DSC) trace of Compound 1 Besylate Salt Form A.

[0039] **Figure 20** depicts a thermogravimetric analysis (TGA) trace of Compound 1 Besylate Salt Form A.

[0040] **Figure 21** depicts depicts depicts an x-ray powder diffraction pattern of Compound 1 Tosylate Salt Form A.

15 [0041] **Figure 22** depicts depicts a differential scanning calorimetry (DSC) trace of Compound 1 Tosylate Salt Form A.

[0042] **Figure 23** depicts depicts a thermogravimetric analysis (TGA) trace of Compound 1 Tosylate Salt Form A.

DETAILED DESCRIPTION OF THE INVENTION

20 [0043] In one aspect, the present invention provides a substantially crystalline and salt free form of Compound 1 referred to as Compound 1 Form A.

[0044] In another aspect, the present invention provides a substantially crystalline form of the HCl salt of Compound 1 referred to as Compound 1 HCl Salt Form A.

25 [0045] In another aspect, the present invention provides a substantially crystalline form of the HCl salt of Compound 1 referred to as Compound 1 HCl Salt Form B.

[0046] In another aspect, the present invention provides a substantially crystalline form of the mesylate salt of Compound 1 referred to as Compound 1 Mesylate Salt Form A.

[0047] In another aspect, the present invention provides a substantially crystalline form of the besylate salt of Compound 1 referred to as Compound 1 Besylate Salt Form A.

[0048] In another aspect, the present invention provides a substantially crystalline form of the tosylate salt of Compound 1 referred to as Compound 1 Tosylate Salt Form A.

[0049] For purposes of this invention, the chemical elements are identified in accordance with the Periodic Table of the Elements, CAS version, Handbook of Chemistry and Physics, 75th Ed. Additionally, general principles of organic chemistry are described in "Organic Chemistry", Thomas Sorrell, University Science Books, Sausalito: 1999, and "March's Advanced Organic Chemistry", 5th Ed., Ed.: Smith, M.B. and March, J., John Wiley & Sons, New York: 2001, the entire contents of which are hereby incorporated by reference.

[0050] The abbreviation "THF" stands for tetrahydrofuran; the abbreviation "DCM" stands for dichloromethane; the abbreviation "IPA" stands for isopropyl alcohol; and the abbreviation "DMA" stands for dimethylacetamide.

[0051] The term "stable", as used herein, refers to compounds that are not substantially altered when subjected to conditions to allow for their production, detection, and preferably their recovery, purification, and use for one or more of the purposes disclosed herein. In some embodiments, a stable compound or chemically feasible compound is one that is not substantially altered when kept at a temperature of 40°C or less, in the absence of moisture or other chemically reactive conditions, for at least a week. When two alkoxy groups are bound to the same atom or adjacent atoms, the two alkoxy groups can form a ring together with the atom(s) to which they are bound.

[0052] In general, the term "substituted," whether preceded by the term "optionally" or not, refers to the replacement of hydrogen radicals in a given structure

with the radical of a specified substituent. Specific substituents are described above in the definitions and below in the description of compounds and examples thereof.

Unless otherwise indicated, an optionally substituted group can have a substituent at each substitutable position of the group, and when more than one position in any

5 given structure can be substituted with more than one substituent selected from a specified group, the substituent can be either the same or different at every position.

A ring substituent, such as a heterocycloalkyl, can be bound to another ring, such as a cycloalkyl, to form a spiro-bicyclic ring system, e.g., both rings share one common atom. As one of ordinary skill in the art will recognize, combinations of substituents

10 envisioned by this invention are those combinations that result in the formation of stable or chemically feasible compounds.

[0053] The phrase "up to", as used herein, refers to zero or any integer number that is equal or less than the number following the phrase. For example, "up to 3" means any one of 0, 1, 2, and 3.

15 [0054] The term "aliphatic", "aliphatic group" or "alkyl" as used herein, means a straight-chain (i.e., unbranched) or branched, substituted or unsubstituted hydrocarbon chain that is completely saturated or that contains one or more units of unsaturation. Unless otherwise specified, aliphatic groups contain 1-20 aliphatic carbon atoms. In some embodiments, aliphatic groups contain 1-10 aliphatic carbon atoms. In other embodiments, aliphatic groups contain 1-8 aliphatic carbon atoms. In still other embodiments, aliphatic groups contain 1-6 aliphatic carbon atoms, and in yet other embodiments aliphatic groups contain 1-4 aliphatic carbon atoms. Suitable aliphatic groups include, but are not limited to, linear or branched, substituted or unsubstituted alkyl, alkenyl, alkynyl groups. The term "cycloaliphatic" or

25 "cycloalkyl" mean a monocyclic hydrocarbon, bicyclic, or tricyclic hydrocarbon that is completely saturated or that contains one or more units of unsaturation, but which is not aromatic and has a single point of attachment to the rest of the molecule. In some embodiments, "cycloaliphatic" refers to a monocyclic C₃-C₈ hydrocarbon or bicyclic C₈-C₁₂ hydrocarbon that is completely saturated or that contains one or more units of

30 unsaturation, but which is not aromatic, that has a single point of attachment to the rest of the molecule wherein any individual ring in said bicyclic ring system has 3-7

members.

[0055] The term "electron withdrawing group", as used herein means an atom or a group that is electronegative relative to hydrogen. See, e.g., "Advanced Organic Chemistry: Reactions, Mechanisms, and Structure," Jerry March, 4th Ed., John Wiley & Sons (1992), e.g., pp. 14-16, 18-19, etc. Exemplary such substituents include halo such as Cl, Br, or F, CN, COOH, CF₃, etc.

[0056] Unless otherwise specified, the term "heterocycle", "heterocyclyl", "heterocycloaliphatic", "heterocycloalkyl" or "heterocyclic" as used herein means non-aromatic, monocyclic, bicyclic, or tricyclic ring systems in which one or more ring atoms in one or more ring members is an independently selected heteroatom. Heterocyclic ring can be saturated or can contain one or more unsaturated bonds. In some embodiments, the "heterocycle", "heterocyclyl", "heterocycloaliphatic", "heterocycloalkyl" or "heterocyclic" group has three to fourteen ring members in which one or more ring members is a heteroatom independently selected from oxygen, sulfur, nitrogen, or phosphorus, and each ring in the ring system contains 3 to 7 ring members.

[0057] The term "heteroatom" means oxygen, sulfur, nitrogen, phosphorus, or silicon (including, any oxidized form of nitrogen, sulfur, phosphorus, or silicon; the quaternized form of any basic nitrogen or; a substitutable nitrogen of a heterocyclic ring, for example N (as in 3,4-dihydro-2H-pyrrolyl), NH (as in pyrrolidinyl) or NR⁺ (as in N-substituted pyrrolidinyl)).

[0058] The term "unsaturated", as used herein, means that a moiety has one or more units of unsaturation but is not aromatic.

[0059] The term "alkoxy", or "thioalkyl", as used herein, refers to an alkyl group, as previously defined, attached to the principal carbon chain through an oxygen ("alkoxy") or sulfur ("thioalkyl") atom.

[0060] The term "aryl" used alone or as part of a larger moiety as in "aralkyl", "aralkoxy", or "aryloxyalkyl", refers to monocyclic, bicyclic, and tricyclic ring systems having a total of five to fourteen ring carbon atoms, wherein at least one ring in the system is aromatic and wherein each ring in the system contains 3 to 7 ring carbon

atoms. The term "aryl" may be used interchangeably with the term "aryl ring".

[0061] The term "heteroaryl", used alone or as part of a larger moiety as in "heteroaralkyl" or "heteroarylalkoxy", refers to monocyclic, bicyclic, and tricyclic ring systems having a total of five to fourteen ring members, wherein at least one ring in the system is aromatic, at least one ring in the system contains one or more heteroatoms, and wherein each ring in the system contains 3 to 7 ring members. The term "heteroaryl" may be used interchangeably with the term "heteroaryl ring" or the term "heteroaromatic".

[0062] The term "alkylidene chain" refers to a straight or branched carbon chain that may be fully saturated or have one or more units of unsaturation and has two points of attachment to the rest of the molecule.

[0063] Unless otherwise stated, structures depicted herein are also meant to include all isomeric (e.g., enantiomeric, diastereomeric, and geometric (or conformational)) forms of the structure; for example, the R and S configurations for each asymmetric center, (Z) and (E) double bond isomers, and (Z) and (E) conformational isomers. Therefore, single stereochemical isomers as well as enantiomeric, diastereomeric, and geometric (or conformational) mixtures of the present compounds are within the scope of the invention.

[0064] Unless otherwise stated, all tautomeric forms of the compounds of the invention are within the scope of the invention. Thus, included within the scope of the invention are tautomers of compounds of formula I.

[0065] Additionally, unless otherwise stated, structures depicted herein are also meant to include compounds that differ only in the presence of one or more isotopically enriched atoms. For example, compounds of formula I, wherein one or more hydrogen atoms are replaced deuterium or tritium, or one or more carbon atoms are replaced by a ^{13}C - or ^{14}C -enriched carbon are within the scope of this invention. Such compounds are useful, for example, as analytical tools, probes in biological assays, or sodium channel blockers with improved therapeutic profile.

[0066] In one aspect, the present invention features (4-isopropoxy-3-methoxyphenyl)(2'-methyl-6'-(trifluoromethyl)-3',4'-dihydro-2'H-spiro[piperidine-4,1'-pyrrolo[1,2-a]pyrazine]-1-yl)methanone characterized as Compound 1 Form A.

[0067] In another embodiment, the Compound 1 Form A is characterized by one or more peaks at 17.0 to 17.4 degrees, 11.0 to 11.4 degrees, and 20.3 to 20.7 degrees in an X-ray powder diffraction obtained using Cu K alpha radiation. In another embodiment, the Compound 1 Form A is characterized by one or more peaks at 17.2, 11.2, and 20.5 degrees. In another embodiment, the Compound 1 Form A is further characterized by a peak at 18.5 to 18.9 degrees. In another embodiment, the Compound 1 Form A is further characterized by a peak at 18.7 degrees. In another embodiment, the Compound 1 Form A is further characterized by a peak at 15.5 to 15.9 degrees. In another embodiment, the Compound 1 Form A is further characterized by a peak at 15.7 degrees. In another embodiment, the Compound 1 Form A is further characterized by a peak at 15.8 to 16.2 degrees. In another embodiment, the Compound 1 Form A is further characterized by a peak at 16.0 degrees. In another embodiment, the Compound 1 Form A is characterized by a diffraction pattern substantially similar to that of Figure 1.

[0068] In another aspect, the invention features a crystal form of (4-isopropoxy-3-methoxyphenyl)(2'-methyl-6'-(trifluoromethyl)-3',4'-dihydro-2'H-spiro[piperidine-4,1'-pyrrolo[1,2-a]pyrazine]-1-yl)methanone having a monoclinic crystal system, a P21/c space group, and the following unit cell dimensions:

[0069] $a = 33.8479 (11) \text{ \AA}$ $\alpha = 90^\circ$

[0070] $b = 6.2867 (2) \text{ \AA}$ $\beta = 109.99^\circ$

[0071] $c = 23.1385 (8) \text{ \AA}$ $\gamma = 90^\circ$.

[0072] In another aspect, the invention features a pharmaceutical composition comprising Compound 1 Form A of any one of the aspects or embodiments described above, and a pharmaceutically acceptable carrier.

[0073] In one aspect, the present invention features (4-isopropoxy-3-methoxyphenyl)(2'-methyl-6'-(trifluoromethyl)-3',4'-dihydro-2'H-spiro[piperidine-4,1'-pyrrolo[1,2-a]pyrazine]-1-yl)methanone HCl salt characterized as Compound 1 HCl

Salt Form B. In another embodiment, the Compound 1 HCl Salt Form B is characterized by one or more peaks at 5.0 to 5.4 degrees, 15.5 to 15.9 degrees, and 10.3 to 10.7 degrees in an X-ray powder diffraction obtained using Cu K alpha radiation. In another embodiment, the Compound 1 HCl Salt Form B is characterized by one or more peaks at 5.2, 15.7, and 10.5 degrees. In another embodiment, the Compound 1 HCl Salt Form B is further characterized by a peak at 26.1 to 26.5 degrees. In another embodiment, the Compound 1 HCl Salt Form B is further characterized by a peak at 26.3 degrees. In another embodiment, the Compound 1 HCl Salt Form B is further characterized by a peak at 20.8 to 21.2 degrees. In another embodiment, the Compound 1 HCl Salt Form B is further characterized by a peak at 21.0 degrees. In another embodiment, the Compound 1 HCl Salt Form B is further characterized by a peak at 23.6 to 24.0 degrees. In another embodiment, the Compound 1 HCl Salt Form B is further characterized by a peak at 23.8 degrees. In another embodiment, the Compound 1 HCl Salt Form B is characterized by a diffraction pattern substantially similar to that of Figure 10.

[0074] In another aspect, the invention features a crystal form of (4-isopropoxy-3-methoxyphenyl)(2'-methyl-6'-(trifluoromethyl)-3',4'-dihydro-2'H-spiro[piperidine-4,1'-pyrrolo[1,2-a]pyrazine]-1-yl)methanone HCl salt having a monoclinic crystal system, a P21/c space group, and the following unit cell dimensions:

[0075] $a = 33.8479 (11) \text{ \AA}$ $\alpha = 90^\circ$

[0076] $b = 6.2867 (2) \text{ \AA}$ $\beta = 109.99^\circ$

[0077] $c = 23.1385 (8) \text{ \AA}$ $\gamma = 90^\circ$.

[0078] In another aspect, the invention features a pharmaceutical composition comprising Compound 1 HCl Salt Form B of any of the above described aspects or embodiments, and a pharmaceutically acceptable carrier.

[0079] In another aspect, the invention features (4-isopropoxy-3-methoxyphenyl)(2'-methyl-6'-(trifluoromethyl)-3',4'-dihydro-2'H-spiro[piperidine-4,1'-pyrrolo[1,2-a]pyrazine]-1-yl)methanone mesylate salt characterized as Compound 1 Mesylate Salt Form A. In another embodiment, the Compound 1 Mesylate Salt Form A is characterized by one or more peaks at 21.6 to 22.0 degrees, 16.4 to 16.8 degrees,

and 21.1 to 21.5 degrees in an X-ray powder diffraction obtained using Cu K alpha radiation. In another embodiment, the Compound 1 Mesylate Salt Form A is characterized by one or more peaks at 21.8, 16.6, and 21.3 degrees. In another embodiment, the Compound 1 Mesylate Salt Form A is further characterized by a peak at 16.7 to 17.1 degrees. In another embodiment, the Compound 1 Mesylate Salt Form A is further characterized by a peak at 16.9 degrees. In another embodiment, the Compound 1 Mesylate Salt Form A is further characterized by a peak at 15.7 to 16.1 degrees. In another embodiment, the Compound 1 Mesylate Salt Form A is further characterized by a peak at 15.9 degrees. In another embodiment, the Compound 1 Mesylate Salt Form A is further characterized by a peak at 15.4 to 15.8 degrees. In another embodiment, the Compound 1 Mesylate Salt Form A is further characterized by a peak at 15.6 degrees. In another embodiment, the Compound 1 Mesylate Salt Form A is characterized by a diffraction pattern substantially similar to that of Figure 15.

[0080] In another aspect, the invention features a pharmaceutical composition comprising Compound 1 Mesylate Salt Form A of any of the above aspects or embodiments, and a pharmaceutically acceptable carrier.

[0081] In one aspect, the invention features (4-isopropoxy-3-methoxyphenyl)(2'-methyl-6'-(trifluoromethyl)-3',4'-dihydro-2'H-spiro[piperidine-4,1'-pyrrolo[1,2-a]pyrazine]-1-yl)methanone mesylate salt characterized as Compound 1 Besylate Salt Form A. In another embodiment, the Compound 1 Besylate Salt Form A is characterized by one or more peaks at 5.7 to 5.9 degrees, 21.3 to 21.7 degrees, and 18.6 to 19.0 degrees in an X-ray powder diffraction obtained using Cu K alpha radiation. In another embodiment, the Compound 1 Besylate Salt Form A is characterized by one or more peaks at 5.9, 21.5, and 18.8 degrees. In another embodiment, the Compound 1 Besylate Salt Form A is further characterized by a peak at 16.5 to 16.9 degrees. In another embodiment, the Compound 1 Besylate Salt Form A is further characterized by a peak at 16.7 degrees. In another embodiment, the Compound 1 Besylate Salt Form A is further characterized by a peak at 19.2 to 19.6 degrees. In another embodiment, the Compound 1 Besylate Salt Form A is further characterized by a peak at 19.4 degrees. In another embodiment, the Compound 1

Besylate Salt Form A is further characterized by a peak at 16.8 to 17.2 degrees. In another embodiment, the Compound 1 Besylate Salt Form A is further characterized by a peak at 17.0 degrees. In another embodiment, the Compound 1 Besylate Salt Form A is characterized by a diffraction pattern substantially similar to that of Figure 18.

5 **[0082]** In one aspect, the invention features a pharmaceutical composition comprising Compound 1 Besylate Salt Form A of any one of the above aspects or embodiments, and a pharmaceutically acceptable carrier.

[0083] In one aspect, the invention features (4-isopropoxy-3-methoxyphenyl)(2'-methyl-6'-(trifluoromethyl)-3',4'-dihydro-2'H-spiro[piperidine-4,1'-pyrrolo[1,2-a]pyrazine]-1-yl)methanone tosylate salt characterized as Compound 1
10 Tosylate Salt Form A. In another embodiment, the Compound 1 Tosylate Salt Form A is characterized by one or more peaks at 5.8 to 6.2 degrees, 20.1 to 20.5 degrees, and 23.9 to 24.3 degrees in an X-ray powder diffraction obtained using Cu K alpha radiation. In another embodiment, the Compound 1 Tosylate Salt Form A is
15 characterized by one or more peaks at 6.0, 20.3, and 24.1 degrees. In another embodiment, the Compound 1 Tosylate Salt Form A is further characterized by a peak at 11.8 to 12.2 degrees. In another embodiment, the Compound 1 Tosylate Salt Form A is further characterized by a peak at 12.0 degrees. In another embodiment, the Compound 1 Tosylate Salt Form A is further characterized by a peak at 22.6 to 23.0
20 degrees. In another embodiment, the Compound 1 Tosylate Salt Form A is further characterized by a peak at 22.8 degrees. In another embodiment, the Compound 1 Tosylate Salt Form A is further characterized by a peak at 16.2 to 16.6 degrees. In another embodiment, the Compound 1 Tosylate Salt Form A is further characterized by a peak at 16.4 degrees. In another embodiment, the Compound 1 Tosylate Salt Form A
25 is characterized by a diffraction pattern substantially similar to that of Figure 21.

[0084] In another aspect, the invention features a pharmaceutical composition comprising Compound 1 Tosylate Salt Form A of any one of the above described aspects or embodiments, and a pharmaceutically acceptable carrier.

[0085] In another aspect, the invention features a method of inhibiting a
30 voltage-gated sodium ion channel in a patient; or a biological sample comprising administering to the patient, or contacting the biological sample, with Compound 1

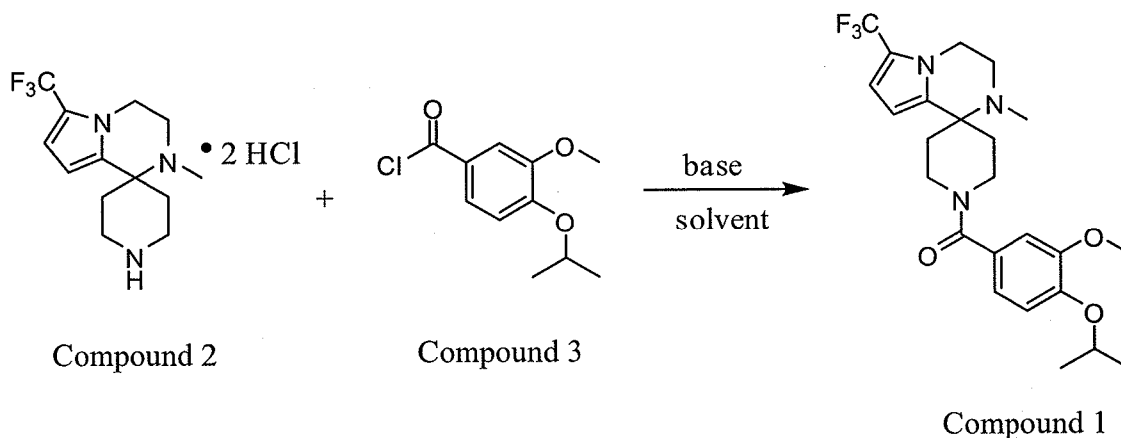
Form A, Compound 1 HCl Salt Form B, Compound 1 Mesylate Salt Form A, Compound 1 Besylate Salt Form A, or Compound 1 Tosylate Salt Form A. In another embodiment, the voltage-gated sodium ion channel is NaV 1.7.

[0086] In another aspect, the invention features a method of treating or lessening the severity in a subject of acute, chronic, neuropathic, or inflammatory pain, arthritis, migraine, cluster headaches, trigeminal neuralgia, herpetic neuralgia, general neuralgias, epilepsy or epilepsy conditions, neurodegenerative disorders, psychiatric disorders, anxiety, depression, bipolar disorder, myotonia, arrhythmia, movement disorders, neuroendocrine disorders, ataxia, multiple sclerosis, irritable bowel syndrome, incontinence, visceral pain, osteoarthritis pain, postherpetic neuralgia, diabetic neuropathy, radicular pain, sciatica, back pain, head or neck pain, severe or intractable pain, nociceptive pain, breakthrough pain, postsurgical pain, cancer pain, stroke, cerebral ischemia, traumatic brain injury, amyotrophic lateral sclerosis, stress- or exercise induced angina, palpitations, hypertension, migraine, or abnormal gastrointestinal motility, comprising administering an effective amount of a pharmaceutical composition comprising Compound 1 Form A, Compound 1 HCl Salt Form B, Compound 1 Mesylate Salt Form A, Compound 1 Besylate Salt Form A, or Compound 1 Tosylate Salt Form A.

[0087] In another embodiment, the method is used for treating or lessening the severity of femur cancer pain; non-malignant chronic bone pain; rheumatoid arthritis; osteoarthritis; spinal stenosis; neuropathic low back pain; neuropathic low back pain; myofascial pain syndrome; fibromyalgia; temporomandibular joint pain; chronic visceral pain, abdominal pain; pancreatic; IBS pain; chronic and acute headache pain; migraine; tension headache, including, cluster headaches; chronic and acute neuropathic pain, post-herpetic neuralgia; diabetic neuropathy; HIV-associated neuropathy; trigeminal neuralgia; Charcot-Marie Tooth neuropathy; hereditary sensory neuropathies; peripheral nerve injury; painful neuromas; ectopic proximal and distal discharges; radiculopathy; chemotherapy induced neuropathic pain; radiotherapy-induced neuropathic pain; post-mastectomy pain; central pain; spinal cord injury pain; post-stroke pain; thalamic pain; complex regional pain syndrome; phantom pain; intractable pain; acute pain, acute post-operative pain; acute musculoskeletal pain; joint

pain; mechanical low back pain; neck pain; tendonitis; injury/exercise pain; acute visceral pain, abdominal pain; pyelonephritis; appendicitis; cholecystitis; intestinal obstruction; hernias; chest pain, cardiac pain; pelvic pain, renal colic pain, acute obstetric pain, labor pain; cesarean section pain; acute inflammatory, burn and trauma pain; acute intermittent pain, endometriosis; acute herpes zoster pain; sickle cell anemia; acute pancreatitis; breakthrough pain; orofacial pain including sinusitis pain, dental pain; multiple sclerosis (MS) pain; pain in depression; leprosy pain; Behcet's disease pain; adiposis dolorosa; phlebotic pain; Guillain-Barre pain; painful legs and moving toes; Haglund syndrome; erythromelalgia pain; Fabry's disease pain; bladder and urogenital disease, including, urinary incontinence; hyperactivity bladder; painful bladder syndrome; interstitial cystitis (IC); prostatitis; complex regional pain syndrome (CRPS), type I and type II; widespread pain, paroxysmal extreme pain, pruritis, tinnitus, or angina-induced pain.

[0088] In another aspect, the present invention provides a process of preparing Compound 1 comprising reacting Compounds 2 and 3 together in a solvent in the presence of a base:



wherein the base is an inorganic base. In another embodiment, the base is potassium carbonate, cesium carbonate, potassium phosphate, sodium carbonate, sodium phosphate, sodium hydroxide, potassium hydroxide or lithium hydroxide. In another embodiment, the base is sodium hydroxide.

[0089] In another embodiment, the invention features the above process, wherein the solvent is an aprotic solvent. In another embodiment, the solvent is 1,2-

dimethoxyethane, dioxane, acetonitrile, toluene, benzene, xylenes, methyl *t*-butyl ether, methyl ethyl ketone, methyl isobutyl ketone, acetone, *N,N*-dimethylformamide, *N,N*-dimethylacetamide, *N*-methylpyrrolidinone, THF, 2-Me-THF, or dimethylsulfoxide. In another embodiment, the solvent is 2-Me-THF.

- 5 **[0090]** In another embodiment, the invention features the above process, wherein the reaction is carried out at about 5 °C to 25 °C. In another embodiment, the reaction is carried out at about 10 °C to 20 °C. In another embodiment, the reaction is carried out at about 15 °C.

- [0091]** In another embodiment, the invention features the above process,
10 wherein the process further comprises recrystallization of Compound 1. In another embodiment, Compound 1 is recrystallized from an aprotic solvent. In another embodiment, Compound 1 is recrystallized from an alkane or cycloalkane solvent. In another embodiment, Compound 1 is recrystallized from cyclohexane.

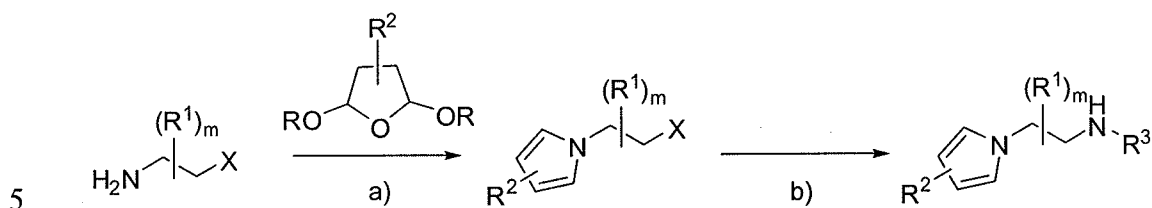
- [0092]** In another embodiment, the invention features the above
15 recrystallization process, wherein prior to recrystallization, the process comprises: a) dissolving Compound 1 in a solvent and treating it with an aqueous acid solution; b) separating the aqueous acid solution and adding a solvent to the separated aqueous acid solution followed by adding a base; and c) separating the solvent and removing it under reduced pressure leaving behind Compound 1 for recrystallization.

- 20 **[0093]** In another embodiment, the solvent in steps a), b), and c) is an aprotic solvent. In another embodiment, the solvent in steps a), b), and c) is ,2-dimethoxyethane, dioxane, acetonitrile, toluene, benzene, xylenes, methyl *t*-butyl ether, methyl ethyl ketone, methyl isobutyl ketone, acetone, *N,N*-dimethylformamide, *N,N*-dimethylacetamide, *N*-methylpyrrolidinone, THF, 2-Me-THF, or
25 dimethylsulfoxide. In another embodiment, the solvent in steps a), b), and c) is toluene.

- [0094]** In another embodiment, the aqueous acid solution is a protic aqueous acid solution. In another embodiment, the aqueous acid solution is selected from hydrochloric, sulfuric, nitric, phosphoric, or boric acid. In another embodiment, the
30 aqueous acid solution is hydrochloric acid.

[0095] Compound 1 of the invention may be prepared readily using the following methods. Illustrated below in Schemes 1 through 4 are methods for preparing Compound 1 and derivatives thereof.

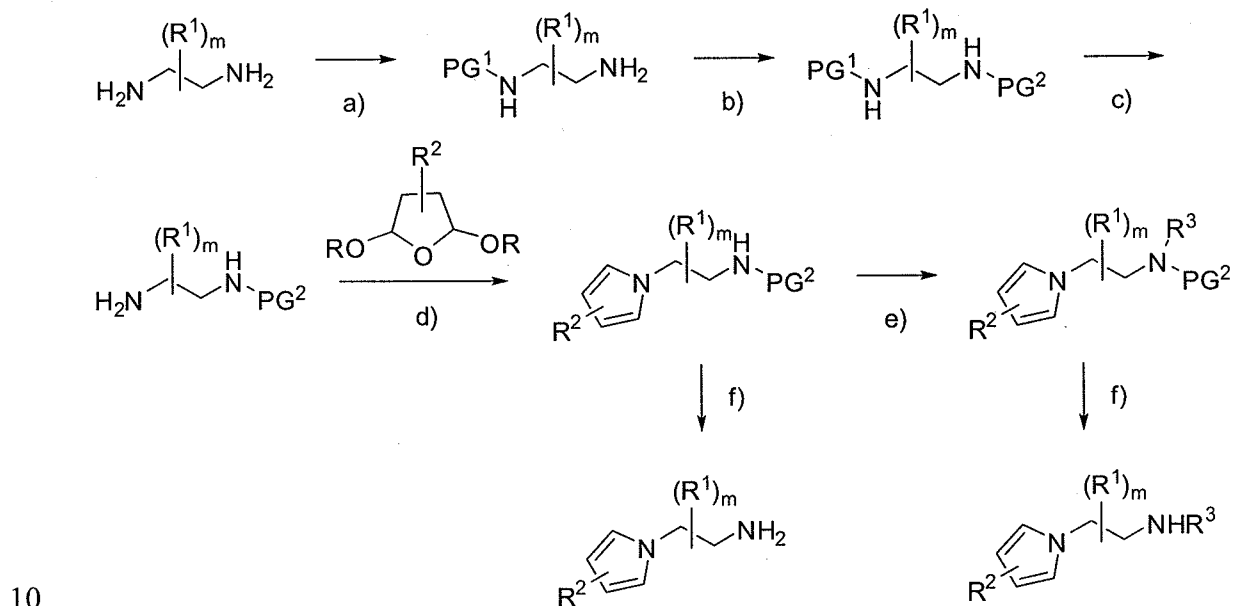
[0096] Scheme 1



X = leaving group or NH_2 ; R^3 = alkyl.

a) H^+ : protic acid such as acetic acid or para-toluene sulfonic acid, NaOAc ; b) H_2NR^3 , solvent (ex: EtOH or CH_3CN).

[0097] Scheme 2

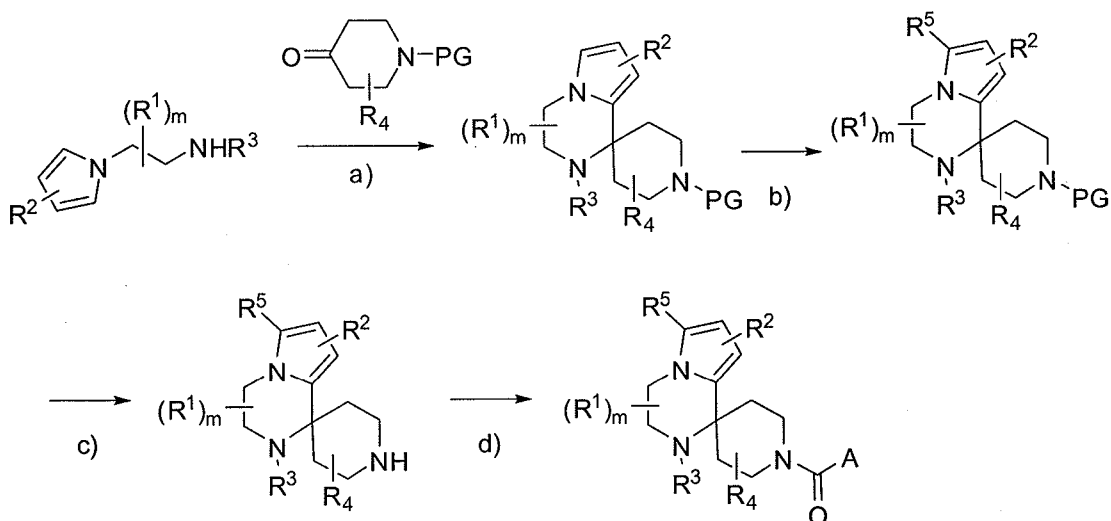


PG^1 = acid-labile protecting group (ex: Boc); PG^2 = acid-stable protecting group (ex: cbz , benzyl); R^3 = alkyl.

a) PG^1 = Boc ; Boc_2O , base (ex: Et_3N), solvent (ex: THF); b) PG^2 = cbz ; benzyl 2,5-dioxopyrrolidin-1-yl carbonate, base (ex: Et_3N), solvent (ex: THF); c) PG^1 = Boc ; H^+ (ex: HCl or TFA), solvent (ex: iPrOH , EtOH , CH_3CN or CH_2Cl_2); d) H^+ : protic acid such as acetic acid or para-toluene sulfonic acid, NaOAc ; e) R^3-X , base (ex: NaH or

K_2CO_3), solvent (ex: DMF, THF or CH_3CN); f) $PG^2 = cbz$; Pd/C , H_2 , solvent (ex: $iPrOH$, $EtOH$ or CH_3CN).

[0098] Scheme 3

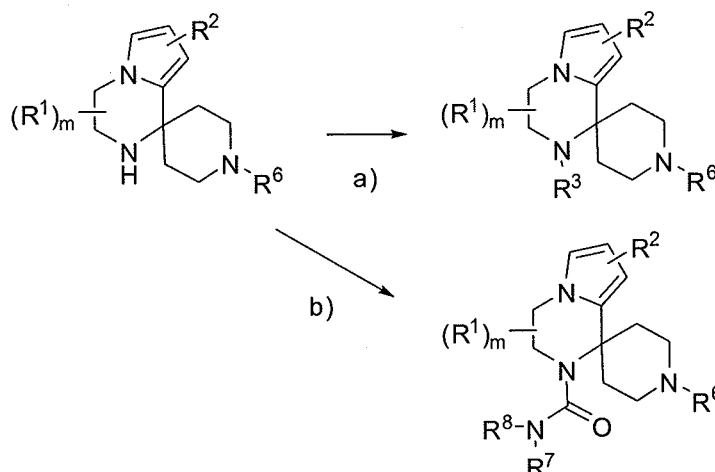


5

PG = protective group such as Boc, benzyl, cbz ; $R^3 = H$ or alkyl.

- a) cat. H^+ : protic acid such as trifluoroacetic acid, para-toluene sulfonic acid or dichloroacetic acid, solvent (ex: $EtOH$); b) $R^5 = CF_3$, 5-(trifluoromethyl)-5H-dibenzo[b,d]thiophenium trifluoromethanesulfonate, base (ex: K_2CO_3), solvent (ex: CH_3CN) or $R^5 = \text{haloalkyl}$; haloalkyl iodide (ex: CF_3I , CF_3CH_2I , or CF_3CF_2I), $FeSO_4 \cdot 6H_2O$, H_2O_2 , solvent (ex: $DMSO$); $R^5 = CN$, chlorosulfonyl isocyanate, solvent (ex: THF or DMF); $R^5 = Cl$, CF_3SO_2Cl , solvent (ex: CH_2Cl_2); $R^5 = R^6C(O)$, acylating agent (ex: $R^6C(O)_2O$, $R^6C(O)Cl$), base (ex: pyridine, Et_3N , or DBN), solvent (ex: CH_2Cl_2 , DCE , or THF) or i) NBS , CH_2Cl_2 ; ii) $CH_3(CH_2)_nOCH=CHR^7$, catalyst (ex: $Pd_2dba_3 \cdot CHCl_3$), solvent (ex: dioxane); c) $PG = Boc$, H^+ (ex: HCl or TFA), solvent (ex: $iPrOH$, $EtOH$, CH_3CN or CH_2Cl_2); $PG = cbz$; Pd/C , H_2 , solvent (ex: $iPrOH$, $EtOH$ or CH_3CN); d) $A-CO_2H$; coupling agent (ex: $HATU$ or $EDCI$), base (ex: Et_3N or iPr_2NEt), solvent (ex: DMF , CH_3CN or CH_2Cl_2); or $A-C(O)-Cl$, $NaOH$, solvent (ex: water and $MTBE$).

[0099] Scheme 4



R^3 = acyl; R^6 = PG or $C(O)A$; R^7 = alkyl.

- a) R^3-X (X = leaving group ex: halo, OTs), base (ex: K_2CO_3 , Et_3N or pyridine), solvent (ex: DMF, THF, ACN, CH_2Cl_2 or pyridine); b) $R^8 = H$; R^7-NCO , base (ex: Et_3N), solvent (ex: THF) or $ClC(O)NR^7R^8$, base (ex: pyridine).

Uses, Formulation and Administration

Pharmaceutically acceptable compositions

- [00100] As discussed above, the invention provides several different solid forms of Compound 1 that are inhibitors of voltage-gated sodium ion channels, and thus are useful for the treatment of diseases, disorders, and conditions including, but not limited to acute, chronic, neuropathic, or inflammatory pain, arthritis, migraine, cluster headaches, trigeminal neuralgia, herpetic neuralgia, general neuralgias, epilepsy or epilepsy conditions, neurodegenerative disorders, psychiatric disorders such as anxiety and depression, myotonia, arrhythmia, movement disorders, neuroendocrine disorders, ataxia, multiple sclerosis, irritable bowel syndrome, and incontinence. Accordingly, in another aspect of the invention, pharmaceutically acceptable compositions are provided, wherein these compositions comprise the various solid forms of Compound 1 as described herein, and optionally comprise a pharmaceutically acceptable carrier, adjuvant or vehicle. In certain embodiments, these compositions optionally further comprise one or more additional therapeutic agents.

[00101] It will also be appreciated that the solid forms of Compound 1 can exist

in free form for treatment, or where appropriate, as a pharmaceutically acceptable derivative thereof. According to the invention, a pharmaceutically acceptable derivative includes, but is not limited to, pharmaceutically acceptable salts, esters, salts of such esters, or any other adduct or derivative which upon administration to a subject in need
5 is capable of providing, directly or indirectly, a compound as otherwise described herein, or a metabolite or residue thereof.

[00102] As used herein, the term “pharmaceutically acceptable salt” refers to those salts which are, within the scope of sound medical judgement, suitable for use in contact with the tissues of humans and lower animals without undue toxicity, irritation,
10 allergic response and the like, and are commensurate with a reasonable benefit/risk ratio. A “pharmaceutically acceptable salt” means any non-toxic salt or salt of an ester of a compound of this invention that, upon administration to a recipient, is capable of providing, either directly or indirectly, a compound of this invention or an inhibitorily active metabolite or residue thereof. As used herein, the term “inhibitorily active
15 metabolite or residue thereof” means that a metabolite or residue thereof is also an inhibitor of a voltage-gated sodium ion channel.

[00103] Pharmaceutically acceptable salts are well known in the art. For example, S. M. Berge, et al. describe pharmaceutically acceptable salts in detail in J. Pharmaceutical Sciences, 1977, 66, 1-19, incorporated herein by reference.
20 Pharmaceutically acceptable salts of the compounds of this invention include those derived from suitable inorganic and organic acids and bases. Examples of pharmaceutically acceptable, nontoxic acid addition salts are salts of an amino group formed with inorganic acids such as hydrochloric acid, hydrobromic acid, phosphoric acid, sulfuric acid and perchloric acid or with organic acids such as acetic acid, oxalic acid, maleic acid, tartaric acid, citric acid, succinic acid or malonic acid or by using
25 other methods used in the art such as ion exchange. Other pharmaceutically acceptable salts include adipate, alginate, ascorbate, aspartate, benzenesulfonate, benzoate, bisulfate, borate, butyrate, camphorate, camphorsulfonate, citrate, cyclopentanepropionate, digluconate, dodecylsulfate, ethanesulfonate, formate, fumarate, glucoheptonate, glycerophosphate, gluconate, hemisulfate, heptanoate,
30 hexanoate, hydroiodide, 2-hydroxy-ethanesulfonate, lactobionate, lactate, laurate,

lauryl sulfate, malate, maleate, malonate, methanesulfonate, 2-naphthalenesulfonate, nicotinate, nitrate, oleate, oxalate, palmitate, pamoate, pectinate, persulfate, 3-phenylpropionate, phosphate, picrate, pivalate, propionate, stearate, succinate, sulfate, tartrate, thiocyanate, p-toluenesulfonate, undecanoate, valerate salts, and the like. Salts derived from appropriate bases include alkali metal, alkaline earth metal, ammonium and $N^+(C_{1-4}alkyl)_4$ salts. This invention also envisions the quaternization of any basic nitrogen-containing groups of the compounds disclosed herein. Water or oil-soluble or dispersible products may be obtained by such quaternization. Representative alkali or alkaline earth metal salts include sodium, lithium, potassium, calcium, magnesium, and the like. Further pharmaceutically acceptable salts include, when appropriate, nontoxic ammonium, quaternary ammonium, and amine cations formed using counterions such as halide, hydroxide, carboxylate, sulfate, phosphate, nitrate, loweralkyl sulfonate and aryl sulfonate.

[00104] As described above, the pharmaceutically acceptable compositions of the invention additionally comprise a pharmaceutically acceptable carrier, adjuvant, or vehicle, which, as used herein, includes any and all solvents, diluents, or other liquid vehicle, dispersion or suspension aids, surface active agents, isotonic agents, thickening or emulsifying agents, preservatives, solid binders, lubricants and the like, as suited to the particular dosage form desired. Remington's Pharmaceutical Sciences, Sixteenth Edition, E. W. Martin (Mack Publishing Co., Easton, Pa., 1980) discloses various carriers used in formulating pharmaceutically acceptable compositions and known techniques for the preparation thereof. Except insofar as any conventional carrier medium is incompatible with the compounds of the invention, such as by producing any undesirable biological effect or otherwise interacting in a deleterious manner with any other component(s) of the pharmaceutically acceptable composition, its use is contemplated to be within the scope of this invention. Some examples of materials which can serve as pharmaceutically acceptable carriers include, but are not limited to, ion exchangers, alumina, aluminum stearate, lecithin, serum proteins, such as human serum albumin, buffer substances such as phosphates, glycine, sorbic acid, or potassium sorbate, partial glyceride mixtures of saturated vegetable fatty acids, water, salts or electrolytes, such as protamine sulfate, disodium hydrogen phosphate, potassium hydrogen phosphate, sodium chloride, zinc salts, colloidal silica, magnesium

trisilicate, polyvinyl pyrrolidone, polyacrylates, waxes, polyethylene-polyoxypropylene-block polymers, wool fat, sugars such as lactose, glucose and sucrose; starches such as corn starch and potato starch; cellulose and its derivatives such as sodium carboxymethyl cellulose, ethyl cellulose and cellulose acetate;

5 powdered tragacanth; malt; gelatin; talc; excipients such as cocoa butter and suppository waxes; oils such as peanut oil, cottonseed oil; safflower oil; sesame oil; olive oil; corn oil and soybean oil; glycols; such a propylene glycol or polyethylene glycol; esters such as ethyl oleate and ethyl laurate; agar; buffering agents such as magnesium hydroxide and aluminum hydroxide; alginic acid; pyrogen-free water;

10 isotonic saline; Ringer's solution; ethyl alcohol, and phosphate buffer solutions, as well as other non-toxic compatible lubricants such as sodium lauryl sulfate and magnesium stearate, as well as coloring agents, releasing agents, coating agents, sweetening, flavoring and perfuming agents, preservatives and antioxidants can also be present in the composition, according to the judgment of the formulator.

15 *Uses of Compounds and Pharmaceutically Acceptable Compositions*

[00105] In yet another aspect, a method for the treatment or lessening the severity of acute, chronic, neuropathic, or inflammatory pain, arthritis, migraine, cluster headaches, trigeminal neuralgia, herpetic neuralgia, general neuralgias, epilepsy or epilepsy conditions, neurodegenerative disorders, psychiatric disorders such as

20 anxiety and depression, dipolar disorder, myotonia, arrhythmia, movement disorders, neuroendocrine disorders, ataxia, multiple sclerosis, irritable bowel syndrome, incontinence, visceral pain, osteoarthritis pain, postherpetic neuralgia, diabetic neuropathy, radicular pain, sciatica, back pain, head or neck pain, severe or intractable pain, nociceptive pain, breakthrough pain, postsurgical pain, or cancer pain is provided

25 comprising administering an effective amount of a solid form of Compound 1, or a pharmaceutically acceptable composition comprising a solid form of Compound 1 to a subject in need thereof.

[00106] In certain embodiments, a method of treatment or lessening the severity of stroke, cerebral ischemia, traumatic brain injury, amyotrophic lateral sclerosis,

30 stress- or exercise induced angina, palpitations, hypertension, migraine, or abnormal gastro-intestinal motility is provided comprising administering an effective amount of a

compound, or a pharmaceutically acceptable composition comprising a compound to a subject in need thereof.

[00107] In certain embodiments, a method for the treatment or lessening the severity of acute, chronic, neuropathic, or inflammatory pain is provided comprising
5 administering an effective amount of a compound or a pharmaceutically acceptable composition to a subject in need thereof. In certain other embodiments, a method for the treatment or lessening the severity of radicular pain, sciatica, back pain, head pain, or neck pain is provided comprising administering an effective amount of a compound or a pharmaceutically acceptable composition to a subject in need thereof. In still other
10 embodiments, a method for the treatment or lessening the severity of severe or intractable pain, acute pain, postsurgical pain, back pain, tinnitus or cancer pain is provided comprising administering an effective amount of a compound or a pharmaceutically acceptable composition to a subject in need thereof.

[00108] In certain embodiments, a method for the treatment or lessening the
15 severity of femur cancer pain; non-malignant chronic bone pain; rheumatoid arthritis; osteoarthritis; spinal stenosis; neuropathic low back pain; neuropathic low back pain; myofascial pain syndrome; fibromyalgia; temporomandibular joint pain; chronic visceral pain, including, abdominal; pancreatic; IBS pain; chronic and acute headache pain; migraine; tension headache, including, cluster headaches; chronic and acute
20 neuropathic pain, including, post-herpetic neuralgia; diabetic neuropathy; HIV-associated neuropathy; trigeminal neuralgia; Charcot-Marie Tooth neuropathy; hereditary sensory neuropathies; peripheral nerve injury; painful neuromas; ectopic proximal and distal discharges; radiculopathy; chemotherapy induced neuropathic pain; radiotherapy-induced neuropathic pain; post-mastectomy pain; central pain; spinal cord
25 injury pain; post-stroke pain; thalamic pain; complex regional pain syndrome; phantom pain; intractable pain; acute pain, acute post-operative pain; acute musculoskeletal pain; joint pain; mechanical low back pain; neck pain; tendonitis; injury/exercise pain; acute visceral pain, including, abdominal pain; pyelonephritis; appendicitis; cholecystitis; intestinal obstruction; hernias; etc; chest pain, including, cardiac Pain;
30 pelvic pain, renal colic pain, acute obstetric pain, including, labor pain; cesarean section pain; acute inflammatory, burn and trauma pain; acute intermittent pain,

including, endometriosis; acute herpes zoster pain; sickle cell anemia; acute pancreatitis; breakthrough pain; orofacial pain including sinusitis pain, dental pain; multiple sclerosis (MS) pain; pain in depression; leprosy pain; behcet's disease pain; adiposis dolorosa; phlebitic pain; Guillain-Barre pain; painful legs and moving toes;

5 Haglund syndrome; erythromelalgia pain; Fabry's disease pain; bladder and urogenital disease, including, urinary incontinence; hyperactivity bladder; painful bladder syndrome; interstitial cystitis (IC); or prostatitis; complex regional pain syndrome (CRPS), type I and type II; angina-induced pain is provided, comprising administering an effective amount of a solid form of Compound 1 or a pharmaceutically acceptable

10 composition to a subject in need thereof.

[00109] In certain embodiments of the invention an "effective amount" of a solid form of Compound 1 or a pharmaceutically acceptable composition thereof is that amount effective for treating or lessening the severity of one or more of acute, chronic, neuropathic, or inflammatory pain, arthritis, migraine, cluster headaches, trigeminal

15 neuralgia, herpetic neuralgia, general neuralgias, epilepsy or epilepsy conditions, neurodegenerative disorders, psychiatric disorders such as anxiety and depression, myotonia, arrhythmia, movement disorders, neuroendocrine disorders, ataxia, multiple sclerosis, irritable bowel syndrome, incontinence, visceral pain, osteoarthritis pain, postherpetic neuralgia, diabetic neuropathy, radicular pain, sciatica, back pain, head or

20 neck pain, severe or intractable pain, nociceptive pain, breakthrough pain, postsurgical pain, tinnitus or cancer pain.

[00110] Solid forms of Compound 1 and compositions thereof, according to the method of the invention, may be administered using any amount and any route of administration effective for treating or lessening the severity of one or more of acute,

25 chronic, neuropathic, or inflammatory pain, arthritis, migraine, cluster headaches, trigeminal neuralgia, herpetic neuralgia, general neuralgias, epilepsy or epilepsy conditions, neurodegenerative disorders, psychiatric disorders such as anxiety and depression, myotonia, arrhythmia, movement disorders, neuroendocrine disorders, ataxia, multiple sclerosis, irritable bowel syndrome, incontinence, visceral pain,

30 osteoarthritis pain, postherpetic neuralgia, diabetic neuropathy, radicular pain, sciatica, back pain, head or neck pain, severe or intractable pain, nociceptive pain, breakthrough

pain, postsurgical pain, tinnitus or cancer pain. The exact amount required will vary from subject to subject, depending on the species, age, and general condition of the subject, the severity of the infection, the particular agent, its mode of administration, and the like. The solid forms of Compound 1 is preferably formulated in dosage unit
5 form for ease of administration and uniformity of dosage. The expression "dosage unit form" as used herein refers to a physically discrete unit of agent appropriate for the subject to be treated. It will be understood, however, that the total daily usage of the compounds and compositions of the invention will be decided by the attending physician within the scope of sound medical judgment. The specific effective dose
10 level for any particular subject or organism will depend upon a variety of factors including the disorder being treated and the severity of the disorder; the activity of the specific compound employed; the specific composition employed; the age, body weight, general health, sex and diet of the subject; the time of administration, route of administration, and rate of excretion of the specific compound employed; the duration
15 of the treatment; drugs used in combination or coincidental with the specific compound employed, and like factors well known in the medical arts. The term "subject" or "patient", as used herein, means an animal, preferably a mammal, and most preferably a human.

[00111] The pharmaceutically acceptable compositions of this invention can be
20 administered to humans and other animals orally, rectally, parenterally, intracisternally, intravaginally, intraperitoneally, topically (as by powders, ointments, or drops), buccally, as an oral or nasal spray, or the like, depending on the severity of the infection being treated. In certain embodiments, the compounds of the invention may be administered orally or parenterally at dosage levels of about 0.01 mg/kg to about 50
25 mg/kg and preferably from about 1 mg/kg to about 25 mg/kg, of subject body weight per day, one or more times a day, to obtain the desired therapeutic effect.

[00112] Liquid dosage forms for oral administration include, but are not limited to, pharmaceutically acceptable emulsions, microemulsions, solutions, suspensions, syrups and elixirs. In addition to the active compounds, the liquid dosage forms may
30 contain inert diluents commonly used in the art such as, for example, water or other solvents, solubilizing agents and emulsifiers such as ethyl alcohol, isopropyl alcohol,

ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propylene glycol, 1,3-butylene glycol, dimethylformamide, oils (in particular, cottonseed, groundnut, corn, germ, olive, castor, and sesame oils), glycerol, tetrahydrofurfuryl alcohol, polyethylene glycols and fatty acid esters of sorbitan, and mixtures thereof. Besides inert diluents, 5 the oral compositions can also include adjuvants such as wetting agents, emulsifying and suspending agents, sweetening, flavoring, and perfuming agents.

[00113] Injectable preparations, for example, sterile injectable aqueous or oleaginous suspensions may be formulated according to the known art using suitable dispersing or wetting agents and suspending agents. The sterile injectable preparation 10 may also be a sterile injectable solution, suspension or emulsion in a nontoxic parenterally acceptable diluent or solvent, for example, as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution, U.S.P. and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any 15 bland fixed oil can be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid are used in the preparation of injectables.

[00114] The injectable formulations can be sterilized, for example, by filtration through a bacterial-retaining filter, or by incorporating sterilizing agents in the form of sterile solid compositions which can be dissolved or dispersed in sterile water or other 20 sterile injectable medium prior to use.

[00115] In order to prolong the effect of a solid form of Compound 1 of the invention, it is often desirable to slow the absorption of the compound from subcutaneous or intramuscular injection. This may be accomplished by the use of a liquid suspension of crystalline or amorphous material with poor water solubility. The 25 rate of absorption of the compound then depends upon its rate of dissolution that, in turn, may depend upon crystal size and crystalline form. Alternatively, delayed absorption of a parenterally administered compound form is accomplished by dissolving or suspending the compound in an oil vehicle. Injectable depot forms are made by forming microencapsule matrices of the compound in biodegradable polymers 30 such as polylactide-polyglycolide. Depending upon the ratio of compound to polymer and the nature of the particular polymer employed, the rate of compound release can be

controlled. Examples of other biodegradable polymers include poly(orthoesters) and poly(anhydrides). Depot injectable formulations are also prepared by entrapping the compound in liposomes or microemulsions that are compatible with body tissues.

[00116] Compositions for rectal or vaginal administration are preferably
5 suppositories which can be prepared by mixing the compounds of this invention with suitable non-irritating excipients or carriers such as cocoa butter, polyethylene glycol or a suppository wax which are solid at ambient temperature but liquid at body temperature and therefore melt in the rectum or vaginal cavity and release the active compound.

10 [00117] Solid dosage forms for oral administration include capsules, tablets, pills, powders, and granules. In such solid dosage forms, the active compound is mixed with at least one inert, pharmaceutically acceptable excipient or carrier such as sodium citrate or dicalcium phosphate and/or a) fillers or extenders such as starches, lactose, sucrose, glucose, mannitol, and silicic acid, b) binders such as, for example,
15 carboxymethylcellulose, alginates, gelatin, polyvinylpyrrolidinone, sucrose, and acacia, c) humectants such as glycerol, d) disintegrating agents such as agar--agar, calcium carbonate, potato or tapioca starch, alginic acid, certain silicates, and sodium carbonate, e) solution retarding agents such as paraffin, f) absorption accelerators such as quaternary ammonium compounds, g) wetting agents such as, for example, cetyl
20 alcohol and glycerol monostearate, h) absorbents such as kaolin and bentonite clay, and i) lubricants such as talc, calcium stearate, magnesium stearate, solid polyethylene glycols, sodium lauryl sulfate, and mixtures thereof. In the case of capsules, tablets and pills, the dosage form may also comprise buffering agents.

[00118] Solid compositions of a similar type may also be employed as fillers in
25 soft and hard-filled gelatin capsules using such excipients as lactose or milk sugar as well as high molecular weight polyethylene glycols and the like. The solid dosage forms of tablets, dragees, capsules, pills, and granules can be prepared with coatings and shells such as enteric coatings and other coatings well known in the pharmaceutical formulating art. They may optionally contain opacifying agents and can also be of a
30 composition that they release the active ingredient(s) only, or preferentially, in a certain part of the intestinal tract, optionally, in a delayed manner. Examples of embedding

compositions that can be used include polymeric substances and waxes. Solid compositions of a similar type may also be employed as fillers in soft and hard-filled gelatin capsules using such excipients as lactose or milk sugar as well as high molecular weight polyethylene glycols and the like.

5 **[00119]** Solid forms of Compound 1 can also be in microencapsulated form with one or more excipients as noted above. The solid dosage forms of tablets, dragees, capsules, pills, and granules can be prepared with coatings and shells such as enteric coatings, release controlling coatings and other coatings well known in the pharmaceutical formulating art. In such solid dosage forms the active compound may
10 be admixed with at least one inert diluent such as sucrose, lactose or starch. Such dosage forms may also comprise, as is normal practice, additional substances other than inert diluents, e.g., tableting lubricants and other tableting aids such as magnesium stearate and microcrystalline cellulose. In the case of capsules, tablets and pills, the dosage forms may also comprise buffering agents. They may optionally contain
15 opacifying agents and can also be of a composition that they release the active ingredient(s) only, or preferentially, in a certain part of the intestinal tract, optionally, in a delayed manner. Examples of embedding compositions that can be used include polymeric substances and waxes.

[00120] Dosage forms for topical or transdermal administration of a compound
20 of this invention include ointments, pastes, creams, lotions, gels, powders, solutions, sprays, inhalants or patches. The active component is admixed under sterile conditions with a pharmaceutically acceptable carrier and any needed preservatives or buffers as may be required. Ophthalmic formulation, eardrops, and eye drops are also contemplated as being within the scope of this invention. Additionally, the invention
25 contemplates the use of transdermal patches, which have the added advantage of providing controlled delivery of a compound to the body. Such dosage forms are prepared by dissolving or dispensing the compound in the proper medium. Absorption enhancers can also be used to increase the flux of the compound across the skin. The rate can be controlled by either providing a rate controlling membrane or by dispersing
30 the compound in a polymer matrix or gel.

[00121] As described generally above, Compound 1 is useful as inhibitors of

voltage-gated sodium ion channels. In one embodiment, Compound 1 and compositions thereof are inhibitors of one or more of NaV1.1, NaV1.2, NaV1.3, NaV1.4, NaV1.5, NaV1.6, NaV1.7, NaV1.8, or NaV1.9, and thus, without wishing to be bound by any particular theory, Compound 1 and compositions thereof are particularly useful for treating or lessening the severity of a disease, condition, or disorder where activation or hyperactivity of one or more of NaV1.1, NaV1.2, NaV1.3, NaV1.4, NaV1.5, NaV1.6, NaV1.7, NaV1.8, or NaV1.9 is implicated in the disease, condition, or disorder. When activation or hyperactivity of NaV1.1, NaV1.2, NaV1.3, NaV1.4, NaV1.5, NaV1.6, NaV1.7, NaV1.8, or NaV1.9 is implicated in a particular disease, condition, or disorder, the disease, condition, or disorder may also be referred to as a “NaV1.1, NaV1.2, NaV1.3, NaV1.4, NaV1.5, NaV1.6, NaV1.7, NaV1.8 or NaV1.9-mediated disease, condition or disorder”. Accordingly, in another aspect, the invention provides a method for treating or lessening the severity of a disease, condition, or disorder where activation or hyperactivity of one or more of NaV1.1, NaV1.2, NaV1.3, NaV1.4, NaV1.5, NaV1.6, NaV1.7, NaV1.8, or NaV1.9 is implicated in the disease state.

[00122] The activity of Compound 1 utilized in this invention as an inhibitor of NaV1.1, NaV1.2, NaV1.3, NaV1.4, NaV1.5, NaV1.6, NaV1.7, NaV1.8, or NaV1.9 may be assayed according to methods described generally in the Examples herein, or according to methods available to one of ordinary skill in the art.

[00123] In certain exemplary embodiments, Compound 1 and compositions thereof are useful as inhibitors of NaV1.7 and/or NaV1.8.

[00124] It will also be appreciated that Compound 1 and pharmaceutically acceptable compositions thereof can be employed in combination therapies, that is, Compound 1 and pharmaceutically acceptable compositions thereof can be administered concurrently with, prior to, or subsequent to, one or more other desired therapeutics or medical procedures. The particular combination of therapies (therapeutics or procedures) to employ in a combination regimen will take into account compatibility of the desired therapeutics and/or procedures and the desired therapeutic effect to be achieved. It will also be appreciated that the therapies employed may achieve a desired effect for the same disorder (for example, an inventive compound

may be administered concurrently with another agent used to treat the same disorder), or they may achieve different effects (e.g., control of any adverse effects). As used herein, additional therapeutic agents that are normally administered to treat or prevent a particular disease, or condition, are known as “appropriate for the disease, or condition, being treated”. For example, exemplary additional therapeutic agents include, but are not limited to: nonopioid analgesics (indoles such as Etodolac, Indomethacin, Sulindac, Tolmetin; naphthylalkanones such as Nabumetone; oxicams such as Piroxicam; para-aminophenol derivatives, such as Acetaminophen; propionic acids such as Fenoprofen, Flurbiprofen, Ibuprofen, Ketoprofen, Naproxen, Naproxen sodium, Oxaprozin; salicylates such as Aspirin, Choline magnesium trisalicylate, Diflunisal; fenamates such as meclofenamic acid, Mefenamic acid; and pyrazoles such as Phenylbutazone); or opioid (narcotic) agonists (such as Codeine, Fentanyl, Hydromorphone, Levorphanol, Meperidine, Methadone, Morphine, Oxycodone, Oxymorphone, Propoxyphene, Buprenorphine, Butorphanol, Dezocine, Nalbuphine, and Pentazocine). Additionally, nondrug analgesic approaches may be utilized in conjunction with administration of one or more compounds of the invention. For example, anesthesiologic (intrapinal infusion, neural blockade), neurosurgical (neurolysis of CNS pathways), neurostimulatory (transcutaneous electrical nerve stimulation, dorsal column stimulation), physiatric (physical therapy, orthotic devices, diathermy), or psychologic (cognitive methods-hypnosis, biofeedback, or behavioral methods) approaches may also be utilized. Additional appropriate therapeutic agents or approaches are described generally in The Merck Manual, Seventeenth Edition, Ed. Mark H. Beers and Robert Berkow, Merck Research Laboratories, 1999, and the Food and Drug Administration website, www.fda.gov, the entire contents of which are hereby incorporated by reference.

[00125] In another embodiment, additional appropriate therapeutic agents are selected from the following:

[00126] (1) an opioid analgesic, e.g. morphine, heroin, hydromorphone, oxymorphone, levorphanol, levallorphan, methadone, meperidine, fentanyl, cocaine, codeine, dihydrocodeine, oxycodone, hydrocodone, propoxyphene, nalmefene, nalorphine, naloxone, naltrexone, buprenorphine, butorphanol, nalbuphine or

pentazocine;

[00127] (2) a nonsteroidal antiinflammatory drug (NSAID), e.g. aspirin, diclofenac, diflusal, etodolac, fenbufen, fenoprofen, flufenisal, flurbiprofen, ibuprofen, indomethacin, ketoprofen, ketorolac, meclofenamic acid, mefenamic acid,
 5 meloxicam, nabumetone, naproxen, nimesulide, nitroflurbiprofen, olsalazine, oxaprozin, phenylbutazone, piroxicam, sulfasalazine, sulindac, tolmetin or zomepirac;

[00128] (3) a barbiturate sedative, e.g. amobarbital, aprobarbital, butabarbital, butabital, mephobarbital, metharbital, methohexital, pentobarbital, phenobarbital, secobarbital, talbutal, theamylal or thiopental;

10 [00129] (4) a benzodiazepine having a sedative action, e.g. chlordiazepoxide, clorazepate, diazepam, flurazepam, lorazepam, oxazepam, temazepam or triazolam;

[00130] (5) an Hi antagonist having a sedative action, e.g. diphenhydramine, pyrilamine, promethazine, chlorpheniramine or chlorcyclizine;

[00131] (6) a sedative such as glutethimide, meprobamate, methaqualone or
 15 dichloralphenazone;

[00132] (7) a skeletal muscle relaxant, e.g. baclofen, carisoprodol, chlorzoxazone, cyclobenzaprine, methocarbamol or orphenadine;

[00133] (8) an NMDA receptor antagonist, e.g. dextromethorphan ((+)-3-hydroxy-N-methylmorphinan) or its metabolite dextrorphan ((+)-3-hydroxy-N-methylmorphinan), ketamine, memantine, pyrroloquinoline quinine, cis-4-(phosphonomethyl)-2-piperidinecarboxylic acid, budipine, EN-3231 (MorphiDex(R), a combination formulation of morphine and dextromethorphan), topiramate, neramexane or perzinfotel including an NR2B antagonist, e.g. ifenprodil, traxoprodil or
 20 (-)-(R)-6-{2-[4-(3-fluorophenyl)-4-hydroxy-1-piperidinyl]-1-hydroxyethyl}-3,4-dihydro-25 2(1H)-quinolinone;

[00134] (9) an alpha-adrenergic, e.g. doxazosin, tamsulosin, clonidine, guanfacine, dexmetatomidine, modafinil, or 4-amino-6,7-dimethoxy-2-(5-methanesulfonamido-1,2,3,4-tetrahydroisoquinol-2-yl)-5-(2-pyridyl) quinazoline;

[00135] (10) a tricyclic antidepressant, e.g. desipramine, imipramine,

amitriptyline or nortriptyline;

[00136] (11) an anticonvulsant, e.g. carbamazepine, lamotrigine, topiramate or valproate;

[00137] (12) a tachykinin (NK) antagonist, particularly an NK-3, NK-2 or NK-1 antagonist, e.g. ([alpha]R,9R)-7-[3,5-bis(trifluoromethyl)benzyl]-8,9,10,11-tetrahydro-9-methyl-5-(4-methylphenyl)-7H-[1,4]diazocino[2,1-g][1,7]-naphthyridine-6,13-dione (TAK-637), 5-[[[(2R,3S)-2-[(1R)-1-[3,5-bis(trifluoromethyl)phenyl]ethoxy-3-(4-fluorophenyl)-4-morpholinyl]-methyl]-1,2-dihydro-3H-1,2,4-triazol-3-one (MK-869), aprepitant, lanepitant, dapitant or 3-[[2-methoxy-5-(trifluoromethoxy)phenyl]-methylamino]-2-phenylpiperidine (2S,3S);

[00138] (13) a muscarinic antagonist, e.g. oxybutynin, tolterodine, propiverine, trospium chloride, darifenacin, solifenacin, temiverine and ipratropium;

[00139] (14) a COX-2 selective inhibitor, e.g. celecoxib, rofecoxib, parecoxib, valdecoxib, deracoxib, etoricoxib, or lumiracoxib;

[00140] (15) a coal-tar analgesic, in particular paracetamol;

[00141] (16) a neuroleptic such as droperidol, chlorpromazine, haloperidol, perphenazine, thioridazine, mesoridazine, trifluoperazine, fluphenazine, clozapine, olanzapine, risperidone, ziprasidone, quetiapine, sertindole, aripiprazole, sonopiprazole, blonanserin, iloperidone, perospirone, raclopride, zotepine, bifeprunox, asenapine, lurasidone, amisulpride, balaperidone, palindore, eplivanserin, osanetant, rimonabant, meclizine, Miraxion(R) or sarizotan;

[00142] (17) a vanilloid receptor agonist (e.g. resiniferatoxin) or antagonist (e.g. capsaicin);

[00143] (18) a beta-adrenergic such as propranolol;

[00144] (19) a local anaesthetic such as mexiletine;

[00145] (20) a corticosteroid such as dexamethasone;

[00146] (21) a 5-HT receptor agonist or antagonist, particularly a 5-HT_{1B/1D} agonist such as eletriptan, sumatriptan, naratriptan, zolmitriptan or rizatriptan;

[00147] (22) a 5-HT_{2A} receptor antagonist such as R(+)-alpha-(2,3-dimethoxy-

phenyl)-1-[2-(4- fluorophenylethyl)]-4-piperidinemethanol (MDL- 100907);

[00148] (23) a cholinergic (nicotinic) analgesic, such as ispronidine (TC-1734), (E)-N-methyl-4- (3-pyridinyl)-3-buten-1 -amine (RJR-2403), (R)-5-(2-azetidylmethoxy)-2-chloropyridine (ABT-594) or nicotine;

5 [00149] (24) Tramadol(R);

[00150] (25) a PDEV inhibitor, such as 5-[2-ethoxy-5-(4-methyl-1-piperazinyl-sulphonyl)phenyl]- 1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one (sildenafil), (6R,12aR)- 2,3,6,7,12,12a-hexahydro-2-methyl-6-(3,4-methylenedioxyphenyl)-pyrazino[2',1':6,1]- pyrido[3,4-b]indole-1,4-dione (IC-351 or
10 tadalafil), 2-[2-ethoxy-5-(4-ethyl-piperazin-1-yl)-sulphonyl]-phenyl]-5-methyl-7-propyl-3H-imidazo[5,1-f][1,2,4]triazin-4-one (vardenafil), 5- (5-acetyl-2-butoxy-3-pyridinyl)-3-ethyl-2-(1-ethyl-3-azetidyl)-2,6-dihydro-7H-pyrazolo[4,3-<i>i</i>]pyrimidin-7-one, 5-(5-acetyl-2-propoxy-3-pyridinyl)-3-ethyl-2-(1-isopropyl- 3-azetidyl)-2,6-dihydro-7H-pyrazolo[4,3-<i>i</i>]pvrimidm-7-one, 5-[2-ethoxy-5-(4-ethylpiperazin-1-ylsulphonyl)pyridin-3-yl]-3-ethyl-2-[2-methoxyethyl]-2,6-dihydro-7H- pyrazolo[4,3-
15 d]pyrimidin-7-one, 4-[(3-chloro-4-methoxybenzyl)amino]-2-[(2S)-2-(hydroxymethyl)pyrrolidin-1 -yl]-N-(pyrimidin-2-ylmethyl)pyrimidine-5-carboxamide, 3-(1 - methyl-7-oxo-3-propyl-6,7-dihydro-1H-pyrazolo[4,3-d]pyrimidin-5-yl)-N-[2-(1-methylpyrrolidin-2-yl)ethyl]-4-propoxybenzenesulfonamide; (z) an alpha-2-delta
20 ligand such as gabapentin, pregabalin, 3 -methyl gabapentin, (1[alpha],3[alpha],5[alpha])(3-amino-methyl-bicyclo[3.2.0]hept-3-yl)-acetic acid, (3S,5R)-3-aminomethyl- 5-methyl-heptanoic acid, (3S,5R)-3-amino-5-methyl-heptanoic acid, (3S,5R)-3-amino- 5-methyl-octanoic acid, (2S,4S)-4-(3-chlorophenoxy)proline, (2S,4S)-4-(3-fluorobenzyl)- proline, [(1R,5R,6S)-6-(aminomethyl)bicyclo[3.2.0]hept-6-yl]acetic acid, 3-(1-aminomethyl-
25 cyclohexylmethyl)-4H-[1,2,4]oxadiazol-5-one, C-[1 -(I H-tetrazol-5-ylmethyl)-cycloheptyl]- methylamine, (3S,4S)-(1-aminomethyl-3,4-dimethyl-cyclopentyl)-acetic acid, (3 S, 5R)- 3-aminomethyl-5-methyl-octanoic acid, (3S,5R)-3-amino-5-methyl-nonanoic acid, (3S,5R)- 3-amino-5-methyl-octanoic acid, (3R,4R,5R)-3-amino-4,5-
30 dimethyl-heptanoic acid and (3R,4R,5R)-3-amino-4,5-dimethyl-octanoic acid;

[00151] (26) a cannabinoid;

[00152] (27) metabotropic glutamate subtype 1 receptor (mGluR1) antagonist;

[00153] (28) a serotonin reuptake inhibitor such as sertraline, sertraline metabolite demethylsertraline, fluoxetine, norfluoxetine (fluoxetine desmethyl metabolite), fluvoxamine, paroxetine, citalopram, citalopram metabolite
 5 desmethylcitalopram, escitalopram, d,l- fenfluramine, femoxetine, ifoxetine, cyanodothiopin, litoxetine, dapoxetine, nefazodone, cericlamine and trazodone;

[00154] (29) a noradrenaline (norepinephrine) reuptake inhibitor, such as maprotiline, lofepramine, mirtazepine, oxaprotiline, fezolamine, tomoxetine, mianserin, bupropion, bupropion metabolite hydroxybupropion, nomifensine and
 10 viloxazine (Vivalan(R)), especially a selective noradrenaline reuptake inhibitor such as reboxetine, in particular (S,S)-reboxetine;

[00155] (30) a dual serotonin-noradrenaline reuptake inhibitor, such as venlafaxine, venlafaxine metabolite O-desmethylvenlafaxine, clomipramine, clomipramine metabolite desmethylclomipramine, duloxetine, milnacipran and
 15 imipramine;

[00156] (31) an inducible nitric oxide synthase (iNOS) inhibitor such as S-[2-[(1-iminoethyl)amino]ethyl]-L-homocysteine, S-[2-[(1-iminoethyl)-amino]ethyl]-4,4-dioxo-L- cysteine, S-[2-[(1-iminoethyl)amino]ethyl]-2-methyl-L-cysteine, (2S,5Z)-2-amino-2-methyl- 7-[(1-iminoethyl)amino]-5-heptenoic acid, 2-[[[(1R,3S)-3-amino-4-
 20 hydroxy- 1-(5-thiazolyl)-butyl]thio]-S-chloro-S-pyridinecarbonitrile; 2-[[[(1R,3S)-3-amino-4-hydroxy-1-(5- thiazolyl)butyl]thio]-4-chlorobenzonitrile, (2S,4R)-2-amino-4-[[2-chloro-5- (trifluoromethyl)phenyl]thio]-5-thiazolebutanol, 2-[[[(1R,3S)-3-amino-4-hydroxy-1-(5-thiazolyl) butyl]thio]-6-(trifluoromethyl)-3 pyridinecarbonitrile, 2-[[[(1R,3S)-3- amino-4-hydroxy- 1 -(5-thiazolyl)butyl]thio]-5- chlorobenzonitrile, N-[4-
 25 [2-(3-chlorobenzylamino)ethyl]phenyl]thiophene-2-carboxamidine, or guanidinoethyldisulfide;

[00157] (32) an acetylcholinesterase inhibitor such as donepezil;

[00158] (33) a prostaglandin E2 subtype 4 (EP4) antagonist such as 7V-[(2-[4-(2-ethyl-4,6- dimethyl-1H-imidazo[4,5-c]pyridin-1-yl)phenyl]ethyl}amino)-carbonyl]-4-
 30 methylbenzenesulfonamide or 4-[(15)-1-([5-chloro-2-(3-fluorophenoxy)pyridin-3-

yl]carbonyl} amino)ethyl]benzoic acid;

[00159] (34) a leukotriene B4 antagonist; such as 1-(3-biphenyl-4-ylmethyl-4-hydroxy-chroman-7-yl)-cyclopentanecarboxylic acid (CP-105696), 5-[2-(2-Carboxyethyl)-3-[6-(4-methoxyphenyl)-5E-hexenyl]oxyphenoxy]-valeric acid (ONO-4057) or DPC-11870,

[00160] (35) a 5-lipoxygenase inhibitor, such as zileuton, 6-[(3-fluoro-5-[4-methoxy-3,4,5,6-tetrahydro-2H-pyran-4-yl]]phenoxy-methyl]-1-methyl-2-quinolone (ZD-2138), or 2,3,5-trimethyl-6-(3-pyridylmethyl)-1,4-benzoquinone (CV-6504);

(36) a sodium channel blocker, such as lidocaine;

[00161] (36) a 5-HT₃ antagonist, such as ondansetron; and the pharmaceutically acceptable salts and solvates thereof.

[00162] In another embodiment, the additional therapeutic agent is an NaV 1.8 inhibitor. NaV 1.7 and NaV 1.8 ion channels are both highly expressed in the sensory neurons of the dorsal root ganglion, where pain signals originate, but the distinct functional behavior of the two channels leads them to fulfill distinct and complementary roles in neuronal excitability. Na_v1.7 controls the general sensitivity of nociceptive neurons, and initiating the painful signal in a nociceptor. Na_v1.8 amplifies and sustains the pain signal once it has been initiated. Because of these distinct roles, inhibiting both channels should increase the effectiveness of pain relief. Preclinical genetic knockout mice support this idea, as double knockouts of Na_v1.7 and Na_v1.8 channels in the sensory DRG neurons surprisingly diminish nociceptive behaviors to a greater degree than knockout of either channel alone.

[00163] In another embodiment, the additional appropriate therapeutic agent is an NaV 1.8 inhibitor selected from the following: 2-(4-fluorophenoxy)-N-(2-oxo-1,2-dihydropyridin-4-yl)benzamide; 2-(4-fluorophenoxy)-N-(2-oxo-1,2-dihydropyridin-4-yl)-5-(trifluoromethyl)benzamide; 2-(4-fluorophenoxy)-N-(6-oxo-1,6-dihydropyridin-3-yl)benzamide; 2-(4-fluorophenoxy)-N-(2-oxo-1,2-dihydropyridin-4-yl)-4-(trifluoromethyl)benzamide; 2-(4-fluorophenoxy)-N-(6-oxo-1,6-dihydropyridin-3-yl)-4-(trifluoromethyl)benzamide; 2-(2,4-difluorophenoxy)-N-(2-oxo-1,2-dihydropyridin-4-yl)-4-(trifluoromethyl)benzamide; 2-(4-(2-methoxyethoxy)phenoxy)-N-(2-oxo-1,2-

- dihydropyridin-4-yl)-4-(trifluoromethyl)benzamide; N-(2-oxo-1,2-dihydropyridin-4-yl)-2-phenoxy-4-(trifluoromethyl)benzamide; 2-(4-fluoro-2-methylphenoxy)-N-(2-oxo-1,2-dihydropyridin-4-yl)-4-(trifluoromethyl)benzamide; N-(2-oxo-1,2-dihydropyridin-4-yl)-2-(o-tolyloxy)-4-(trifluoromethyl)benzamide; N-(2-oxo-1,2-dihydropyridin-4-yl)-2-(p-tolyloxy)-4-(trifluoromethyl)benzamide; 4-chloro-2-(2,4-difluorophenoxy)-N-(2-oxo-1,2-dihydropyridin-4-yl)benzamide; 4-chloro-2-(2-chloro-4-fluorophenoxy)-N-(2-oxo-1,2-dihydropyridin-4-yl)benzamide; 4-chloro-2-(4-fluorophenoxy)-N-(2-oxo-1,2-dihydropyridin-4-yl)benzamide; 4-chloro-2-(4-fluoro-2-methoxyphenoxy)-N-(2-oxo-1,2-dihydropyridin-4-yl)benzamide; 4-chloro-2-(2-fluoro-6-methylphenoxy)-N-(2-oxo-1,2-dihydropyridin-4-yl)benzamide; 4-chloro-2-(2-chloro-6-fluorophenoxy)-N-(2-oxo-1,2-dihydropyridin-4-yl)benzamide; 4-chloro-2-(2,6-difluorophenoxy)-N-(2-oxo-1,2-dihydropyridin-4-yl)benzamide; 4-chloro-2-(4-fluoro-2-methylphenoxy)-N-(2-oxo-1,2-dihydropyridin-4-yl)benzamide; 4-cyano-2-(4-fluorophenoxy)-N-(2-oxo-1,2-dihydropyridin-4-yl)benzamide; 4-cyano-2-(4-fluoro-2-methoxyphenoxy)-N-(2-oxo-1,2-dihydropyridin-4-yl)benzamide; 4-cyano-2-(4-fluoro-2-methylphenoxy)-N-(2-oxo-1,2-dihydropyridin-4-yl)benzamide; 2-(2,4-difluorophenoxy)-N-(2-oxo-1,2-dihydropyridin-4-yl)-5-(trifluoromethyl)benzamide; 2-(4-cyanophenoxy)-N-(2-oxo-1,2-dihydropyridin-4-yl)-5-(trifluoromethyl)benzamide; 2-(2,6-difluorophenoxy)-N-(2-oxo-1,2-dihydropyridin-4-yl)-5-(trifluoromethyl)benzamide; N-(2-oxo-1,2-dihydropyridin-4-yl)-2-(p-tolyloxy)-5-(trifluoromethyl)benzamide; N-(2-oxo-1,2-dihydropyridin-4-yl)-2-(o-tolyloxy)-5-(trifluoromethyl)benzamide; 2-(2-chloro-4-fluorophenoxy)-N-(2-oxo-1,2-dihydropyridin-4-yl)-5-(trifluoromethyl)benzamide; 2-(4-fluoro-2-methoxyphenoxy)-N-(2-oxo-1,2-dihydropyridin-4-yl)-5-(trifluoromethyl)benzamide; 2-(4-fluoro-2-methylphenoxy)-N-(2-oxo-1,2-dihydropyridin-4-yl)-5-(trifluoromethyl)benzamide; N-(2-oxo-1,2-dihydropyridin-4-yl)-5-(trifluoromethyl)benzamide; N-(2-oxo-1,2-dihydropyridin-4-yl)-2-phenoxy-5-(trifluoromethyl)benzamide; 2-(2,4-difluorophenoxy)-N-(2-oxo-1,2-dihydropyridin-4-yl)-5-(trifluoromethoxy)benzamide; 2-(2,6-difluorophenoxy)-N-(2-oxo-1,2-dihydropyridin-4-yl)-5-(trifluoromethoxy)benzamide; N-(2-oxo-1,2-dihydropyridin-4-yl)-2-(p-tolyloxy)-5-(trifluoromethoxy)benzamide; N-(2-oxo-1,2-dihydropyridin-4-yl)-2-(o-tolyloxy)-5-(trifluoromethoxy)benzamide; 2-(2-chloro-4-fluorophenoxy)-N-(2-oxo-1,2-dihydropyridin-4-yl)-5-(trifluoromethoxy)benzamide; 2-(4-fluorophenoxy)-N-(2-oxo-1,2-dihydropyridin-4-yl)-5-(trifluoromethoxy)benzamide;

- 2-(2-fluoro-6-methylphenoxy)-N-(2-oxo-1,2-dihydropyridin-4-yl)-5-(trifluoromethoxy)benzamide; 2-(4-fluoro-2-methylphenoxy)-N-(2-oxo-1,2-dihydropyridin-4-yl)-5-(trifluoromethoxy)benzamide; N-(2-oxo-1,2-dihydropyridin-4-yl)-2-phenoxy-5-(trifluoromethoxy)benzamide; 2-(4-fluoro-2-methoxyphenoxy)-N-(2-oxo-1,2-dihydropyridin-4-yl)-5-(trifluoromethoxy)benzamide; 2-(4-fluorophenoxy)-N-(2-oxo-1,2-dihydropyridin-4-yl)-6-(trifluoromethyl)benzamide; 2-(4-ethoxyphenoxy)-N-(2-oxo-1,2-dihydropyridin-4-yl)-5-(trifluoromethyl)benzamide; 2-(4-methoxyphenoxy)-N-(2-oxo-1,2-dihydropyridin-4-yl)-5-(trifluoromethyl)benzamide; 2-(2-ethoxyphenoxy)-N-(2-oxo-1,2-dihydropyridin-4-yl)-5-(trifluoromethyl)benzamide;
- 10 2-(2-methoxy-4-methylphenoxy)-N-(2-oxo-1,2-dihydropyridin-4-yl)-5-(trifluoromethyl)benzamide; 2-(2-fluoro-6-methoxyphenoxy)-N-(2-oxo-1,2-dihydropyridin-4-yl)-5-(trifluoromethyl)benzamide; 2-(2-chloro-4-methoxyphenoxy)-N-(2-oxo-1,2-dihydropyridin-4-yl)-5-(trifluoromethyl)benzamide; 2-(4-chloro-2-methylphenoxy)-N-(2-oxo-1,2-dihydropyridin-4-yl)-5-(trifluoromethyl)benzamide; 2-(4-chloro-2-fluorophenoxy)-N-(2-oxo-1,2-dihydropyridin-4-yl)-5-(trifluoromethyl)benzamide; 2-(5-fluoro-2-methoxyphenoxy)-N-(2-oxo-1,2-dihydropyridin-4-yl)-5-(trifluoromethyl)benzamide; N-(2-oxo-1,2-dihydropyridin-4-yl)-2-(4-propoxyphenoxy)-5-(trifluoromethyl)benzamide; 2-(3-fluoro-2-methoxyphenoxy)-N-(2-oxo-1,2-dihydropyridin-4-yl)-5-(trifluoromethyl)benzamide; 2-(2-fluoro-4-methoxyphenoxy)-N-(2-oxo-1,2-dihydropyridin-4-yl)-5-(trifluoromethyl)benzamide; 2-(5-fluoro-2-methylphenoxy)-N-(2-oxo-1,2-dihydropyridin-4-yl)-5-(trifluoromethyl)benzamide; 2-(3-fluoro-5-methoxyphenoxy)-N-(2-oxo-1,2-dihydropyridin-4-yl)-5-(trifluoromethyl)benzamide; 2-(4-chlorophenoxy)-N-(2-oxo-1,2-dihydropyridin-4-yl)-5-(trifluoromethyl)benzamide; 2-(3-fluoro-4-methoxyphenoxy)-N-(2-oxo-1,2-dihydropyridin-4-yl)-5-(trifluoromethyl)benzamide; N-(6-chloro-2-oxo-1,2-dihydropyridin-4-yl)-2-(4-fluoro-2-methylphenoxy)-5-(trifluoromethyl)benzamide; 2-(4-fluoro-2-methylphenoxy)-N-(6-methyl-2-oxo-1,2-dihydropyridin-4-yl)-5-(trifluoromethyl)benzamide; N-(2-oxo-1,2-dihydropyridin-4-yl)-2-(2-propoxyphenoxy)-5-(trifluoromethyl)benzamide; 2-(4-methoxy-2-methylphenoxy)-N-(2-oxo-1,2-dihydropyridin-4-yl)-5-(trifluoromethyl)benzamide; 2-(2-isopropoxyphenoxy)-N-(2-oxo-1,2-dihydropyridin-4-yl)-5-(trifluoromethyl)benzamide; 2-(2-chlorophenoxy)-N-(2-oxo-1,2-dihydropyridin-

- 4-yl)-5-(trifluoromethyl)benzamide; 5-chloro-2-(2-chloro-4-fluorophenoxy)-N-(2-oxo-1,2-dihydropyridin-4-yl)benzamide; 5-chloro-2-(4-fluorophenoxy)-N-(2-oxo-1,2-dihydropyridin-4-yl)benzamide; 5-chloro-2-(4-fluoro-2-methylphenoxy)-N-(2-oxo-1,2-dihydropyridin-4-yl)benzamide; 5-chloro-2-(2,4-difluorophenoxy)-N-(2-oxo-1,2-dihydropyridin-4-yl)benzamide; 5-chloro-2-(4-fluoro-2-methoxyphenoxy)-N-(2-oxo-1,2-dihydropyridin-4-yl)benzamide; 5-chloro-2-(3-fluoro-4-methoxyphenoxy)-N-(2-oxo-1,2-dihydropyridin-4-yl)benzamide; N-(2-oxo-1,2-dihydropyridin-4-yl)-2-(4-(trifluoromethoxy)phenoxy)-5-(trifluoromethyl)benzamide; N-(2-oxo-1,2-dihydropyridin-4-yl)-5-(trifluoromethyl)-2-(4-(trifluoromethyl)phenoxy)benzamide; N-(2-oxo-1,2-dihydropyridin-4-yl)-2-(2-(trifluoromethoxy)phenoxy)-5-(trifluoromethyl)benzamide; 2-(2-(difluoromethoxy)phenoxy)-N-(2-oxo-1,2-dihydropyridin-4-yl)-5-(trifluoromethyl)benzamide; 2-(2-chloro-4-fluorophenoxy)-N-(2-oxo-1,2-dihydropyridin-4-yl)-4-(trifluoromethyl)benzamide; 2-(4-chlorophenoxy)-N-(2-oxo-1,2-dihydropyridin-4-yl)-4-(trifluoromethyl)benzamide; N-(2-oxo-1,2-dihydropyridin-4-yl)-2-(4-(trifluoromethoxy)phenoxy)-4-(trifluoromethyl)benzamide; N-(2-oxo-1,2-dihydropyridin-4-yl)-2-(2-(trifluoromethoxy)phenoxy)-4-(trifluoromethyl)benzamide; 2-(3-fluoro-4-methoxyphenoxy)-N-(2-oxo-1,2-dihydropyridin-4-yl)-4-(trifluoromethyl)benzamide; 2-(4-(difluoromethoxy)phenoxy)-N-(2-oxo-1,2-dihydropyridin-4-yl)-4-(trifluoromethyl)benzamide; 2-(2-(difluoromethoxy)phenoxy)-N-(2-oxo-1,2-dihydropyridin-4-yl)-4-(trifluoromethyl)benzamide; 2-(2-fluoro-4-methoxyphenoxy)-N-(2-oxo-1,2-dihydropyridin-4-yl)-4-(trifluoromethyl)benzamide; 2-(4-fluorophenoxy)-N-(1-(2-hydroxyethyl)-2-oxo-1,2-dihydropyridin-4-yl)-4-(trifluoromethyl)benzamide; 2-(4-fluoro-2-methylphenoxy)-N-(5-methyl-2-oxo-1,2-dihydropyridin-4-yl)-4-(trifluoromethyl)benzamide; 2-(3-fluoro-2-methoxyphenoxy)-N-(2-oxo-1,2-dihydropyridin-4-yl)-4-(trifluoromethyl)benzamide; 2-(4-fluorophenoxy)-N-(2-oxo-1,2-dihydropyridin-4-yl)-4-(perfluoroethyl)benzamide; 2-(3-fluoro-4-methoxyphenoxy)-N-(2-oxo-1,2-dihydropyridin-4-yl)-4-(perfluoroethyl)benzamide; N-(2-oxo-1,2-dihydropyridin-4-yl)-5-(trifluoromethyl)-2-(2,3,4-trifluorophenoxy)benzamide; N-(2-oxo-1,2-dihydropyridin-4-yl)-5-(trifluoromethyl)-2-(2,3,5-trimethylphenoxy)benzamide; 2-(2,3-difluoro-4-methylphenoxy)-N-(2-oxo-1,2-dihydropyridin-4-yl)-5-(trifluoromethyl)benzamide; N-(2-oxo-1,2-dihydropyridin-4-

- yl)-5-(trifluoromethyl)-2-(2,4,5-trimethylphenoxy)benzamide; 5-fluoro-N-(2-oxo-1,2-dihydropyridin-4-yl)-2-(2,3,5-trimethylphenoxy)benzamide; 5-fluoro-N-(2-oxo-1,2-dihydropyridin-4-yl)-2-phenoxybenzamide; 2-(4-cyclopropylphenoxy)-5-fluoro-N-(2-oxo-1,2-dihydropyridin-4-yl)benzamide; 2-(4-(tert-butoxy)phenoxy)-5-fluoro-N-(2-oxo-1,2-dihydropyridin-4-yl)benzamide; 2-(4-ethoxyphenoxy)-5-fluoro-N-(2-oxo-1,2-dihydropyridin-4-yl)benzamide; 5-fluoro-2-(4-isopropylphenoxy)-N-(2-oxo-1,2-dihydropyridin-4-yl)benzamide; 5-fluoro-N-(2-oxo-1,2-dihydropyridin-4-yl)-2-(4-propoxyphenoxy)benzamide; 5-fluoro-N-(2-oxo-1,2-dihydropyridin-4-yl)-2-(4-(trifluoromethoxy)phenoxy)benzamide; 5-fluoro-2-(4-(2-methoxyethyl)phenoxy)-N-(2-oxo-1,2-dihydropyridin-4-yl)benzamide; 2-(2-chloro-4-methoxyphenoxy)-5-fluoro-N-(2-oxo-1,2-dihydropyridin-4-yl)benzamide; 5-fluoro-2-(4-methoxyphenoxy)-N-(2-oxo-1,2-dihydropyridin-4-yl)benzamide; 5-fluoro-N-(2-oxo-1,2-dihydropyridin-4-yl)-2-(2,4,5-trimethylphenoxy)benzamide; 2-(4-fluoro-2-methylphenoxy)-N-(2-oxo-1,2-dihydropyridin-4-yl)-5-(trifluoromethyl)benzamide; 5-fluoro-N-(2-oxo-1,2-dihydropyridin-4-yl)-2-(4-(2,2,2-trifluoroethoxy)phenoxy)benzamide; 2-(4-(cyclopropylmethoxy)phenoxy)-5-fluoro-N-(2-oxo-1,2-dihydropyridin-4-yl)benzamide; 4-chloro-2-(2-chloro-4-fluorophenoxy)-5-fluoro-N-(2-oxo-1,2-dihydropyridin-4-yl)benzamide; 2-(2-chloro-3-fluoro-4-methoxyphenoxy)-N-(2-oxo-1,2-dihydropyridin-4-yl)-4-(trifluoromethyl)benzamide; 2-(4-fluoro-2-methoxyphenoxy)-N-(2-oxo-1,2-dihydropyridin-4-yl)-4-(perfluoroethyl)benzamide; 2-(4-fluoro-2-methylphenoxy)-N-(2-oxo-1,2-dihydropyridin-4-yl)-4-(perfluoroethyl)benzamide; 4,5-dichloro-2-(4-fluorophenoxy)-N-(2-oxo-1,2-dihydropyridin-4-yl)benzamide; 4,5-dichloro-2-(4-fluoro-2-methoxyphenoxy)-N-(2-oxo-1,2-dihydropyridin-4-yl)benzamide; 4,5-dichloro-2-(3-fluoro-4-methoxyphenoxy)-N-(2-oxo-1,2-dihydropyridin-4-yl)benzamide; 2-(isopentyloxy)-N-(2-oxo-1,2-dihydropyridin-4-yl)-4-(trifluoromethyl)benzamide; 2-isobutoxy-N-(2-oxo-1,2-dihydropyridin-4-yl)-4-(trifluoromethyl)benzamide; 2-((2R)-bicyclo[2.2.1]heptan-2-yloxy)-N-(2-oxo-1,2-dihydropyridin-4-yl)-4-(trifluoromethyl)benzamide; 2-((1-methylcyclopropyl)methoxy)-N-(2-oxo-1,2-dihydropyridin-4-yl)-4-(trifluoromethyl)benzamide; 2-(cyclopentylmethoxy)-N-(2-oxo-1,2-dihydropyridin-4-yl)-4-(trifluoromethyl)benzamide; N-(2-oxo-1,2-dihydropyridin-4-yl)-2-(((tetrahydrofuran-3-yl)methoxy)-4-(trifluoromethyl)benzamide; 2-cyclobutoxy-N-(2-

- oxo-1,2-dihydropyridin-4-yl)-4-(trifluoromethyl)benzamide; N-(2-oxo-1,2-dihydropyridin-4-yl)-2-(4,4,4-trifluorobutoxy)-4-(trifluoromethyl)benzamide; 2-((2,2-dimethylcyclopropyl)methoxy)-N-(2-oxo-1,2-dihydropyridin-4-yl)-4-(trifluoromethyl)benzamide; 2-((1R,5S)-bicyclo[3.1.0]hexan-3-yloxy)-N-(2-oxo-1,2-dihydropyridin-4-yl)-4-(trifluoromethyl)benzamide; 2-((2,2-difluorocyclopropyl)methoxy)-N-(2-oxo-1,2-dihydropyridin-4-yl)-4-(trifluoromethyl)benzamide; 2-(bicyclo[2.2.1]heptan-2-yloxy)-N-(2-oxo-1,2-dihydropyridin-4-yl)-4-(trifluoromethyl)benzamide; 2-(cyclohexyloxy)-N-(2-oxo-1,2-dihydropyridin-4-yl)-4-(trifluoromethyl)benzamide; 4-chloro-N-(2-oxo-1,2-dihydropyridin-4-yl)-2-(4,4,4-trifluorobutoxy)benzamide; 2-(cyclopentylmethoxy)-N-(2-oxo-1,2-dihydropyridin-4-yl)-5-(trifluoromethyl)benzamide; 2-isobutoxy-N-(2-oxo-1,2-dihydropyridin-4-yl)-5-(trifluoromethyl)benzamide; N-(2-oxo-1,2-dihydropyridin-4-yl)-5-(trifluoromethyl)-2-(3,3,3-trifluoropropoxy)benzamide; N-(2-oxo-1,2-dihydropyridin-4-yl)-2-(4,4,4-trifluorobutoxy)-5-(trifluoromethyl)benzamide; 2-((2,2-dimethylcyclopropyl)methoxy)-N-(2-oxo-1,2-dihydropyridin-4-yl)-5-(trifluoromethyl)benzamide; 2-(cyclopentylmethoxy)-N-(2-oxo-1,2-dihydropyridin-4-yl)-5-(trifluoromethoxy)benzamide; 2-(cyclohexyloxy)-N-(2-oxo-1,2-dihydropyridin-4-yl)-5-(trifluoromethoxy)benzamide; N-(2-oxo-1,2-dihydropyridin-4-yl)-5-(trifluoromethoxy)-2-(3,3,3-trifluoropropoxy)benzamide; N-(2-oxo-1,2-dihydropyridin-4-yl)-2-(4,4,4-trifluorobutoxy)-5-(trifluoromethoxy)benzamide; 2-((2,2-dimethylcyclopropyl)methoxy)-N-(2-oxo-1,2-dihydropyridin-4-yl)-5-(trifluoromethoxy)benzamide; 4-(tert-butyl)-N-(2-oxo-1,2-dihydropyridin-4-yl)-2-((6-(trifluoromethyl)pyridin-3-yl)oxy)benzamide; 4-(tert-butyl)-N-(6-oxo-1,6-dihydropyridin-3-yl)-2-((6-(trifluoromethyl)pyridin-3-yl)oxy)benzamide; 4-chloro-N-(2-oxo-1,2-dihydropyridin-4-yl)-2-((6-(trifluoromethyl)pyridin-3-yl)oxy)benzamide; N-(2-oxo-1,2-dihydropyridin-4-yl)-4-(trifluoromethyl)-2-((6-(trifluoromethyl)pyridin-3-yl)oxy)benzamide; N-(6-oxo-1,6-dihydropyridin-3-yl)-4-(trifluoromethyl)-2-((6-(trifluoromethyl)pyridin-3-yl)oxy)benzamide; 2-((6-methylpyridin-3-yl)oxy)-N-(2-oxo-1,2-dihydropyridin-4-yl)-4-(trifluoromethyl)benzamide; 2-((2-methylpyridin-3-yl)oxy)-N-(2-oxo-1,2-dihydropyridin-4-yl)-4-(trifluoromethyl)benzamide; 4-(tert-butyl)-N-(1-methyl-2-oxo-1,2-dihydropyridin-4-yl)-2-((6-(trifluoromethyl)pyridin-3-yl)oxy)benzamide; 4-(tert-butyl)-N-(1-methyl-6-oxo-1,6-dihydropyridin-3-yl)-2-((6-

- (trifluoromethyl)pyridin-3-yl)oxy)benzamide; 2-((2-methylpyridin-3-yl)oxy)-N-(2-oxo-1,2-dihydropyridin-4-yl)-5-(trifluoromethyl)benzamide; 2-((2-methylpyridin-3-yl)oxy)-N-(2-oxo-1,2-dihydropyridin-4-yl)-5-(trifluoromethoxy)benzamide; 2-(2,4-difluorophenoxy)-N-(2-oxo-1,2-dihydropyridin-4-yl)-4,6-
- 5 bis(trifluoromethyl)benzamide; 2-(4-fluoro-2-methylphenoxy)-N-(2-oxo-1,2-dihydropyridin-4-yl)-4,6-bis(trifluoromethyl)benzamide; 2-(4-fluoro-2-methoxyphenoxy)-N-(2-oxo-1,2-dihydropyridin-4-yl)-4,6-bis(trifluoromethyl)benzamide; 2-(4-fluorophenoxy)-N-(2-oxo-1,2-dihydropyridin-4-yl)-4,6-bis(trifluoromethyl)benzamide; N-(2-oxo-1,2-dihydropyridin-4-yl)-2-phenoxy-
- 10 4,6-bis(trifluoromethyl)benzamide; 2-(4-fluoro-2-(hydroxymethyl)phenoxy)-N-(2-oxo-1,2-dihydropyridin-4-yl)-4-(trifluoromethyl)benzamide; 2-(4-fluoro-2-methoxyphenoxy)-N-(2-oxo-1,2-dihydropyridin-4-yl)-4-(trifluoromethyl)benzamide; 2-((5-fluoro-2-hydroxybenzyl)oxy)-N-(2-oxo-1,2-dihydropyridin-4-yl)-4-(trifluoromethyl)benzamide; 5-fluoro-N-(2-oxo-1,2-dihydropyridin-4-yl)-2-(4-(4,4,4-
- 15 trifluorobutoxy)phenoxy)benzamide, or combinations thereof.

- [00164]** In another embodiment, the additional appropriate therapeutic agent is an NaV 1.8 inhibitor selected from the following: 3-(4-fluorophenoxy)-N-(3-sulfamoylphenyl)quinoxaline-2-carboxamide; 3-(4-fluoro-2-methoxyphenoxy)-N-(3-sulfamoylphenyl)quinoxaline-2-carboxamide; N-(3-sulfamoylphenyl)-3-(4-
- 20 (trifluoromethoxy)phenoxy)quinoxaline-2-carboxamide; 3-(2-chloro-4-methoxyphenoxy)-N-(3-sulfamoylphenyl)quinoxaline-2-carboxamide; 3-(2,4-difluorophenoxy)-N-(3-sulfamoylphenyl)quinoxaline-2-carboxamide; 3-(2-chloro-4-fluorophenoxy)-N-(3-sulfamoylphenyl)quinoxaline-2-carboxamide; 3-(3-fluoro-4-methoxyphenoxy)-N-(3-sulfamoylphenyl)quinoxaline-2-carboxamide; 3-(2,4-
- 25 dimethoxyphenoxy)-N-(3-sulfamoylphenyl)quinoxaline-2-carboxamide; 3-(4-chloro-2-methylphenoxy)-N-(3-sulfamoylphenyl)quinoxaline-2-carboxamide; 3-(2-(difluoromethoxy)phenoxy)-N-(3-sulfamoylphenyl)quinoxaline-2-carboxamide; 3-(4-chloro-2-methoxyphenoxy)-N-(3-sulfamoylphenyl)quinoxaline-2-carboxamide; 3-(2-fluoro-4-methoxyphenoxy)-N-(3-sulfamoylphenyl)quinoxaline-2-carboxamide; 3-
- 30 phenoxy-N-(3-sulfamoylphenyl)quinoxaline-2-carboxamide; 3-(4-fluoro-2-methylphenoxy)-N-(3-sulfamoylphenyl)quinoxaline-2-carboxamide; N-(3-sulfamoylphenyl)-3-(4-(2,2,2-trifluoroethoxy)phenoxy)quinoxaline-2-carboxamide; 3-

- (4-fluoro-2-methoxyphenoxy)-N-(3-(N-methylsulfamoyl)phenyl)quinoxaline-2-carboxamide; 4-(3-(4-(trifluoromethoxy)phenoxy)quinoxaline-2-carboxamido)benzoic acid; 5-(3-(4-fluorophenoxy)quinoxaline-2-carboxamido)picolinic acid; 5-(3-(4-fluoro-2-methylphenoxy)quinoxaline-2-carboxamido)picolinic acid; 5-(3-phenoxyquinoxaline-2-carboxamido)picolinic acid; 5-(3-(2-fluoro-4-methoxyphenoxy)quinoxaline-2-carboxamido)picolinic acid; 5-(3-(4-(2,2,2-trifluoroethoxy)phenoxy)quinoxaline-2-carboxamido)picolinic acid; 5-(3-(4-chloro-2-methoxyphenoxy)quinoxaline-2-carboxamido)picolinic acid; 5-(3-(2-(difluoromethoxy)phenoxy)quinoxaline-2-carboxamido)picolinic acid; 5-(3-(4-chloro-2-methylphenoxy)quinoxaline-2-carboxamido)picolinic acid; 5-(3-(2,4-dimethoxyphenoxy)quinoxaline-2-carboxamido)picolinic acid; 5-(3-(3-fluoro-4-methoxyphenoxy)quinoxaline-2-carboxamido)picolinic acid; 5-(3-(2-chloro-4-fluorophenoxy)quinoxaline-2-carboxamido)picolinic acid; 5-(3-(2,4-difluorophenoxy)quinoxaline-2-carboxamido)picolinic acid; 5-(3-(2-chloro-4-methoxyphenoxy)quinoxaline-2-carboxamido)picolinic acid; 5-(3-(4-(trifluoromethoxy)phenoxy)quinoxaline-2-carboxamido)picolinic acid; 5-(3-(4-fluoro-2-methoxyphenoxy)quinoxaline-2-carboxamido)picolinic acid; 4-(3-(4-(trifluoromethoxy)phenoxy)quinoxaline-2-carboxamido)picolinic acid; 4-(3-(4-fluoro-2-methoxyphenoxy)quinoxaline-2-carboxamido)picolinic acid; 3-(4-fluorophenoxy)-N-(2-oxo-1,2-dihydropyridin-4-yl)quinoxaline-2-carboxamide; 3-(3-(4-fluoro-2-methoxyphenoxy)quinoxaline-2-carboxamido)benzoic acid; 2-(3-(4-fluoro-2-methoxyphenoxy)quinoxaline-2-carboxamido)thiazole-4-carboxylic acid; 3-(4-fluoro-2-methoxyphenoxy)-N-(1H-1,2,4-triazol-3-yl)quinoxaline-2-carboxamide; 2-(3-(4-fluoro-2-methoxyphenoxy)quinoxaline-2-carboxamido)oxazole-4-carboxylic acid; 3-(4-fluoro-2-methoxyphenoxy)-N-(1H-pyrazol-3-yl)quinoxaline-2-carboxamide; 3-(4-fluoro-2-methoxyphenoxy)-N-(1H-tetrazol-5-yl)quinoxaline-2-carboxamide; N-(1H-benzo[d][1,2,3]triazol-5-yl)-3-(4-fluoro-2-methoxyphenoxy)quinoxaline-2-carboxamide; 3-(4-fluoro-2-methoxyphenoxy)-N-(1H-pyrazol-4-yl)quinoxaline-2-carboxamide; 3-(4-fluoro-2-methoxyphenoxy)-N-(2-(hydroxymethyl)-1H-benzo[d]imidazol-5-yl)quinoxaline-2-carboxamide; N-(3-(1H-tetrazol-5-yl)phenyl)-3-(4-fluoro-2-methoxyphenoxy)quinoxaline-2-carboxamide; 3-(4-fluoro-2-methoxyphenoxy)-N-(3-(methylsulfonyl)phenyl)quinoxaline-2-carboxamide; 3-(4-

- fluoro-2-methoxyphenoxy)-N-(1H-indazol-6-yl)quinoxaline-2-carboxamide; 3-(4-fluoro-2-methoxyphenoxy)-N-(1H-indazol-5-yl)quinoxaline-2-carboxamide; N-(1H-benzo[d]imidazol-6-yl)-3-(4-fluoro-2-methoxyphenoxy)quinoxaline-2-carboxamide; N-(4-cyanopyridin-2-yl)-3-(4-fluoro-2-methoxyphenoxy)quinoxaline-2-carboxamide;
- 5 N-(6-cyanopyridin-3-yl)-3-(4-fluoro-2-methoxyphenoxy)quinoxaline-2-carboxamide; N-(5-cyanopyridin-2-yl)-3-(4-fluoro-2-methoxyphenoxy)quinoxaline-2-carboxamide; 3-(4-fluoro-2-methoxyphenoxy)-N-(pyridin-4-yl)quinoxaline-2-carboxamide; 3-(4-fluoro-2-methoxyphenoxy)-N-(pyridin-3-yl)quinoxaline-2-carboxamide; N-(4-cyanophenyl)-3-(4-fluoro-2-methoxyphenoxy)quinoxaline-2-carboxamide; N-(3-
- 10 cyanophenyl)-3-(4-fluoro-2-methoxyphenoxy)quinoxaline-2-carboxamide; 3-(4-fluoro-2-methoxyphenoxy)-N-(2-oxo-2,3-dihydro-1H-benzo[d]imidazol-5-yl)quinoxaline-2-carboxamide; N-(4-carbamoylphenyl)-3-(4-fluoro-2-methoxyphenoxy)quinoxaline-2-carboxamide; N-(3-carbamoylphenyl)-3-(4-fluoro-2-methoxyphenoxy)quinoxaline-2-carboxamide; 2-(4-fluorophenoxy)-N-(3-sulfamoylphenyl)quinoline-3-carboxamide; 2-
- 15 (4-fluoro-2-methoxyphenoxy)-N-(3-sulfamoylphenyl)quinoline-3-carboxamide; 2-(3-fluoro-4-methoxyphenoxy)-N-(3-sulfamoylphenyl)quinoline-3-carboxamide; 2-(4-fluoro-2-methylphenoxy)-N-(3-sulfamoylphenyl)quinoline-3-carboxamide; 2-phenoxy-N-(3-sulfamoylphenyl)quinoline-3-carboxamide; 2-(2,4-difluorophenoxy)-N-(3-sulfamoylphenyl)quinoline-3-carboxamide; 2-(2-chloro-4-fluorophenoxy)-N-(3-
- 20 sulfamoylphenyl)quinoline-3-carboxamide; N-(3-sulfamoylphenyl)-2-(4-(2,2,2-trifluoroethoxy)phenoxy)quinoline-3-carboxamide; N-(3-sulfamoylphenyl)-2-(4-(trifluoromethoxy)phenoxy)quinoline-3-carboxamide; 2-(2-chloro-4-methoxyphenoxy)-N-(3-sulfamoylphenyl)quinoline-3-carboxamide; 2-(2-fluoro-4-methoxyphenoxy)-N-(3-sulfamoylphenyl)quinoline-3-carboxamide; 2-(4-chloro-2-
- 25 methylphenoxy)-N-(3-sulfamoylphenyl)quinoline-3-carboxamide; 2-(2,4-dimethoxyphenoxy)-N-(3-sulfamoylphenyl)quinoline-3-carboxamide; 2-(4-chloro-2-methoxyphenoxy)-N-(3-sulfamoylphenyl)quinoline-3-carboxamide; 2-(2-(difluoromethoxy)phenoxy)-N-(3-sulfamoylphenyl)quinoline-3-carboxamide; 4-(2-(2,4-difluorophenoxy)quinoline-3-carboxamido)benzoic acid; 4-(2-(4-fluoro-2-
- 30 methylphenoxy)quinoline-3-carboxamido)benzoic acid; 4-(2-(2-(difluoromethoxy)phenoxy)quinoline-3-carboxamido)benzoic acid; 4-(2-(2,4-dimethoxyphenoxy)quinoline-3-carboxamido)benzoic acid; 5-(2-(2-chloro-4-

fluorophenoxy)quinoline-3-carboxamido)picolinic acid; 5-(2-(2,4-difluorophenoxy)quinoline-3-carboxamido)picolinic acid, or combinations thereof.

- [00165] In another embodiment, the additional appropriate therapeutic agent is an NaV 1.8 inhibitor selected from the following:
- 4-(2-(2-chloro-4-fluorophenoxy)-4-(perfluoroethyl)benzamido)benzoic acid; 4-(2-(2,4-difluorophenoxy)-4-(perfluoroethyl)benzamido)benzoic acid; 4-(2-(4-fluoro-2-methylphenoxy)-4-(perfluoroethyl)benzamido)benzoic acid; 4-(2-(2-chloro-4-fluorophenoxy)-4-(trifluoromethyl)benzamido)benzoic acid; 4-(2-(4-fluoro-2-methylphenoxy)-4-(trifluoromethyl)benzamido)benzoic acid; 4-(2-(2,4-difluorophenoxy)-4-(trifluoromethyl)benzamido)benzoic acid; 4-(2-(4-(trifluoromethoxy)phenoxy)-4-(trifluoromethyl)benzamido)benzoic acid; 4-(2-(2,4-difluorophenoxy)-4,6-bis(trifluoromethyl)benzamido)benzoic acid; 4-(2-(4-fluoro-2-methylphenoxy)-4,6-bis(trifluoromethyl)benzamido)benzoic acid; 4-(2-(4-fluoro-2-methoxyphenoxy)-4,6-bis(trifluoromethyl)benzamido)benzoic acid; 4-(2-(4-fluorophenoxy)-4,6-bis(trifluoromethyl)benzamido)benzoic acid; 4-(4,5-dichloro-2-(4-fluoro-2-methoxyphenoxy)benzamido)benzoic acid; 4-(4,5-dichloro-2-(4-fluorophenoxy)benzamido)benzoic acid; 4-(4,5-dichloro-2-(4-fluoro-2-methylphenoxy)benzamido)benzoic acid; 4-(4,5-dichloro-2-phenoxybenzamido)benzoic acid; 4-(4,5-dichloro-2-(2-fluoro-4-methoxyphenoxy)benzamido)benzoic acid; 4-(4,5-dichloro-2-(4-(2,2,2-trifluoroethoxy)phenoxy)benzamido)benzoic acid; 4-(4,5-dichloro-2-(4-chloro-2-methoxyphenoxy)benzamido)benzoic acid; 4-(4,5-dichloro-2-(2-(difluoromethoxy)phenoxy)benzamido)benzoic acid; 4-(4,5-dichloro-2-(4-chloro-2-methylphenoxy)benzamido)benzoic acid; 4-(4,5-dichloro-2-(2,4-dimethoxyphenoxy)benzamido)benzoic acid; 4-(4,5-dichloro-2-(3-fluoro-4-methoxyphenoxy)benzamido)benzoic acid; 4-(4,5-dichloro-2-(2-chloro-4-fluorophenoxy)benzamido)benzoic acid; 4-(4,5-dichloro-2-(2,4-difluorophenoxy)benzamido)benzoic acid; 4-(4,5-dichloro-2-(2-chloro-4-methoxyphenoxy)benzamido)benzoic acid; 4-(4,5-dichloro-2-(4-(trifluoromethoxy)phenoxy)benzamido)benzoic acid; 4-(2-(4-fluoro-2-methoxyphenoxy)-4-(perfluoroethyl)benzamido)benzoic acid; 4-(2-(4-fluoro-2-methylphenoxy)-5-(trifluoromethyl)benzamido)benzoic acid; 4-(2-(4-fluoro-2-

- methylphenoxy)-5-(trifluoromethyl)benzamido)benzoic acid; 5-(4,5-dichloro-2-(4-fluorophenoxy)benzamido)picolinic acid; 5-(4,5-dichloro-2-(4-(isopentyloxy)phenoxy)benzamido)picolinic acid; 5-(4,5-dichloro-2-(4-fluoro-2-methylphenoxy)benzamido)picolinic acid; 5-(4,5-dichloro-2-phenoxybenzamido)picolinic acid; 5-(4,5-dichloro-2-(2-fluoro-4-methoxyphenoxy)benzamido)picolinic acid; 5-(4,5-dichloro-2-(4-(2,2,2-trifluoroethoxy)phenoxy)benzamido)picolinic acid; 5-(4,5-dichloro-2-(4-chloro-2-methoxyphenoxy)benzamido)picolinic acid; 5-(4,5-dichloro-2-(2-(difluoromethoxy)phenoxy)benzamido)picolinic acid; 5-(4,5-dichloro-2-(4-chloro-2-methylphenoxy)benzamido)picolinic acid; 5-(4,5-dichloro-2-(2,4-dimethoxyphenoxy)benzamido)picolinic acid; 5-(4,5-dichloro-2-(3-fluoro-4-methoxyphenoxy)benzamido)picolinic acid; 5-(4,5-dichloro-2-(2-chloro-4-fluorophenoxy)benzamido)picolinic acid; 5-(4,5-dichloro-2-(2,4-difluorophenoxy)benzamido)picolinic acid; 5-(4,5-dichloro-2-(2-chloro-4-methoxyphenoxy)benzamido)picolinic acid; 5-(4,5-dichloro-2-(4-(trifluoromethoxy)phenoxy)benzamido)picolinic acid; 5-(2-(2-methoxyphenoxy)-4,6-bis(trifluoromethyl)benzamido)picolinic acid; 5-(2-(4-methoxyphenoxy)-4,6-bis(trifluoromethyl)benzamido)picolinic acid; 5-(2-(4-fluoro-2-methylphenoxy)-4,6-bis(trifluoromethyl)benzamido)picolinic acid; 5-(2-(4-fluoro-2-methoxyphenoxy)-4,6-bis(trifluoromethyl)benzamido)picolinic acid; 5-(2-(2,4-dimethoxyphenoxy)-4,6-bis(trifluoromethyl)benzamido)picolinic acid; 5-(2-(4-fluorophenoxy)-4,6-bis(trifluoromethyl)benzamido)picolinic acid; 5-(4,5-dichloro-2-(4-fluoro-2-methoxyphenoxy)benzamido)picolinic acid; 5-(4-(tert-butyl)-2-(4-fluoro-2-methoxyphenoxy)benzamido)picolinic acid; 5-(4-(tert-butyl)-2-(4-fluoro-2-methylphenoxy)benzamido)picolinic acid; 5-(4-(tert-butyl)-2-(4-fluorophenoxy)benzamido)picolinic acid; 5-(2-(4-fluorophenoxy)benzamido)picolinic acid; 5-(2-(4-fluorophenoxy)-4-(trifluoromethyl)benzamido)picolinic acid; 5-(2-(4-fluoro-2-methoxyphenoxy)-5-(trifluoromethyl)benzamido)picolinic acid; 5-(2-(2-chloro-4-fluorophenoxy)-5-(trifluoromethyl)benzamido)picolinic acid; 5-(2-(5-fluoro-2-methoxyphenoxy)-5-(trifluoromethyl)benzamido)picolinic acid; 5-(2-(2-(difluoromethoxy)phenoxy)-5-(trifluoromethyl)benzamido)picolinic acid; 5-(2-(4-chloro-2-methylphenoxy)-5-(trifluoromethyl)benzamido)picolinic acid; 5-(2-(2-

- methoxyphenoxy)-5-(trifluoromethyl)benzamido)picolinic acid; 5-(2-(2-chlorophenoxy)-5-(trifluoromethyl)benzamido)picolinic acid; 5-(2-(2-isopropoxyphenoxy)-5-(trifluoromethyl)benzamido)picolinic acid; 5-(2-(2,4-dimethoxyphenoxy)-5-(trifluoromethyl)benzamido)picolinic acid; 5-(2-(4-chloro-2-methoxyphenoxy)-5-(trifluoromethyl)benzamido)picolinic acid; 5-(2-(4-methoxy-2-methylphenoxy)-5-(trifluoromethyl)benzamido)picolinic acid; 5-(2-(2-chloro-4-methoxyphenoxy)-5-(trifluoromethyl)benzamido)picolinic acid; 5-(2-(3-fluoro-2-methoxyphenoxy)-5-(trifluoromethyl)benzamido)picolinic acid; 5-(2-phenoxy-5-(trifluoromethyl)benzamido)picolinic acid; 5-(2-(4-fluorophenoxy)-5-(trifluoromethyl)benzamido)picolinic acid; 5-(2-(4-fluoro-2-methoxyphenoxy)-4-(perfluoroethyl)benzamido)picolinic acid; 5-(2-(4-fluorophenoxy)-4-(perfluoroethyl)benzamido)picolinic acid; 5-(2-(2-chloro-4-fluorophenoxy)-6-(trifluoromethyl)benzamido)picolinic acid; 5-(2-(4-fluoro-2-methylphenoxy)-5-(trifluoromethyl)benzamido)picolinic acid; 5-(4,5-dichloro-2-(4-fluoro-2-methoxyphenoxy)benzamido)picolinic acid, or combinations thereof.

- [00166] The amount of additional therapeutic agent present in the compositions of this invention will be no more than the amount that would normally be administered in a composition comprising that therapeutic agent as the only active agent. Preferably the amount of additional therapeutic agent in the presently disclosed compositions will range from about 50% to 100% of the amount normally present in a composition comprising that agent as the only therapeutically active agent.

- [00167] The solid forms of Compound 1 of this invention or pharmaceutically acceptable compositions thereof may also be incorporated into compositions for coating an implantable medical device, such as prostheses, artificial valves, vascular grafts, stents and catheters. Accordingly, the invention, in another aspect, includes a composition for coating an implantable device comprising a compound of the invention as described generally above, and in classes and subclasses herein, and a carrier suitable for coating said implantable device. In still another aspect, the invention includes an implantable device coated with a composition comprising a compound of the invention as described generally above, and in classes and subclasses herein, and a carrier suitable for coating said implantable device. Suitable coatings and

the general preparation of coated implantable devices are described in US Patents 6,099,562; 5,886,026; and 5,304,121. The coatings are typically biocompatible polymeric materials such as a hydrogel polymer, polymethyldisiloxane, polycaprolactone, polyethylene glycol, polylactic acid, ethylene vinyl acetate, and mixtures thereof. The coatings may optionally be further covered by a suitable topcoat of fluorosilicone, polysaccharides, polyethylene glycol, phospholipids or combinations thereof to impart controlled release characteristics in the composition.

[00168] Another aspect of the invention relates to inhibiting one or more of NaV1.1, NaV1.2, NaV1.3, NaV1.4, NaV1.5, NaV1.6, NaV1.7, NaV1.8, or NaV1.9, activity in a biological sample or a subject, which method comprises administering to the subject, or contacting said biological sample with a compound of formula I or a composition comprising said compound. The term "biological sample", as used herein, includes, without limitation, cell cultures or extracts thereof; biopsied material obtained from a mammal or extracts thereof; and blood, saliva, urine, feces, semen, tears, or other body fluids or extracts thereof.

[00169] Inhibition of one or more of NaV1.1, NaV1.2, NaV1.3, NaV1.4, NaV1.5, NaV1.6, NaV1.7, NaV1.8, or NaV1.9, activity in a biological sample is useful for a variety of purposes that are known to one of skill in the art. Examples of such purposes include, but are not limited to, the study of sodium ion channels in biological and pathological phenomena; and the comparative evaluation of new sodium ion channel inhibitors.

EXAMPLES

[00170] **General methods.** ^1H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were obtained as solutions in deuterioacetonitrile (CD_3CN), chloroform- d (CDCl_3) or dimethyl sulfoxide- D_6 (DMSO). Mass spectra (MS) were obtained using an Applied Biosystems API EX LC/MS system equipped with a Phenomenex 50 x 4.60 mm luna-5 μ C18 column. The LC/MS eluting system was 1-99% or 10-99% acetonitrile in H_2O with 0.035% v/v trifluoroacetic acid, 0.035% v/v formic acid, 5 mM HCl or 5 mM ammonium formate using a 3 or 15 minute linear gradient and a flow rate of 12 mL/minute. Silica gel chromatography was performed using silica gel-60 with a particle size of 230-400 mesh. Pyridine, dichloromethane (CH_2Cl_2),

tetrahydrofuran (THF), dimethylformamide (DMF), acetonitrile (ACN), methanol (MeOH), and 1,4-dioxane were from Aldrich Sure-Seal bottles kept under dry nitrogen. All reactions were stirred magnetically unless otherwise noted.

[00171] X-ray Powder Diffraction Analysis (XRPD) X-ray Powder

5 Diffraction was used to characterize the physical form of the lots produced to date and to characterize different polymorphs identified. The powder x-ray diffraction measurements were performed using PANalytical's X-pert Pro diffractometer at room temperature with copper radiation (1.54060 Å). The incident beam optic was comprised of a variable divergence slit to ensure a constant illuminated length on the
10 sample and on the diffracted beam sides. A fast linear solid state detector was used with an active length of 2.12 degrees 2 theta measured in a scanning mode. The powder sample was packed on the indented area of a zero background silicon holder and spinning was performed to achieve better statistics. A symmetrical scan was measured from 4 – 40 degrees 2 theta with a step size of 0.017 degrees and a scan step time of
15 15.5s.

[00172] Differential Scanning Calorimetry (DSC) and Modulated

Differential Scanning Calorimetry (MDSC) DSC was used to determine the melting point of crystalline materials and to discriminate between different polymorphs. Modulated DSC was used to determine the glass transition temperature of the
20 amorphous material. DSC and MDSC were performed using TA DSC Q2000 differential scanning calorimeter (TA Instruments, New Castle, DE). The instrument was calibrated with indium. Samples of approximately 1-3 mg were weighed into hermetic pans that were crimped using lids with one hole. The DSC samples were scanned from 25°C to 150°C at a heating rate of 10°C/min. The MDSC samples were
25 scanned from -20°C to 200°C at a heating rate of 2°C/min with +/- 1°C of modulation within 1 minute. Data was collected by Thermal Advantage Q Series™ software and analyzed by Universal Analysis software (TA Instruments, New Castle, DE).

[00173] Thermogravimetric Analysis (TGA) TGA was used to investigate

the presence of residual solvents in the lots characterized, and identify the temperature
30 at which decomposition of the sample occurs. TGA data were collected on a TA Q500 Thermogravimetric Analyzer (TA Instruments, New Castle, DE). A sample with

weight of approximately 1-3 mg was scanned from 25 °C to 300 °C at a heating rate of 10 °C/min. Data were collected by Thermal Advantage Q Series™ software and analyzed by Universal Analysis software (TA Instruments, New Castle, DE).

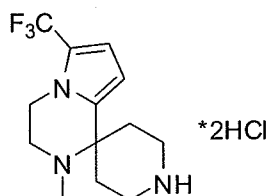
[00174] Single Crystal Structure Analysis Diffraction data were acquired on
5 Bruker Apex II diffractometer equipped with sealed tube Cu K-alpha source and an Apex II CCD detector. The structure was solved and refined using SHELX program (Sheldrick, G.M., Acta Cryst., (2008) A64, 112-122).

[00175] FTIR Spectra FTIR spectra were collected from a Thermo Scientific, Nicolet 6700 FT-IR spectrometer, with smart orbit sampling compartment (multi-
10 bounce Attenuated Total Reflection accessory), diamond window. The Software used for data collection and analysis is: Omnic, 7.4. The collection settings were as follows:

Detector: DTGS KBr;
Beamsplitter: KBr;
Source: IR;
15 Scan range: 4000 – 400 cm⁻¹;
Gain: 8.0;
Optical velocity: 0.6329;
Aperture: 100;
No. of scans: 32;
20 Resolution: 4.

The powder sample was placed directly on the diamond crystal and pressure was added to conform the surface of the sample to the surface of the diamond crystal. The background spectrum was collected and then the sample spectrum was collected.

**[00176] 2'-Methyl-6'-(trifluoromethyl)-3',4'-dihydro-2'H-spiro[piperidine-
25 4,1'-pyrrolo[1,2-a]pyrazine] dihydrochloride (Compound 2)**



[00177] Step 1:

[00178] A mixture of 2,5-dimethoxytetrahydrofuran (15 g, 113.5 mmol), 2-chloroethanamine hydrochloride (44.76 g, 385.9 mmol), and sodium acetate (46.55 g, 567.5 mmol) in acetic acid (55 mL) was heated at 110 °C. After 2 h, the reaction was poured into brine and the product was extracted with dichloromethane. The organics were washed with brine, saturated Na₂CO₃, and brine again. The organics were dried over sodium sulfate and evaporated. The crude material was filtered through a plug of Florisil (80 g) using hexane as the eluent to give 1-(2-chloroethyl)pyrrole (10.1 g, 69%). ¹H NMR (400 MHz, CDCl₃) δ 6.70 (t, J = 1.9 Hz, 2H), 6.18 (t, J = 1.9 Hz, 2H), 4.20 (t, J = 6.5 Hz, 2H), 3.73 (t, J = 6.5 Hz, 2H).

10 [00179] Step 2:

[00180] 1-(2-Chloroethyl)pyrrole (2.0 g, 15.43 mmol) was combined with a solution of 33% methylamine in ethanol (7.3 mL of 33 %w/v, 77.15 mmol). The mixture was heated at 90 °C for 16 h before it was concentrated under reduced pressure to provide N-methyl-2-pyrrol-1-yl-ethanamine (2.19 g, 88%) which was used directly in next reaction. ESI-MS m/z calc. 124.1, found 125.3 (M+1)⁺; Retention time: 0.22 minutes (3 min run). ¹H NMR (400 MHz, CDCl₃) δ 6.73 – 6.68 (m, 2H), 6.22 – 6.14 (m, 2H), 4.05 (t, J = 5.9 Hz, 2H), 2.94 (t, J = 5.9 Hz, 2H), 2.45 (s, 3H).

[00181] Step 3:

[00182] N-Methyl-2-pyrrol-1-yl-ethanamine (2.19 g, 17.64 mmol), tert-butyl 4-oxopiperidine-1-carboxylate (3.51 g, 17.64 mmol), and pTsOH·H₂O (0.334 g, 1.76 mmol) were combined in ethanol (87.60 mL) and heated at 70 °C for 4h. The reaction was concentrated and the residue was dissolved in dichloromethane. The organics were washed with a saturated NaHCO₃ solution and brine. The organics were dried over sodium sulfate and evaporated. The crude material was purified by silica gel chromatography eluting with 0-10% methanol in dichloromethane with 2% triethylamine to give tert-butyl 2-methylspiro[3,4-dihydropyrrolo[1,2-a]pyrazine-1,4'-piperidine]-1'-carboxylate (4.2 g, 78%). ESI-MS m/z calc. 305.4, found 306.3 (M+1)⁺; Retention time: 0.97 minutes (3 min run). ¹H NMR (400 MHz, CDCl₃) δ 6.55 – 6.52 (m, 1H), 6.15 – 6.11 (m, 1H), 5.92 – 5.89 (m, 1H), 3.92 (t, J = 6.0 Hz, 2H), 3.91 – 3.75 (m, 2H), 3.29 (t, J = 6.0 Hz, 2H), 3.26 – 3.12 (m, 2H), 2.36 (s, 3H), 2.10 – 1.99 (m, 2H), 1.83 – 1.69 (m, 2H), 1.47 (s, 9H).

[00183] Step 4:

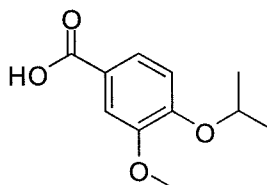
[00184] Method A: tert-Butyl 2-methylspiro[3,4-dihydropyrrolo[1,2-a]pyrazine-1,4'-piperidine]-1'-carboxylate (1.0 g, 3.27 mmol), potassium carbonate (497.7 mg, 3.60 mmol) and trifluoromethanesulfonate; 5-
5 (trifluoromethyl)dibenzothiophen-5-ium (1.32 g, 3.27 mmol) were combined in acetonitrile (10 mL). The reaction mixture was heated at 60 °C for 16 h. The reaction was evaporated to dryness and the residue was dissolved in dichloromethane. The organics were washed with water and brine, dried over sodium sulfate and evaporated. The crude material was purified by silica gel chromatography eluting with 0-50% ethyl
10 acetate in hexanes to give tert-butyl 2-methyl-6-(trifluoromethyl)spiro[3,4-dihydropyrrolo[1,2-a]pyrazine-1,4'-piperidine]-1'-carboxylate (812 mg, 66%). ESI-MS *m/z* calc. 373.2, found 374.5 (M+1)⁺; Retention time: 1.21 minutes (3 min run). ¹H NMR (400 MHz, CDCl₃) δ 6.52 (d, *J* = 3.8 Hz, 1H), 5.91 (d, *J* = 3.8 Hz, 1H), 3.98 (t, *J* = 6.0 Hz, 2H), 3.93 – 3.76 (m, 2H), 3.32 (t, *J* = 6.0 Hz, 2H), 3.26 – 3.08 (m, 2H), 2.36
15 (s, 3H), 2.11 – 1.99 (m, 2H), 1.81 – 1.65 (m, 2H), 1.47 (s, 9H).

[00185] Method B: To tert-butyl 2-methylspiro[3,4-dihydropyrrolo[1,2-a]pyrazine-1,4'-piperidine]-1'-carboxylate (10.0 g, 32.7 mmol) in DMSO (164 mL) was added ferrous sulfate heptahydrate (9.8 mL of 1.0 M, 9.8 mmol) followed by CF₃I (6.41 g, 32.7 mmol) by slow bubbling through the solution and taking the weight
20 difference of the cannister. The mixture was cooled with a ice-water bath before H₂O₂ (3.71 mL of 30 %w/v, 32.7 mmol) dropwise over 15 min keeping the internal temperature <20 °C. The mixture was poured onto 300 mL of ice water and was extracted with EtOAc (2x400 mL). The combined organic phases were washed with brine, dried over MgSO₄, filtered and concentrated in vacuo. The crude material was
25 purified column chromatography eluting with 0-10% methanol in dichloromethane with 2% iPr₂NEt to give tert-butyl 2-methyl-6-(trifluoromethyl)spiro[3,4-dihydropyrrolo[1,2-a]pyrazine-1,4'-piperidine]-1'-carboxylate (7.8 g, 64%). ESI-MS *m/z* calc. 373.2, found 374.5 (M+1)⁺; Retention time: 1.21 minutes (3 min run). ¹H NMR (400 MHz, CDCl₃) δ 6.52 (d, *J* = 3.8 Hz, 1H), 5.91 (d, *J* = 3.8 Hz, 1H), 3.98 (t, *J* = 6.0 Hz, 2H), 3.93 – 3.76 (m, 2H), 3.32 (t, *J* = 6.0 Hz, 2H), 3.26 – 3.08 (m, 2H), 2.36
30 (s, 3H), 2.11 – 1.99 (m, 2H), 1.81 – 1.65 (m, 2H), 1.47 (s, 9H).

[00186] Step 5:

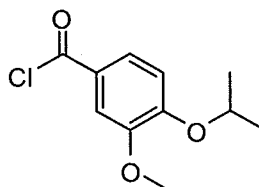
[00187] *tert*-Butyl 2-methyl-6-(trifluoromethyl)spiro[3,4-dihydropyrrolo[1,2-a]pyrazine-1,4'-piperidine]-1'-carboxylate (7.8 g, 20.89 mmol) was stirred in 4M HCl in dioxane (26.10 mL of 4 M, 104.4 mmol) and methanol (22 mL) at room temperature for 1 h. The reaction mixture was evaporated to dryness and the residue was co-evaporated with 100 mL of MTBE to afford 2'-methyl-6'-(trifluoromethyl)-3',4'-dihydro-2'H-spiro[piperidine-4,1'-pyrrolo[1,2-a]pyrazine] dihydrochloride as a yellow foam/solid (7.23 g, quantitative). ESI-MS *m/z* calc. 273.2, found 274.5 (M+1)⁺; Retention time: 0.44 minutes (3 min run).

10 **[00188] 4-Isopropoxy-3-methoxybenzoic acid**

**[00189] Step 1:**

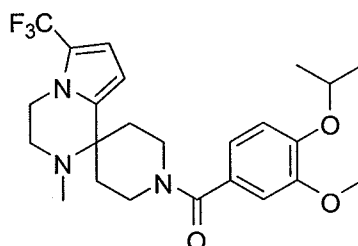
[00190] Under a balloon of N₂, *tert*-butyllithium (2.14 mL of 1.6 M, 3.43 mmol) was added drop-wise to a solution of 4-bromo-1-isopropoxy-2-methoxybenzene (400 mg, 1.63 mmol) in THF (6.0 mL) at -78 °C. The mixture was allowed to stir for 1h at -78 °C before it was added drop-wise to a flask containing CO₂ (1.80 g, 40.8 mmol)(solid, dry ice) in THF (2.0 mL). The mixture was allowed to stir for 30 min as it warmed to room temperature (caution: CO₂ gas evolution). Water (20 mL) was added and the volatiles were removed under reduced pressure. The resultant aqueous layer was acidified with 1N HCl to pH ~1-2 and the mixture was extracted with ethyl acetate (3 x 15 mL). The combined organics were washed with brine, dried over sodium sulfate, filtered and concentrated to give 4-isopropoxy-3-methoxybenzoic acid (≥94% pure, 310 mg, 85%) as a white solid. ESI-MS *m/z* calc. 210.1, found 210.9 (M+1)⁺; Retention time: 1.23 min. ¹H NMR (400 MHz, DMSO) δ 12.63 (s, 1H), 7.53 (dd, *J* = 8.4, 2.0 Hz, 1H), 7.44 (d, *J* = 2.0 Hz, 1H), 7.04 (d, *J* = 8.7 Hz, 1H), 4.67 (dt, *J* = 12.1, 6.0 Hz, 1H), 3.78 (s, 3H), 1.28 (d, *J* = 6.0 Hz, 6H).

[00191] 4-Isopropoxy-3-methoxybenzoyl chloride (Compound 3)



[00192] To a reactor, 4-isopropoxy-3-methoxybenzoic acid (385 g, 1.82 mol, 1.00 eq), toluene (1.9 L, 5.0 vol), pyridine (7.19 g, 7.35 ml, 90.9 mmol, 0.05 eq) was added and heated to 60 °C while stirring under an N₂ purge. SOCl₂ (346 g, 212 ml, 2.91 mol, 1.60 eq) was added via syringe pump and stirred at 60 °C. Compound 3 formation was followed by HPLC; the reaction was complete whe sampled after the SOCl₂ addition was completed. The reaction solution was concentrated and flushed with toluene (765 ml), then again with toluene (765 ml) and then with 2-Me-THF (765 ml) to afford Compound 3 as an amber oil solids on the flask walls (salts) and used directly in the synthesis of Compound 1, Method B.

[00193] (4-Isopropoxy-3-methoxyphenyl)(2'-methyl-6'-(trifluoromethyl)-3',4'-dihydro-2'H-spiro[piperidine-4,1'-pyrrolo[1,2-a]pyrazine]-1-yl)methanone (Compound 1)



15 Method A

[00194] A mixture of 2'-methyl-6'-(trifluoromethyl)-3',4'-dihydro-2'H-spiro[piperidine-4,1'-pyrrolo[1,2-a]pyrazine] dihydrochloride (69 mg, 0.20 mmol), 4-isopropoxy-3-methoxybenzoic acid (42 mg, 0.20 mmol), HATU (76 mg, 0.20 mmol), Et₃N (112 μL, 0.80 mmol) and DMF (2 mL) was allowed to stir at room temperature for 3h. The mixture was filtered and purified by reverse-phase preparatory HPLC (10-99% ACN/water). The desired fractions were concentrated to give (4-isopropoxy-3-methoxyphenyl)(2'-methyl-6'-(trifluoromethyl)-3',4'-dihydro-2'H-spiro[piperidine-4,1'-pyrrolo[1,2-a]pyrazine]-1-yl)methanone as a white solid. ESI-MS m/z calc. 465.2, found 466.3 (M+1)⁺; Retention time: 1.23 minutes (3 min run). ¹H NMR (400 MHz,

CDCl₃) δ 7.01 (d, J = 1.7 Hz, 1H), 6.97 (dd, J = 8.2, 1.7 Hz, 1H), 6.88 (d, J = 8.3 Hz, 1H), 6.53 (d, J = 3.0 Hz, 1H), 5.94 (d, J = 3.5 Hz, 1H), 4.57 (dt, J = 12.2, 6.1 Hz, 1H), 4.52 (s, 1H), 3.99 (s, 2H), 3.87 (s, 3H), 3.69 (s, 1H), 3.40 (s, 1H), 3.34 (t, J = 5.4 Hz, 3H), 2.39 (s, 3H), 2.11 (s, 2H), 1.82 (s, 2H), 1.38 (d, J = 6.1 Hz, 6H).

5 Method B

[00195] To a 30 L jacketed reactor was added 2-Me-THF (3.150 L, 7.0 vol) and Compound 2 (450 g, 1.300 mol, 1.0 eq) and the mixture was stirred at 10 °C while a solution of NaOH (2.600 L or 10.0 % w/v, 6.500 mol, 5.0 eq) was added over 15-20 minutes, maintaining reaction temperature around 15 °C and stirred 45 minutes to freebase the amine. Stirring increased to 200 rpm. Compound 3 (327.0 g, 1.430 mol) in 2-Me-THF (2.250 L) (some salts precipitate, set salts aside, added only the sol'n) was added via addition funnel over 30 minutes maintaining a reaction temperature between 15 °C and 20 °C (no exotherm). Reaction progress was followed by HPLC. Reaction was complete at 1 hr; HPLC shows one large by-product (~12% of area), stirring was turned off, aqueous layer dropped and the organic layer was then washed with brine (1.35 L, 3.0 vol), dried over Na₂SO₄, filtered through Celite, washed with 2Me-THF (450ml, 1.0 vol). The filtrate was concentrated in a rotovap, and flushed with cyclohexane (1.800 L, 4.0 vol). An amber oil was obtained.

[00196] Table 1 below recites the analytical data for Compound 1.

20 **Table 1.**

Cmpd.	LC/MS M+1	LC/RT min	NMR
Compound 1	466.5	1.23	1H NMR (400 MHz, CDCl ₃) δ 7.01 (d, J = 1.9 Hz, 1H), 6.97 (dd, J = 8.2, 1.9 Hz, 1H), 6.88 (d, J = 8.3 Hz, 1H), 6.53 (d, J = 3.5 Hz, 1H), 5.94 (d, J = 3.7 Hz, 1H), 4.56 (dq, J = 12.2, 6.1 Hz, 1H), 4.52 - 4.34 (m, 1H), 4.05 - 3.94 (m, 2H), 3.87 (s, 3H), 3.69 (s, 1H), 3.50 (s, 1H), 3.34 (s, 1H), 3.34 (t, J = 5.7 Hz, 2H), 2.39 (s, 3H), 2.13 (s, 2H), 1.84 (s, 2H), 1.38 (d, J = 6.1 Hz, 6H).

[00197] Compound 1 Form A

[00198] The starting point for the various solid forms for Compound 1 is Compound 1 itself. The solubility of Compound 1 was determined first. Solubility of Compound 1 in organic solvents was determined by adding 100 μ l increment of

various organic solvents into about 100 mg of Compound 1 until clear solution was achieved. The visual results will be reported due to very high solubility of Compound 1 in various organic solvents (see Table 2).

Table 2.

5		Solvent	Solubility (mg/ml), Compound 1
		Acetonitrile	>500
		2 methyl THF	>500
		EtOAc	>500
		Acetone	>500
		IPA	~200-250
		Ethanol	>250
10		Methanol	> 500
		MTBE	> 60
		Toluene	>333
		Acetic acid	~200-250
		Propyl acetate	>250
		DMA	~200-250
		Water*	0.052
15		Heptane*	1.5

[00199] From Compound 1, Compound 1 Form A was prepared by three methods: alkane recrystallization, anti-solvent addition, and solvent slurry.

[00200] *Alkane Recrystallization*

20 [00201] 540 g Of the amber oil from Method B above was dissolved in toluene (5.40 L, 10.0 vol). Aq 6N HCl solution (4.833 L, 6M, 25.0 eq) was added and the solution was stirred at room temperature (20-25 °C) for one hour. Stirring stopped and layers were tested; by-product remained in the organic layer with product in the aqueous acidic layer. The organic layer was removed, and to the acidic aqueous layer
 25 was added toluene (5.40 L, 10.0 vol), stirred at 15 °C, then began slow addition of NaOH, 50% (2.32 L of 50.0 %w/v, 29.00 mol, 25.0 vol) maintaining internal temperature at 20 ± 5 °C. The resulting mixture was stirred at room temp, then allowed to split (aq layer pH basic, was drained). The toluene layer was washed with

brine (2.70 L, 5.0 vol), dried over Na₂SO₄, filtered, (cake washed with toluene) (540ml, 1.0 vol). The toluene solution was concentrated to a white solid, flushed with cyclohexane (540.0 ml, 10.0 vol), then additional cyclohexane (4.320 L, 8.0 vol) was added and heated to 55 °C with good stirring to dissolve residual oil. The solution was then ramped to 50 °C over 30 minutes. After another 30 minutes, gradual cooling began to 20 °C over 90 minutes and then stirred at room temperature for 2 hrs. The bath was cooled to 15 °C, stirred 5-10 min. The mixture was filtered (fast) and cake washed with cyclohexane (540.0 ml, 1.0 vol), and pulled dry with N₂ blanket. The wet cake was scooped into a glass tray and covered with a sheet of paper, placed in an oven, and dried *in vacuo* over two days (30 °C, no bleed). Compound 1 Form A (394 g, 846.4 mmol, 72.96%) was obtained as an off-white solid with 97.3 % AUC purity by HPLC.

[00202] Anti-Solvent Addition

[00203] Solubility of Compound 1 in water and heptane is less than 2 mg/ml and can be used as anti-solvent. About 0.7 ml of solutions of Compound 1 in acetic acid, acetonitrile, EtOAc, propyl acetate, acetone, MEK, methanol, ethanol, IPA, 2-methyl THF, DCM, and DMA at 100 mg/ml were prepared and either water or heptane was added slowly while stirring until slightly cloudy or just clear and left on the bench for overnight without stirring (Table 3). Next morning, the solutions were stirred vigorously to generate crystalline solids. All the conditions generate either clear solutions or oil except alcohols with water and DMA/water, solids were able to precipitate out. The solids precipitated out were subject to PXRD and confirmed to be crystalline Form A.

Table 3.

#	Solvent	Anti-solvent	Amount of Anti-solvent to cloudy point or just clear	Overnight leave on bench. Then vigorously stirring for 1 hr
1	Acetic acid	Water	0.7 ml/7 ml-Clear	Clear
2	ACN	Water	0.7 ml/1 ml - Oil	Oil
3	EtOAc	Heptane	0.7 ml/7 ml - Clear	Clear
4	Propyl Acetate	Heptane	0.7 ml/7 ml - Clear	Clear
5	Acetone	Water	0.7ml/0.5 ml -Oil	Oil
6	MEK	Water	0.7 ml/0.3 ml - Oil	Oil

7	Methanol	Water	0.7 ml/0.3 ml - Oil	White solid (Form A)
8	Ethanol	Water	0.7 ml/0.2 ml - Clear	Additional 0.4 ml of water, cloudy white solid precipitates, stir for 1hr, oil Add seed Compound 1 Form A, left on bench, white solid precipitates (Compound 1 Form A)
9	IPA	Water	0.7 ml/0.1 ml - Clear	Additional 0.7 ml of water, just cloudy. Add seed Compound 1 Form A, left on bench, 10 minutes later, white solid precipitates (Compound 1 Form A)
10	2- methyl THF	Heptanes	0.7 ml/0.7 ml - Clear	Clear
11	DCM	Heptanes	0.7 ml/2.1ml - Clear	Clear
12	DMA	Water	0.7 ml/0.3ml – Solid gum-Clear	Additional 0.1 ml DMA and stir, white solid forms (Compound 1 Form A)

[00204] Solvent Slurry

[00205] Stable form identification and hydrate form identification were performed by slurry method. Due to extremely higher solubility of Compound 1 in various neat organic solvents, the mixture of organic solvents with anti-solvents such as water or heptane along with pure water or heptane was used for slurring method. Additional water was added into above anti-solvent experiments (Table 3: condition 2, 5, 6, 7, 8, 9 and 12) and kept stirring at RT for up to three weeks. The suspensions were subject to centrifuge and the residue solids were collected for powder x-ray diffraction analysis at the end of the 3 week. If no new pattern was found, no further analysis was performed. In conclusion, slurring Compound 1 in certain organic/water system for up to 3 weeks resulted in Compound 1 Form A only (see Table 4).

Table 4.

Solvent/Anti-solvent	PXRD
ACN/Water = 1/2	Oil

Acetone/water = 1/1	Form A
MEK/water = 1/1	Oil
MeOH/water = 1/2	Form A
EtOH/water = 1/2	Form A
IPA/Water = 1/2	Form A
DMA/Water = 1/2	Form A

[00206] A similar experiment was performed on Compound 1 Form A. About 40 mg of Compound 1 Form A was added into HPLC vials and solvent was added first followed by anti-solvent. The final solid/solvent ratio is 30 mg/ml. The suspension
 5 was stirred at RT for 1 week. At the end of one week, the suspensions were subject to centrifuge and the residue solids were collected for powder x-ray diffraction analysis. The supernatant was diluted with methanol as needed and injected into HPLC for assay. Results are reported in Table 5.

Table 5.

10

Solvent/Anti-solvent	Solubility (mg/ml)	PXRD
Water at RT	0.052	Form A
Water at 45°C	0.532	Form A
Heptane	1.518	Form A
Acetone/water = 1/2	2.386	Form A
MeOH/water = 1/1	3.648	Form A
EtOH/water = 2/3	3.025	Form A
IPA/Water = 1/2	2.739	Form A
DMA/Water = 1/1	2.697	Form A

[00207] Various crystallization methods were used to search for hydrate and more stable neat solid forms other than Form A, but they only resulted in Compound 1 Form A. Form A is a highly thermodynamically stable solid form for Compound 1 making Compound 1 Form A amenable to various pharmaceutical formulations.

[00208] Table 6 presents the XRPD list for Compound 1 Form A according to relative intensity (see Figure 1).

Table 6.

2-Theta (degrees) [°2 Th]	Rel. Int. [%]
17.2	100
11.2	76
20.5	58
18.7	54
15.7	49
16.0	31
5.5	24
22.9	23
8.0	18
16.2	15

[00209] From DSC (Figure 2), one can see that Compound 1 Form A melted at 109-114°C. From thermogravimetric analysis (TGA) (Figure 3), one can see that the material has now weight loss up to 205°C and degraded after that.

[00210] The FTIR spectra of Compound 1 Form A is shown in Figure 4 and the peak list is presented below in Table 7.

Table 7.

Position (cm-1)	% Transmittance
794.1	56.8
821.0	63.9
841.2	69.0
1032.1	49.8
1082.5	32.8
1131.1	50.7
1243.9	59.6

1259.4	48.8
1428.9	59.5
1468.6	63.4
1627.0	51.0
2973.9	87.5
3097.5	97.0

[00211] Vapor diffusion and anti-solvent methodologies have been used to grow a single crystal of Compound 1 Form A for single crystal structure elucidation. Compound 1 Form A is monoclinic with the space group of $P2_1/c$ and the following unit cell dimensions: $a = 33.8479(11) \text{ \AA}$, $b = 6.2867(2) \text{ \AA}$, $c = 23.1385(8) \text{ \AA}$, $\alpha = \gamma = 90.00^\circ$, $\beta = 109.99^\circ$, $V = 4627.04 \text{ \AA}^3$, $Z = 8$. Density of form A calculated from structural data is 1.336 g/cm^3 at 100 K. The crystal structure confirms absolute configuration of the molecule (See Figures 5 and 6).

[00212] Compound 1 HCl Salt Form A

[00213] Compound 1 HCl Salt Form A was prepared by dissolving Compound 1 in dichloromethane to form a 100 mg/ml solution. 1 Molar equivalent of 2M HCl in diethyl ether was added resulting in a precipitate. Compound 1 HCl Salt Form A was collected by filtration under a nitrogen blanket as a hygroscopic solid. Figure 7 depicts the XRPD of Compound 1 HCl Salt Form A. A differential scanning calorimetry (DSC) trace of Compound 1 HCl Salt Form A is depicted in Figure 8. A thermogravimetric analysis (TGA) trace of Compound 1 HCl Salt Form A is depicted in Figure 9.

[00214] Compound 1 HCl Salt Form B

[00215] Solubility of Compound 1 HCl salt in organic solvents was determined by adding 1.5 ml of various organic solvents into about 60 mg of Compound 1 HCl salt. The suspension was stirred at RT for 10 days. The supernatant was obtained by centrifuge with filter at 15,000rpm for 3 minutes. The supernatant was diluted with methanol as needed and injected into HPLC for solubility assay. The residue solids were collected and subject to powder x-ray diffraction measurement. See results on Table 8.

Table 8.

Solvent	HCl salt, Solubility (mg/ml)	Screening method	Residue Solid
Acetonitrile	>40	Slow evaporation	Amorphous
Acetone	>40	Slow evaporation	HCl-acetone solvate
MTBE	0.012	Slurry	HCl-B
MIBK	2.68	Slurry	HCl-B
IPAc	0.87	Slurry	HCl-B
DCM	>40	Slow evaporation	Amorphous
Toluene	0.46	Slurry	HCl-B
Heptane	0	Slurry	HCl-B
Cyclohexane	0	Slurry	HCl-B
2-Butanone (MEK)	>40	Slow evaporation	HCl-MEK solvate
EtOAc	4.18	Slurry	HCl-B
2-Methyl-THF	1.37	Slurry	HCl-B
MeOH	>60 (starting material is HCl-B*)	Slow evaporation	Amorphous
EtOH	>40 (starting material is HCl-B*)	Slow evaporation	Amorphous
THF	8.7 (starting material is HCl-B ^Δ)	Slurry for 1 day	HCl-B
THF	8.3 (starting material is HCl-B ^Δ)	Slurry for 10 day	1: 0.64 API: THF solvate

- [00216] Stable form identification was performed by slurry method using both Compound 1 HCl salt and Compound 1 HCl Salt Form B as starting material. About 60 mg of either Compound 1 HCl salt or Compound 1 HCl Salt Form B was added into HPLC vials and 1.0 or 1.5 mL of various organic solvents were added subsequently. The suspension was stirred at RT for 10 days. At the end of 10 days, the aliquots were removed and subject to centrifuge. The supernatant diluted with methanol for HPLC solubility analysis and the residue solids subject to powder x-ray diffraction analysis.
- See results on Table 8. All slurry conditions generated Compound 1 HCl Salt Form B except in THF. After 1 day, slurry Compound 1 HCl Salt Form B in THF was not changed. After 10 days of slurry in THF, a THF solvate due to increasing level of

water over time from the environment formed. It is believed that slurry of Compound 1 HCl salt and Compound 1 HCl Salt Form B in pure THF without water should result in Compound 1 HCl Salt Form B. The THF solvate or THF/water mixture forms only formed when the water level in the mixture reaches certain level.

- 5 **[00217]** Stable form identification was also performed by anti-solvent method. About 100 mg of Compound 1 HCl Salt Form B was added into shell vials and 1.0 mL of various organic solvents was added and heated at 60°C for 10-15 minutes. Then various anti-solvents were added until cloudy. The mixtures were then slowly cooled down to 15°C and stored in a refrigerator overnight. The resulting mixtures were
- 10 subject to centrifuge. The supernatant thus obtained was diluted with methanol for HPLC solubility analysis (Table 9) and the residue solid was subjected to powder x-ray diffraction analysis (see Table 10 and Figure 10).

Table 9.

Solvent/Anti-solvent	Solubility (mg/ml, FB)	Residue solid XRPD
IPAc/CAN/5:2	16.5	Compound 1 HCl Salt Form B
MTBE/EtOH/1:1	26.8	Compound 1 HCl Salt Form B
EtOH/MTBE/1:8	1.9	Compound 1 HCl Salt Form B
DCM/Cyclohexane/1:2	0.9	Compound 1 HCl Salt Form B
DCM/Toluene/1:8	0.7	Compound 1 HCl Salt Form B
DCM/Heptane/1:2	1.2	Compound 1 HCl Salt Form B
DCM/MTBE/1:8	0.2	Compound 1 HCl Salt Form B
CAN/MTBE/1:8	1.0	Compound 1 HCl Salt Form B
IPA/MTBE/1:8	2.1	Compound 1 HCl Salt Form B
EtOH/Cyclohexane/1:8	0.9	Compound 1 HCl Salt Form B
EtOH/Heptane/1:6	1.6	Compound 1 HCl Salt Form B
MeOH/MTBE/1:8	3.8	Compound 1 HCl Salt Form B

- 15 **[00218]** Table 10 presents the XRPD list for Compound 1 HCl Salt Form B according to relative intensity.

Table 10.

2-Theta (degrees) [°2 Th]	Rel. Int. [%]
5.2	100
15.7	65

10.5	62
26.3	38
21.0	29
23.8	15
18.7	15
25.9	14
18.2	11
19.2	11

[00219] The differential scanning calorimetry (DSC) and thermogravimetric analysis (TGA) thermographs were obtained using a TA instruments DSC Q2000 and TGA Q500 respectively at a scan rate of 10°C/min over a temperature range of 25-250°C or 300°C (see Figures 11 and 12, respectively). For DSC analysis, samples were weighed into aluminum hermetic T-zero pans that were sealed and punctured with a single hole. For TGA analysis, samples were placed in hermetic pans without seal. From DSC, one can see that Compound 1 HCl Salt Form B melted at ~200°C. From TGA, one can see that the material has no weight loss up to 205°C and degraded after that.

[00220] Figure 13 depicts the FTIR spectrum for Compound 1 HCl Salt Form B. Table 11 provides a peak list of the FTIR spectrum for Compound 1 HCl Salt Form B.

Table 11.

Position (cm-1)	% Transmittance
411.0	84.6
451.5	81.5
495.9	83.3
516.8	84.2
548.0	78.2
574.7	76.5
615.3	70.6
644.8	75.8
667.7	84.3
682.9	71.9
706.5	74.8
749.9	58.5
772.4	63.7
791.9	59.2
807.3	61.8

856.7	65.1
884.0	76.8
903.4	71.8
917.5	72.4
931.9	64.4
951.0	60.2
967.7	56.1
1017.1	59.3
1035.7	51.8
1081.4	40.4
1099.9	40.9
1133.0	39.8
1175.9	59.5
1228.8	50.9
1255.1	43.5
1290.6	83.1
1324.5	53.3
1351.0	66.6
1380.6	66.1
1432.5	57.0
1453.5	67.6
1475.3	74.3
1498.9	69.2
1561.7	79.2
1574.9	77.5
1625.3	63.3
2122.7	95.0
2304.6	84.1
2859.1	94.9
2980.7	87.5
3094.5	94.4

[00221] Single crystal was grown in the following conditions: 111 mg/ml of stock solution of Compound 1 HCl Salt Form B in EtOH was prepared and filtered. Either 4 mL or 2.5 mL of MTBE was added into above 0.25 mL of the solution while stirring. The resulting clear solution was left for slow evaporation. After two weeks, single crystals were generated. In addition, single crystals can also be formed by vapor diffusion of Compound 1 HCl Salt Form B solution in EtOH at 111 mg/ml with heptane as vapor diffusion. After two weeks, needle shape crystals were formed. The single crystal structure of Compound 1 HCl Salt Form B was elucidated and the result is shown in Table 12 and Figure 14.

Table 12.

	Space group	Cell Length a, b, c	Cell Angles α , β , γ	Cell volume	Z	R
Compound 1 HCl Salt Form B	P21/c Monoclinic	33.8479 (11) 6.2867 (2) 23.1385 (8)	90 109.99 90	4627.04	8	11.5

[00222] Compound 1 Mesylate Salt Form A

[00223] A stock solution of Compound 1 in EtOAc at 200 mg/ml

- 5 concentration was prepared. An equal molar amount of methanesulfonic acid was added. Initially, a clear solution resulted., but a white solid precipitated after stirring at room temperature. The suspension was allowed to stir at room temperature overnight. The solids formed were collected by filtration under an N₂ blanket and washed with EtOAc. The solids were then dried under vacuum.

- 10 **[00224]** The powder x-ray diffraction measurements were performed using PANalytical's X-pert Pro diffractometer at room temperature with copper radiation (1.54060 Å). The incident beam optic was comprised of a variable divergence slit to ensure a constant illuminated length on the sample and on the diffracted beam side; a fast linear solid state detector was used with an active length of 2.12 degrees 2 theta
- 15 measured in a scanning mode. The powder sample was packed on the indented area of a zero background silicon holder and spinning was performed to achieve better statistics. A symmetrical scan was measured from 4 – 40 degrees 2 theta with a step size of 0.017 degrees and a scan step time of 15.5s (see Figure 15). Table 13 presents the XRPD list for Compound 1 Mesylate Salt Form A according to relative intensity.

20 **Table 13.**

2-Theta (degrees) [°2 Th]	Rel. Int. [%]
21.8	100
16.6	96
21.3	96
16.9	69
15.9	66

15.6	55
20.7	52
22.4	49
17.2	43
19.1	42

[00225] The differential scanning calorimetry (DSC) and thermogravimetric analysis (TGA) thermographs were obtained using a TA instruments DSC Q2000 and TGA Q500 respectively at a scan rate of 10°C/min over a temperature range of 25-210°C or 300°C (see Figures 16 and 17, respectively). For DSC analysis, samples were weighed into aluminum hermetic T-zero pans that were sealed and punctured with a single hole. For TGA analysis, samples were placed in hermetic pans without seal. From DSC, one can see that Compound 1 Mesylate Salt Form A melted at ~186°C. From TGA, one can see that the material has no weight loss up to 205°C and degraded after that.

[00226] Compound 1 Besylate Salt Form A

[00227] Compound 1 Besylate Salt Form A was prepared by reacting 200 mL solution of Compound 1 in acetone (100 mg/mL) with 270 µL of 0.1 N benzenesulfonic acid. Initially, the solution is clear. After overnight stirring at room temperature, solids precipitated, were washed with acetone, and air dried. Alternatively, Compound 1 Besylate Salt Form A was prepared by reacting 200 mL solution of Compound 1 in THF (100 mg/mL) with 13.5 µL of 2 N benzenesulfonic acid. Initially, the solution is clear. After overnight stirring at room temperature, solids precipitated, were washed with THF, and air dried.

[00228] The powder x-ray diffraction measurements were performed using PANalytical's X-pert Pro diffractometer at room temperature with copper radiation (1.54060 Å). The incident beam optic was comprised of a variable divergence slit to ensure a constant illuminated length on the sample and on the diffracted beam side; a fast linear solid state detector was used with an active length of 2.12 degrees 2 theta measured in a scanning mode. The powder sample was packed on the indented area of a zero background silicon holder and spinning was performed to achieve better statistics. A symmetrical scan was measured from 4 – 40 degrees 2 theta with a step

size of 0.017 degrees and a scan step time of 15.5s (see Figure 18). Table 14 presents the XRPD list for Compound 1 Besylate Salt Form A according to relative intensity.

Table 14.

2-Theta (degrees) [°2 Th]	Rel. Int. [%]
5.9	100
21.5	88
18.8	76
16.7	75
19.4	64
17.0	62
11.9	47
22.2	41
15.6	27
16.4	27

- 5 **[00229]** The differential scanning calorimetry (DSC) and thermogravimetric analysis (TGA) thermographs were obtained using a TA instruments DSC Q2000 and TGA Q500 respectively at a scan rate of 10°C/min over a temperature range of 25-230°C or 300°C (see Figures 19 and 20, respectively). For DSC analysis, samples were weighed into aluminum hermetic T-zero pans that were sealed and punctured
- 10 with a single hole. For TGA analysis, samples were placed in hermetic pans without seal. From DSC, one can see that crystalline Besylate salt form A melted at ~219°C.

[00230] Compound 1 Tosylate Salt Form A

- [00231]** Compound 1 Tosylate Salt Form A was prepared by reacting 200 mL solution of Compound 1 in acetone (100 mg/mL) with 270 µL of 0.1 N *p*-toluenesulfonic acid. Initially, the solution is clear. After overnight stirring at room
- 15 temperature, solids precipitated, were washed with acetone, and air dried.
- Alternatively, Compound 1 Tosylate Salt Form A was prepared by reacting 200 mL solution of Compound 1 in THF (100 mg/mL) with 13.5 µL of 2 N *p*-toluenesulfonic acid. Initially, the solution is clear. After overnight stirring at room temperature,
- 20 solids precipitated, were washed with THF, and air dried.

[00232] The powder x-ray diffraction measurements were performed using PANalytical's X-pert Pro diffractometer at room temperature with copper radiation (1.54060 Å). The incident beam optic was comprised of a variable divergence slit to ensure a constant illuminated length on the sample and on the diffracted beam side; a fast linear solid state detector was used with an active length of 2.12 degrees 2 theta measured in a scanning mode. The powder sample was packed on the indented area of a zero background silicon holder and spinning was performed to achieve better statistics. A symmetrical scan was measured from 4 – 40 degrees 2 theta with a step size of 0.017 degrees and a scan step time of 15.5s (see Figure 21). Table 15 presents the XRPD list for Compound 1 Tosylate Salt Form A according to relative intensity.

Table 15.

2-Theta (degrees) [°2 Th]	Rel. Int. [%]
6.0	100
20.3	67
24.1	41
12.0	37
22.8	33
16.4	31
19.2	15
16.7	14
20.9	13
9.1	13

[00233] The differential scanning calorimetry (DSC) and thermogravimetric analysis (TGA) thermographs were obtained using a TA instruments DSC Q2000 and TGA Q500 respectively at a scan rate of 10°C/min over a temperature range of 25-245°C or 300°C (see Figures 22 and 23, respectively). For DSC analysis, samples
5 were weighed into aluminum hermetic T-zero pans that were sealed and punctured with a single hole. For TGA analysis, samples were placed in hermetic pans without seal. From DSC, one can see that crystalline Tosylate salt form A melted at ~227-230°C.

10 ASSAYS FOR DETECTING AND MEASURING NaV INHIBITION PROPERTIES OF COMPOUND

E-VIPR optical membrane potential assay method with electrical stimulation

[00234] Sodium channels are voltage-dependent proteins that can be activated by inducing membrane voltage changes by applying electric fields. The electrical stimulation instrument and methods of use are described in Ion Channel Assay
15 Methods PCT/US01/21652, herein incorporated by reference and are referred to as E-VIPR. The instrument comprises a microtiter plate handler, an optical system for exciting the coumarin dye while simultaneously recording the coumarin and oxonol emissions, a waveform generator, a current- or voltage-controlled amplifier, and a device for inserting electrodes in well. Under integrated computer control, this
20 instrument passes user-programmed electrical stimulus protocols to cells within the wells of the microtiter plate.

[00235] 24 hours before the assay on E-VIPR, HEK cells expressing human NaV subtype, like NaV 1.7, are seeded in 384-well poly-lysine coated plates at 15,000-20,000 cells per well. Other subtypes are performed in an analogous mode in a cell
25 line expressing the NaV of interest. HEK cells are grown in media (exact composition is specific to each cell type and NaV subtype) supplemented with 10% FBS (Fetal Bovine Serum, qualified; GibcoBRL #16140-071) and 1% Pen-Strep (Penicillin-Streptomycin; GibcoBRL #15140-122). Cells are grown in vented cap flasks, in 90% humidity and 10% CO₂, to 100% confluence. They are usually split by trypsinization
30 1:10 or 1:20, depending on scheduling needs, and grown for 2-3 days before the next split.

Reagents and Solutions:

[00236] 100 mg/mL Pluronic F-127 (Sigma #P2443), in dry DMSO

[00237] Compound Plates: 384-well round bottom plate, e.g. Corning 384-well Polypropylene Round Bottom #3656

5 [00238] Cell Plates: 384-well tissue culture treated plate, e.g. Greiner #781091-1B

[00239] 10 mM DiSBAC₆(3) (Aurora #00-100-010) in dry DMSO

[00240] 10 mM CC2-DMPE (Aurora #00-100-008) in dry DMSO

[00241] 200 mM ABSC1 in H₂O

10 [00242] Bath1 buffer. Glucose 10mM (1.8g/L), Magnesium Chloride (Anhydrous), 1mM (0.095g/L), Calcium Chloride, 2mM (0.222g/L), HEPES 10mM (2.38g/L), Potassium Chloride, 4.5mM (0.335g/L), Sodium Chloride 160mM (9.35g/L).

[00243] Hexyl Dye Solution: Bath1 Buffer + 0.5% β -cyclodextrin (make this
15 prior to use, Sigma #C4767), 8 μ M CC2-DMPE + 2.5 μ M DiSBAC₆(3). To make the solution Add volume of 10% Pluronic F127 stock equal to volumes of CC2-DMPE + DiSBAC₆(3). The order of preparation is first mix Pluronic and CC2-DMPE, then add DiSBAC₆(3) while vortexing, then add Bath1 + β -Cyclodextrin.

Assay Protocol:

20 [00244] 1) Pre-spot compounds (in neat DMSO) into compound plates. Vehicle control (neat DMSO), the positive control (20mM DMSO stock tetracaine, 125 μ M final in assay) and test compounds are added to each well at 160x desired final concentration in neat DMSO. Final compound plate volume will be 80 μ L (80-fold intermediate dilution from 1 μ L DMSO spot; 160-fold final dilution after transfer to
25 cell plate). Final DMSO concentration for all wells in assay is 0.625%.

[00245] 2) Prepare Hexyl Dye Solution.

[00246] 3) Prepare cell plates. On the day of the assay, medium is aspirated and cells are washed three times with 100 μ L of Bath1 Solution, maintaining 25 μ L residual volume in each well.

[00247] 4) Dispense 25 μ L per well of Hexyl Dye Solution into cell plates.
5 Incubate for 20-35 minutes at room temp or ambient conditions.

[00248] 5) Dispense 80 μ L per well of Bath1 into compound plates. Acid Yellow-17 (1 mM) is added and Potassium Chloride can be altered from 4.5 to 20 mM depending on the NaV subtype and assay sensitivity.

[00249] 6) Wash cell plates three times with 100 μ L per well of Bath1, leaving
10 25 μ L of residual volume. Then transfer 25 μ L per well from Compound Plates to Cell Plates. Incubate for 20-35 minutes at room temp/ambient condition

[00250] 7) Read Plate on E-VIPR. Use the current-controlled amplifier to deliver stimulation wave pulses for typically 9 seconds and a scan rate of 400Hz. A pre-stimulus recording is performed for 0.5seconds to obtain the un-stimulated
15 intensities baseline. The stimulatory waveform is applied for 9 seconds followed by 0.5 seconds of post-stimulation recording to examine the relaxation to the resting state. The stimulatory waveform of the electrical stimulation is specific for each cell type and can vary the magnitude, duration and frequency of the applied current to provide an optimal assay signal.

20 Data Analysis

[00251] Data are analyzed and reported as normalized ratios of background-subtracted emission intensities measured in the 460 nm and 580 nm channels. Background intensities are then subtracted from each assay channel. Background intensities are obtained by measuring the emission intensities during the same time
25 periods from identically treated assay wells in which there are no cells. The response as a function of time is then reported as the ratios obtained using the following formula:

$$R(t) = \frac{(\text{intensity}_{460 \text{ nm}} - \text{background}_{460 \text{ nm}})}{\text{intensity}_{580 \text{ nm}} - \text{background}_{580 \text{ nm}}}$$

(intensity_{580 nm} - background_{580 nm})

[00252] The data is further reduced by calculating the initial (R_i) and final (R_f) ratios. These are the average ratio values during part or all of the pre-stimulation period, and during sample points during the stimulation period. The response to the stimulus $R_{\square\square} = R_f/R_i$ is then calculated and reported as a function of time.

[00253] Control responses are obtained by performing assays in the presence of a compound with the desired properties (positive control), such as tetracaine, and in the absence of pharmacological agents (negative control). Responses to the negative (N) and positive (P) controls are calculated as above. The compound antagonist activity A is defined as:

$$A = \frac{R - P}{N - P} * 100 .$$

where R is the ratio response of the test compound

ELECTROPHYSIOLOGY ASSAYS FOR NaV ACTIVITY AND INHIBITION OF TEST COMPOUNDS

[00254] Patch clamp electrophysiology was used to assess the efficacy and selectivity of sodium channel blockers in dorsal root ganglion neurons. Rat neurons were isolated from the dorsal root ganglions and maintained in culture for 2 to 10 days in the presence of NGF (50 ng/ml) (culture media consisted of NeurobasalA supplemented with B27, glutamine and antibiotics). Small diameter neurons (nociceptors, 8-12 μm in diameter) have been visually identified and probed with fine tip glass electrodes connected to an amplifier (Axon Instruments). The “voltage clamp” mode has been used to assess the compound’s IC₅₀ holding the cells at – 60 mV. In addition, the “current clamp” mode has been employed to test the efficacy of the compounds in blocking action potential generation in response to current injections. The results of these experiments have contributed to the definition of the efficacy profile of the compounds.

IonWorks assays.

[00255] Sodium currents were recorded using the automated patch clamp system, IonWorks (Molecular Devices Corporation, Inc.). Cells expressing Nav subtypes are harvested from tissue culture and placed in suspension at 0.5-4 million

cells per mL Bath1. The IonWorks instrument measures changes in sodium currents in response to applied voltage clamp similarly to the traditional patch clamp assay, except in a 384-well format. Using the IonWorks, dose-response relationships were determined in voltage clamp mode by depolarizing the cell from the experiment specific holding potential to a test potential of about 0 mV before and following addition of the test compound. The influence of the compound on currents are measured at the test potential.

1-Benzazepin-2-one binding assay

[00256] The sodium channel inhibiting properties of the compounds of the invention can also be determined by assay methods described in Williams, B. S. et al., “Characterization of a New Class of Potent Inhibitors of the Voltage-Gated Sodium Channel NaV 1.7,” *Biochemistry*, **2007**, 46, 14693-14703, the entire contents of which are incorporated herein by reference.

[00257] Compound 1 herein is active against one or more sodium channels as measured using the assays described herein above as presented in Table 16.

Table 16.

IC50: +++ <= 2.0 μ M < ++ <= 5.0 μ M < +	
Cmpd.	Binned Activity Data
Compound 1	+++

[00258] Many modifications and variations of the embodiments described herein may be made without departing from the scope, as is apparent to those skilled in the art. The specific embodiments described herein are offered by way of example only.

We claim:

1. (4-Isopropoxy-3-methoxyphenyl)(2'-methyl-6'-(trifluoromethyl)-3',4'-dihydro-2'H-spiro[piperidine-4,1'-pyrrolo[1,2-a]pyrazine]-1-yl)methanone characterized as Compound 1 Form A.
- 5 2. Compound 1 Form A of claim 1, wherein the Compound 1 Form A is characterized by one or more peaks at 17.0 to 17.4 degrees, 11.0 to 11.4 degrees, and 20.3 to 20.7 degrees in an X-ray powder diffraction obtained using Cu K alpha radiation.
3. Compound 1 Form A of claim 2, wherein the Compound 1 Form A is characterized by one or more peaks at 17.2, 11.2, and 20.5 degrees.
- 10 4. Compound 1 Form A of claim 2 or 3, wherein the Compound 1 Form A is further characterized by a peak at 18.5 to 18.9 degrees.
5. Compound 1 Form A of any one of claims 2 to 4, wherein the Compound 1 Form A is further characterized by a peak at 18.7 degrees.
6. Compound 1 Form A of any one of claims 2 to 5, wherein the Compound 1 Form
- 15 A is further characterized by a peak at 15.5 to 15.9 degrees.
7. Compound 1 Form A of any one of claims 2 to 6, wherein the Compound 1 Form A is further characterized by a peak at 15.7 degrees.
8. Compound 1 Form A of any one of claims 2 to 7, wherein the Compound 1 Form A is further characterized by a peak at 15.8 to 16.2 degrees.
- 20 9. Compound 1 Form A of any one of claims 2 to 8, wherein the Compound 1 Form A is further characterized by a peak at 16.0 degrees.
10. Compound 1 Form A of claim 1, wherein the Compound 1 Form A is characterized by a diffraction pattern substantially similar to that of Figure 1.
11. A crystal form of (4-isopropoxy-3-methoxyphenyl)(2'-methyl-6'-(trifluoromethyl)-3',4'-dihydro-2'H-spiro[piperidine-4,1'-pyrrolo[1,2-a]pyrazine]-1-yl)methanone having a monoclinic crystal system, a P21/c space group, and the following unit cell dimensions:
- 25

$$a = 33.8479 (11) \text{ \AA} \quad \alpha = 90^\circ$$

$$b = 6.2867 (2) \text{ \AA} \quad \beta = 109.99^\circ$$

$$c = 23.1385 (8) \text{ \AA} \quad \gamma = 90^\circ.$$

12. A pharmaceutical composition comprising Compound 1 Form A of any one of claims 1 to 11, and a pharmaceutically acceptable carrier.
- 5 13. (4-Isopropoxy-3-methoxyphenyl)(2'-methyl-6'-(trifluoromethyl)-3',4'-dihydro-2'H-spiro[piperidine-4,1'-pyrrolo[1,2-a]pyrazine]-1-yl)methanone HCl salt characterized as Compound 1 HCl Salt Form B.
14. Compound 1 HCl Salt Form B of claim 13, wherein the Compound 1 HCl Salt Form B is characterized by one or more peaks at 5.0 to 5.4 degrees, 15.5 to 15.9
10 degrees, and 10.3 to 10.7 degrees in an X-ray powder diffraction obtained using Cu K alpha radiation.
15. Compound 1 HCl Salt Form B of claim 14, wherein the Compound 1 HCl Salt Form B is characterized by one or more peaks at 5.2, 15.7, and 10.5 degrees.
16. Compound 1 HCl Salt Form B of claim 14 or 15, wherein the Compound 1 HCl
15 Salt Form B is further characterized by a peak at 26.1 to 26.5 degrees.
17. Compound 1 HCl Salt Form B of any one of claims 14 to 16, wherein the Compound 1 HCl Salt Form B is further characterized by a peak at 26.3 degrees.
18. Compound 1 HCl Salt Form B of any one of claims 14 to 17, wherein the Compound 1 HCl Salt Form B is further characterized by a peak at 20.8 to 21.2
20 degrees.
19. Compound 1 HCl Salt Form B of any one of claims 14 to 18, wherein the Compound 1 HCl Salt Form B is further characterized by a peak at 21.0 degrees.
20. Compound 1 HCl Salt Form B of any one of claims 14 to 19, wherein the Compound 1 HCl Salt Form B is further characterized by a peak at 23.6 to 24.0
25 degrees.
21. Compound 1 HCl Salt Form B of any one of claims 14 to 20, wherein the Compound 1 HCl Salt Form B is further characterized by a peak at 23.8 degrees.

22. Compound 1 HCl Salt Form B of claim 1, wherein the Compound 1 HCl Salt Form B is characterized by a diffraction pattern substantially similar to that of Figure 10.
23. A crystal form of (4-isopropoxy-3-methoxyphenyl)(2'-methyl-6'-(trifluoromethyl)-3',4'-dihydro-2'H-spiro[piperidine-4,1'-pyrrolo[1,2-a]pyrazine]-1-yl)methanone HCl salt having a monoclinic crystal system, a P21/c space group, and the following unit cell dimensions:
- $$\begin{aligned}a &= 33.8479 (11) \text{ \AA} & \alpha &= 90^\circ \\b &= 6.2867 (2) \text{ \AA} & \beta &= 109.99^\circ \\c &= 23.1385 (8) \text{ \AA} & \gamma &= 90^\circ.\end{aligned}$$
24. A pharmaceutical composition comprising Compound 1 HCl Salt Form B of any one of claims 13 to 23, and a pharmaceutically acceptable carrier.
25. (4-Isopropoxy-3-methoxyphenyl)(2'-methyl-6'-(trifluoromethyl)-3',4'-dihydro-2'H-spiro[piperidine-4,1'-pyrrolo[1,2-a]pyrazine]-1-yl)methanone mesylate salt characterized as Compound 1 Mesylate Salt Form A.
26. Compound 1 Mesylate Salt Form A of claim 25, wherein the Compound 1 Mesylate Salt Form A is characterized by one or more peaks at 21.6 to 22.0 degrees, 16.4 to 16.8 degrees, and 21.1 to 21.5 degrees in an X-ray powder diffraction obtained using Cu K alpha radiation.
27. Compound 1 Mesylate Salt Form A of claim 26, wherein the Compound 1 Mesylate Salt Form A is characterized by one or more peaks at 21.8, 16.6, and 21.3 degrees.
28. Compound 1 Mesylate Salt Form A of claim 26 or 27, wherein the Compound 1 Mesylate Salt Form A is further characterized by a peak at 16.7 to 17.1 degrees.
29. Compound 1 Mesylate Salt Form A of any one of claims 26 to 28, wherein the Compound 1 Mesylate Salt Form A is further characterized by a peak at 16.9 degrees.
30. Compound 1 Mesylate Salt Form A of any one of claims 26 to 29, wherein the Compound 1 Mesylate Salt Form A is further characterized by a peak at 15.7 to 16.1 degrees.

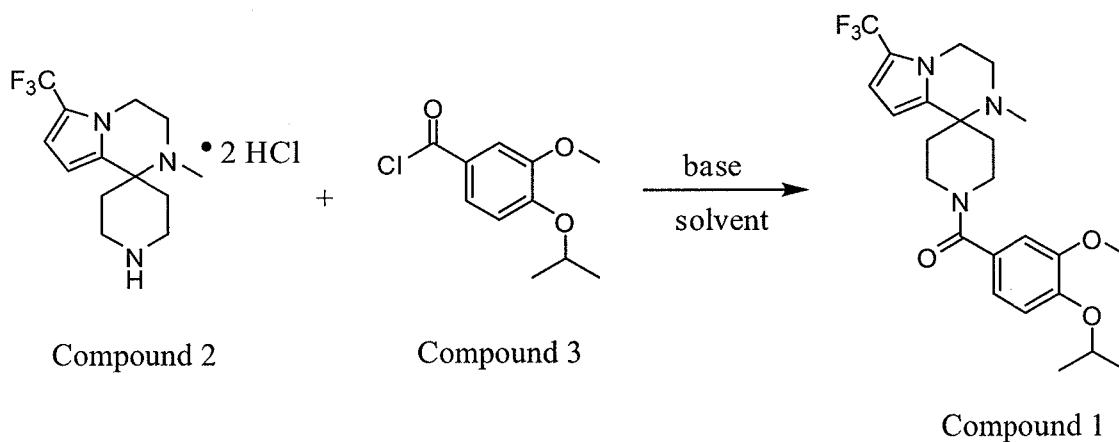
31. Compound 1 Mesylate Salt Form A of any one of claims 26 to 30, wherein the Compound 1 Mesylate Salt Form A is further characterized by a peak at 15.9 degrees.
32. Compound 1 Mesylate Salt Form A of any one of claims 26 to 31, wherein the Compound 1 Mesylate Salt Form A is further characterized by a peak at 15.4 to 15.8
5 degrees.
33. Compound 1 Mesylate Salt Form A of any one of claims 26 to 32, wherein the Compound 1 Mesylate Salt Form A is further characterized by a peak at 15.6 degrees.
34. Compound 1 Mesylate Salt Form A of claim 25, wherein the Compound 1 Mesylate Salt Form A is characterized by a diffraction pattern substantially similar to
10 that of Figure 15.
35. A pharmaceutical composition comprising Compound 1 Mesylate Salt Form A of any one of claims 25 to 34, and a pharmaceutically acceptable carrier.
36. (4-Isopropoxy-3-methoxyphenyl)(2'-methyl-6'-(trifluoromethyl)-3',4'-dihydro-2'H-spiro[piperidine-4,1'-pyrrolo[1,2-a]pyrazine]-1-yl)methanone mesylate salt
15 characterized as Compound 1 Besylate Salt Form A.
37. Compound 1 Besylate Salt Form A of claim 36, wherein the Compound 1 Besylate Salt Form A is characterized by one or more peaks at 5.7 to 5.9 degrees, 21.3 to 21.7 degrees, and 18.6 to 19.0 degrees in an X-ray powder diffraction obtained using Cu K alpha radiation.
- 20 38. Compound 1 Besylate Salt Form A of claim 37, wherein the Compound 1 Besylate Salt Form A is characterized by one or more peaks at 5.9, 21.5, and 18.8 degrees.
39. Compound 1 Besylate Salt Form A of claim 37 or 38, wherein the Compound 1 Besylate Salt Form A is further characterized by a peak at 16.5 to 16.9 degrees.
- 25 40. Compound 1 Besylate Salt Form A of any one of claims 37 to 39, wherein the Compound 1 Besylate Salt Form A is further characterized by a peak at 16.7 degrees.
41. Compound 1 Besylate Salt Form A of any one of claims 37 to 40, wherein the Compound 1 Besylate Salt Form A is further characterized by a peak at 19.2 to 19.6 degrees.

42. Compound 1 Besylate Salt Form A of any one of claims 37 to 41, wherein the Compound 1 Besylate Salt Form A is further characterized by a peak at 19.4 degrees.
43. Compound 1 Besylate Salt Form A of any one of claims 37 to 42, wherein the Compound 1 Besylate Salt Form A is further characterized by a peak at 16.8 to 17.2
5 degrees.
44. Compound 1 Besylate Salt Form A of any one of claims 37 to 43, wherein the Compound 1 Besylate Salt Form A is further characterized by a peak at 17.0 degrees.
45. Compound 1 Besylate Salt Form A of claim 36, wherein the Compound 1 Besylate Salt Form A is characterized by a diffraction pattern substantially similar to
10 that of Figure 18.
46. A pharmaceutical composition comprising Compound 1 Besylate Salt Form A of any one of claims 36 to 45, and a pharmaceutically acceptable carrier.
47. (4-Isopropoxy-3-methoxyphenyl)(2'-methyl-6'-(trifluoromethyl)-3',4'-dihydro-2'H-spiro[piperidine-4,1'-pyrrolo[1,2-a]pyrazine]-1-yl)methanone tosylate salt
15 characterized as Compound 1 Tosylate Salt Form A.
48. Compound 1 Tosylate Salt Form A of claim 47, wherein the Compound 1 Tosylate Salt Form A is characterized by one or more peaks at 5.8 to 6.2 degrees, 20.1 to 20.5 degrees, and 23.9 to 24.3 degrees in an X-ray powder diffraction obtained using Cu K alpha radiation.
- 20 49. Compound 1 Tosylate Salt Form A of claim 48, wherein the Compound 1 Tosylate Salt Form A is characterized by one or more peaks at 6.0, 20.3, and 24.1 degrees.
50. Compound 1 Tosylate Salt Form A of claim 48 or 49, wherein the Compound 1 Tosylate Salt Form A is further characterized by a peak at 11.8 to 12.2 degrees.
- 25 51. Compound 1 Tosylate Salt Form A of any one of claims 48 to 50, wherein the Compound 1 Tosylate Salt Form A is further characterized by a peak at 12.0 degrees.
52. Compound 1 Tosylate Salt Form A of any one of claims 48 to 51, wherein the Compound 1 Tosylate Salt Form A is further characterized by a peak at 22.6 to 23.0 degrees.

53. Compound 1 Tosylate Salt Form A of any one of claims 48 to 52, wherein the Compound 1 Tosylate Salt Form A is further characterized by a peak at 22.8 degrees.
54. Compound 1 Tosylate Salt Form A of any one of claims 48 to 53, wherein the Compound 1 Tosylate Salt Form A is further characterized by a peak at 16.2 to 16.6 degrees.
55. Compound 1 Tosylate Salt Form A of any one of claims 48 to 54, wherein the Compound 1 Tosylate Salt Form A is further characterized by a peak at 16.4 degrees.
56. Compound 1 Tosylate Salt Form A of claim 47, wherein the Compound 1 Tosylate Salt Form A is characterized by a diffraction pattern substantially similar to that of Figure 21.
57. A pharmaceutical composition comprising Compound 1 Tosylate Salt Form A of any one of claims 47 to 56, and a pharmaceutically acceptable carrier.
58. A method of inhibiting a voltage-gated sodium ion channel in:
- a patient; or
- a biological sample;
- comprising administering to the patient, or contacting the biological sample, with the compound of claim 1, 13, 25, 36, or 47.
59. The method of claim 58, wherein the voltage-gated sodium ion channel is NaV 1.7.
60. A method of treating or lessening the severity in a subject of acute, chronic, neuropathic, or inflammatory pain, arthritis, migraine, cluster headaches, trigeminal neuralgia, herpetic neuralgia, general neuralgias, epilepsy or epilepsy conditions, neurodegenerative disorders, psychiatric disorders, anxiety, depression, bipolar disorder, myotonia, arrhythmia, movement disorders, neuroendocrine disorders, ataxia, multiple sclerosis, irritable bowel syndrome, incontinence, visceral pain, osteoarthritis pain, postherpetic neuralgia, diabetic neuropathy, radicular pain, sciatica, back pain, head or neck pain, severe or intractable pain, nociceptive pain, breakthrough pain, postsurgical pain, cancer pain, stroke, cerebral ischemia, traumatic brain injury, amyotrophic lateral sclerosis, stress- or exercise induced angina,

palpitations, hypertension, migraine, or abnormal gastro-intestinal motility, comprising administering an effective amount of the pharmaceutical composition of claim 12, 24, 35, 46, or 57.

61. The method of 60, wherein said method is used for treating or lessening the severity of femur cancer pain; non-malignant chronic bone pain; rheumatoid arthritis; osteoarthritis; spinal stenosis; neuropathic low back pain; neuropathic low back pain; myofascial pain syndrome; fibromyalgia; temporomandibular joint pain; chronic visceral pain, abdominal pain; pancreatic; IBS pain; chronic and acute headache pain; migraine; tension headache, including, cluster headaches; chronic and acute neuropathic pain, post-herpetic neuralgia; diabetic neuropathy; HIV-associated neuropathy; trigeminal neuralgia; Charcot-Marie Tooth neuropathy; hereditary sensory neuropathies; peripheral nerve injury; painful neuromas; ectopic proximal and distal discharges; radiculopathy; chemotherapy induced neuropathic pain; radiotherapy-induced neuropathic pain; post-mastectomy pain; central pain; spinal cord injury pain; post-stroke pain; thalamic pain; complex regional pain syndrome; phantom pain; intractable pain; acute pain, acute post-operative pain; acute musculoskeletal pain; joint pain; mechanical low back pain; neck pain; tendonitis; injury/exercise pain; acute visceral pain, abdominal pain; pyelonephritis; appendicitis; cholecystitis; intestinal obstruction; hernias; chest pain, cardiac pain; pelvic pain, renal colic pain, acute obstetric pain, labor pain; cesarean section pain; acute inflammatory, burn and trauma pain; acute intermittent pain, endometriosis; acute herpes zoster pain; sickle cell anemia; acute pancreatitis; breakthrough pain; orofacial pain including sinusitis pain, dental pain; multiple sclerosis (MS) pain; pain in depression; leprosy pain; Behcet's disease pain; adiposis dolorosa; phlebitic pain; Guillain-Barre pain; painful legs and moving toes; Haglund syndrome; erythromelalgia pain; Fabry's disease pain; bladder and urogenital disease, including, urinary incontinence; hyperactivity bladder; painful bladder syndrome; interstitial cystitis (IC); prostatitis; complex regional pain syndrome (CRPS), type I and type II; widespread pain, paroxysmal extreme pain, pruritis, tinnitus, or angina-induced pain.
62. A process of preparing Compound 1 comprising reacting Compounds 2 and 3 together in a solvent in the presence of a base:



63. The process of claim 62, wherein the process further comprises recrystallization of Compound 1.
- 5 64. The process of claim 63, wherein Compound 1 is recrystallized from an aprotic solvent.
65. The process of claim 63, wherein Compound 1 is recrystallized from an alkane or cycloalkane solvent.
66. The process of claim 63, wherein Compound 1 is recrystallized from
- 10 cyclohexane.

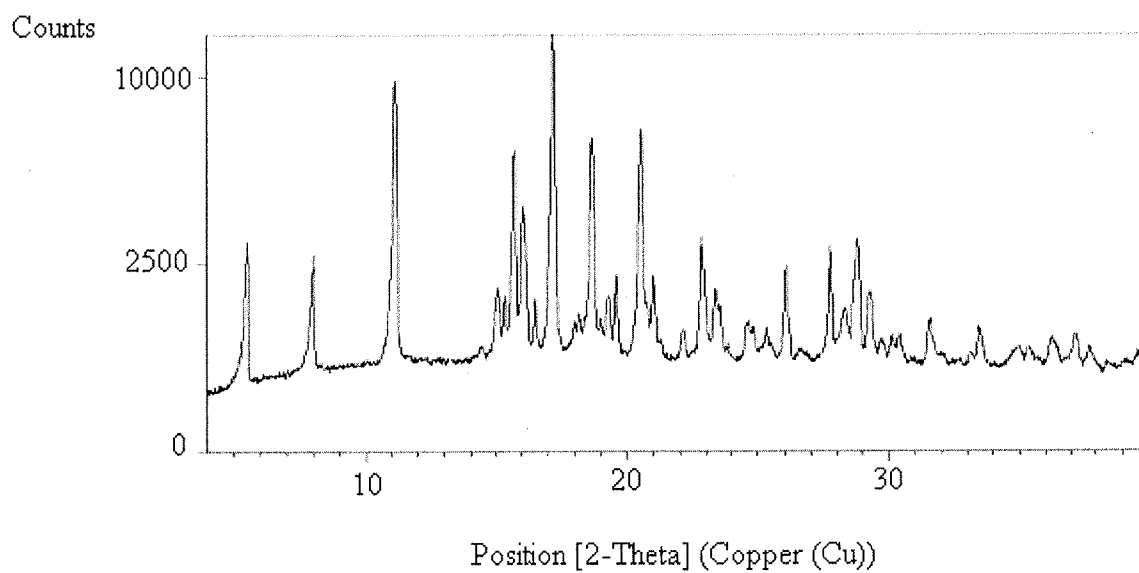
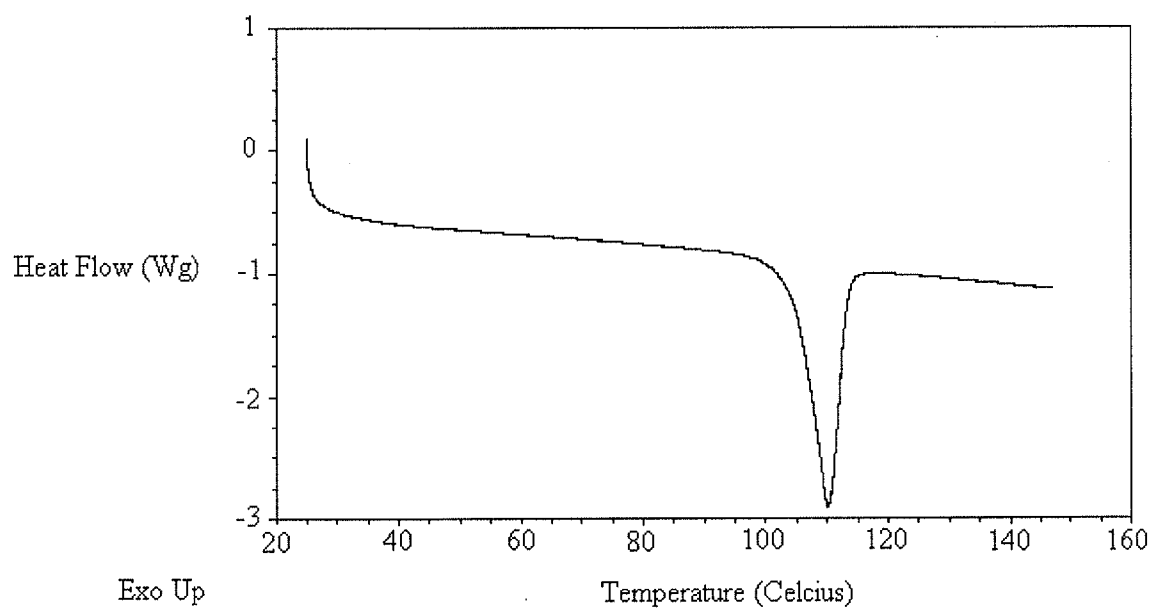
Figure 1**Figure 2**

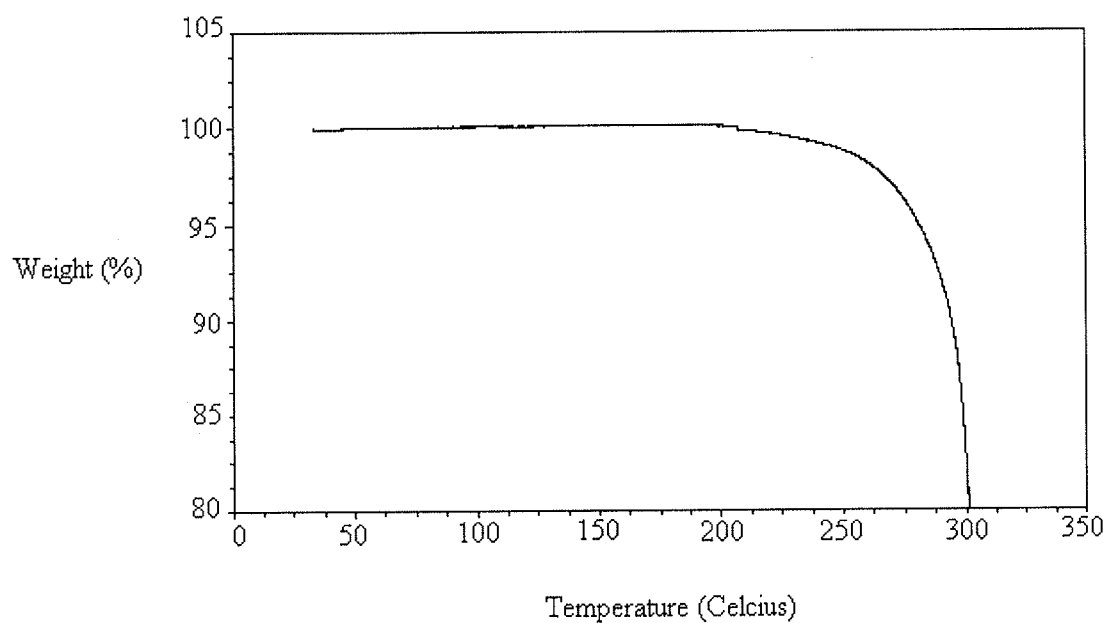
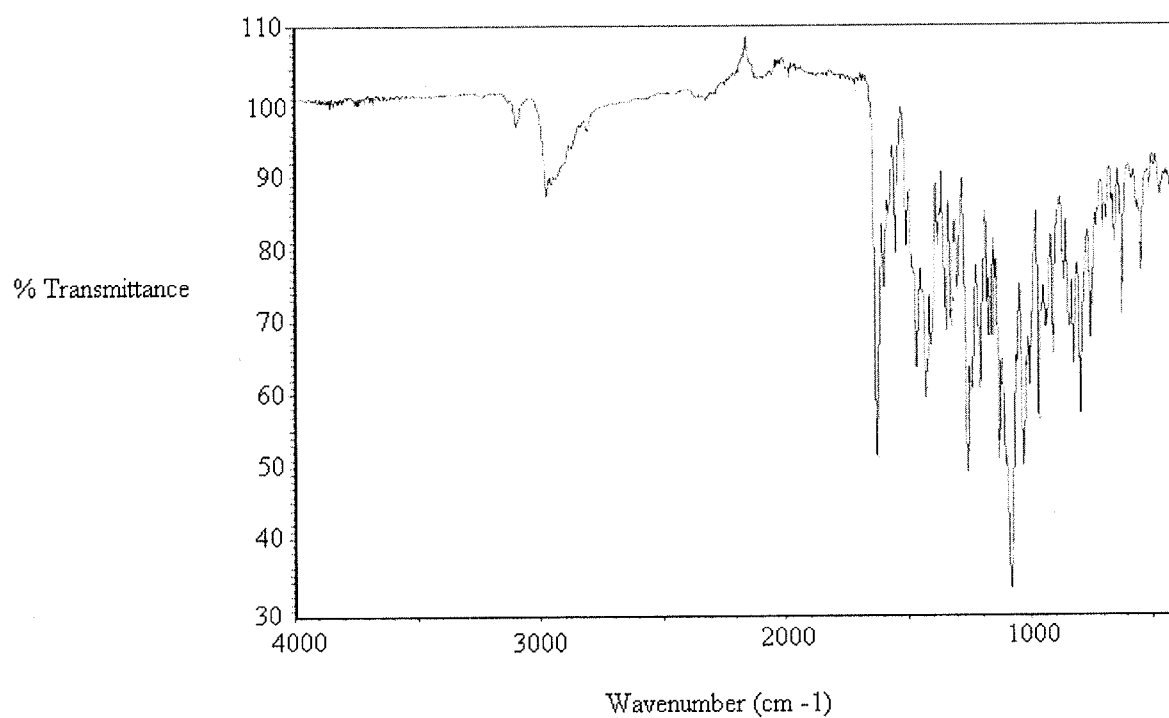
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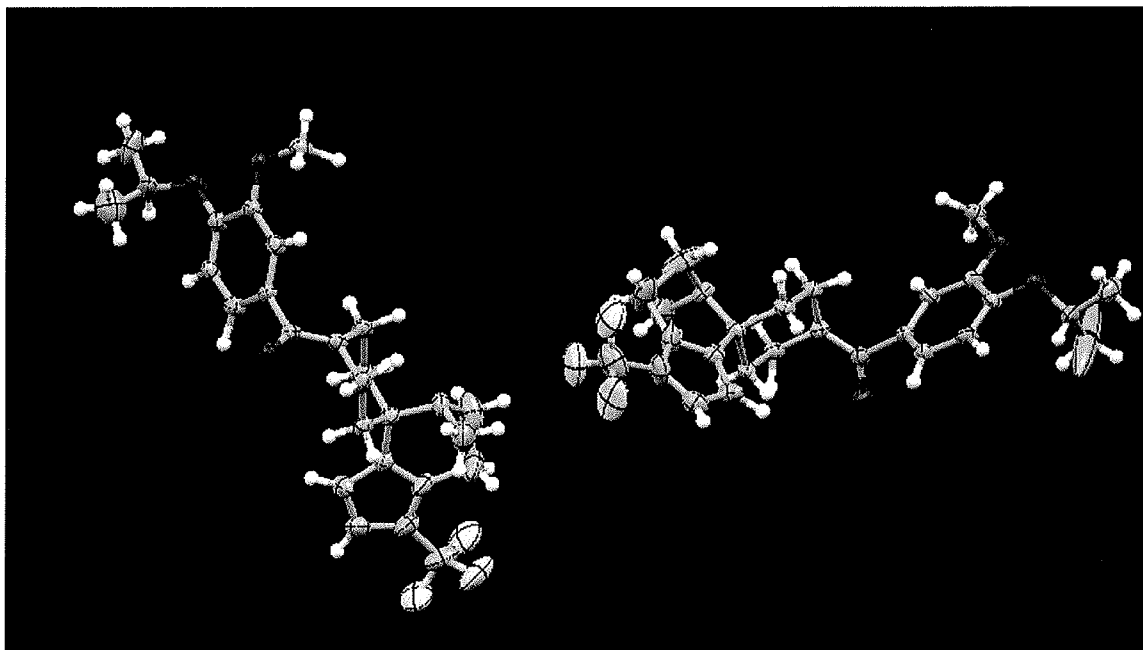
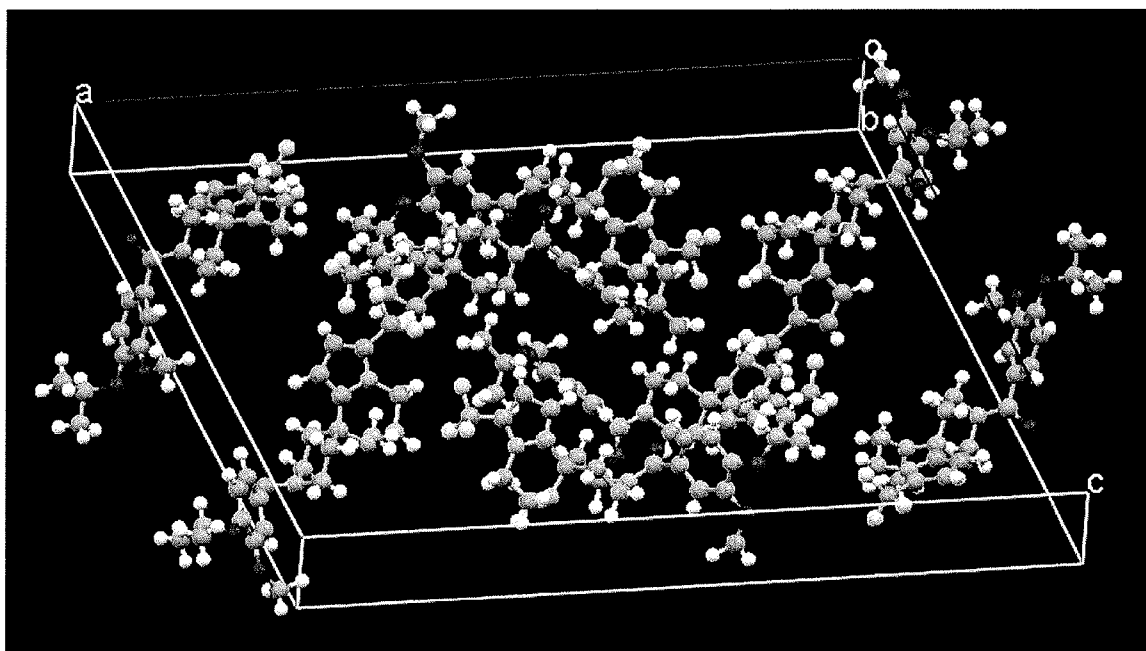
Figure 5**Figure 6**

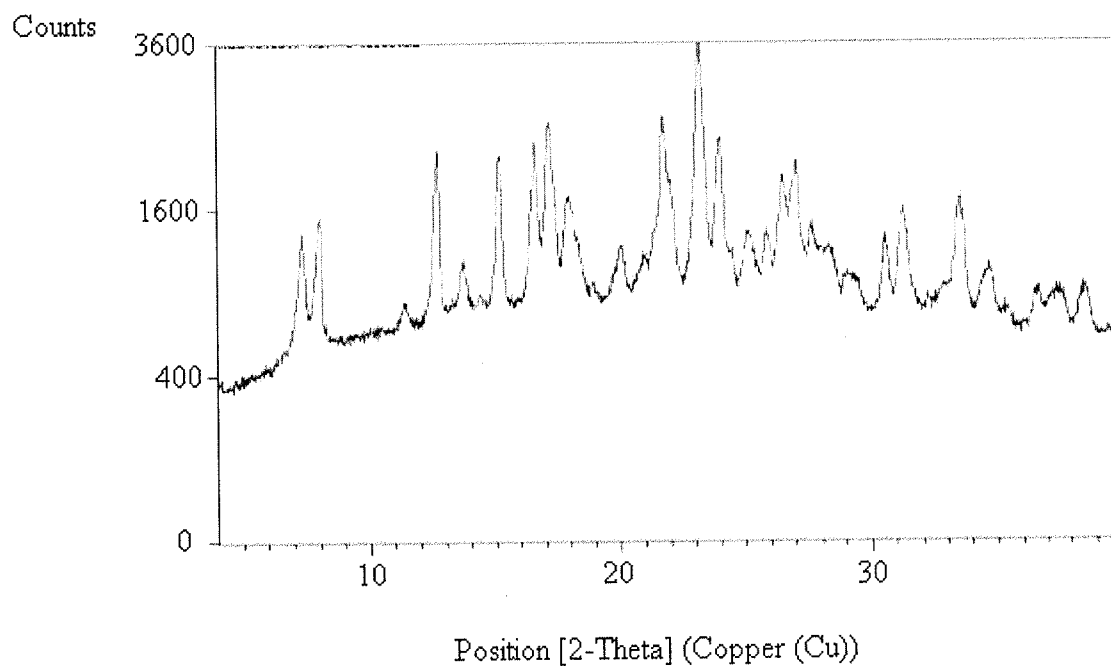
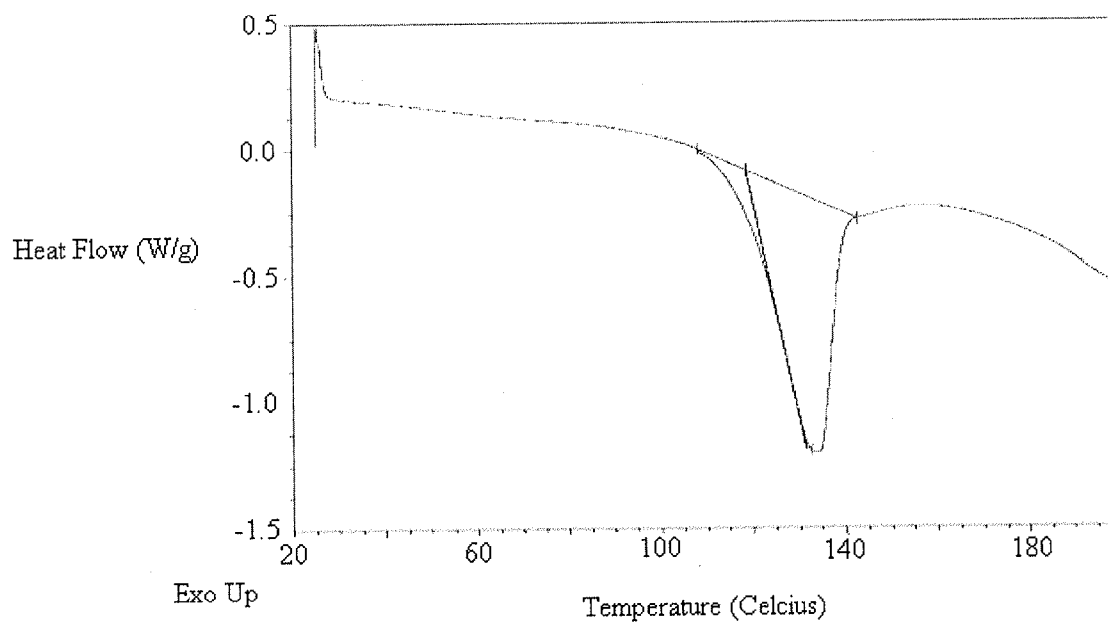
Figure 7**Figure 8**

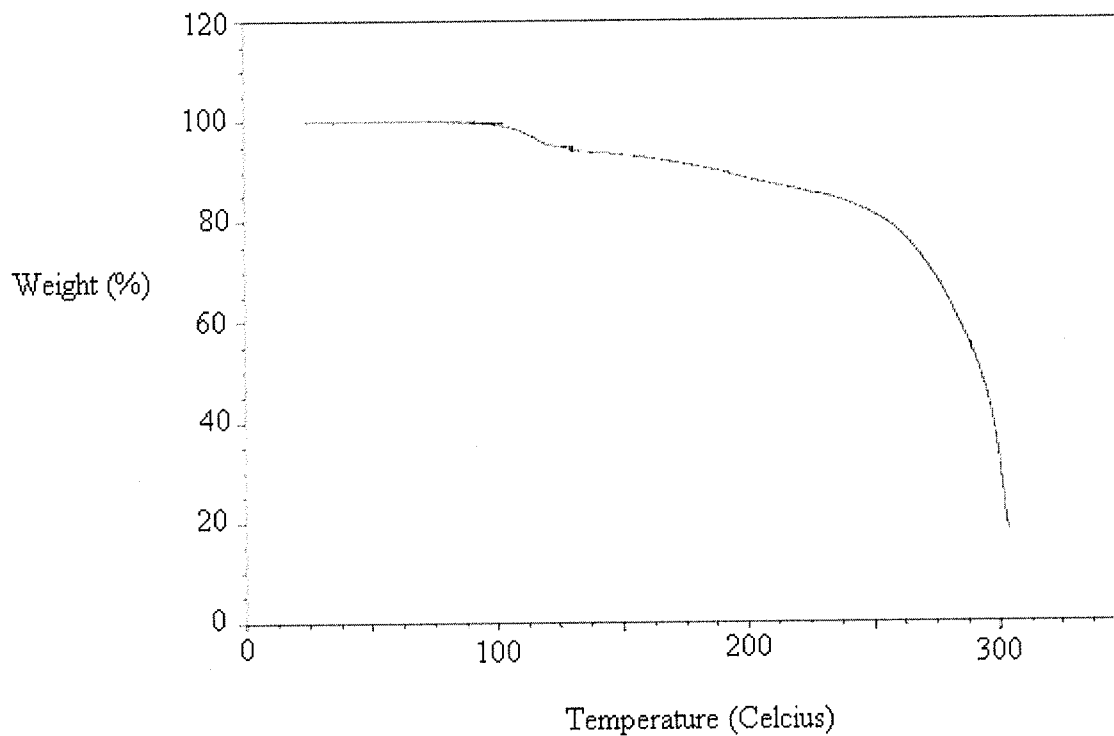
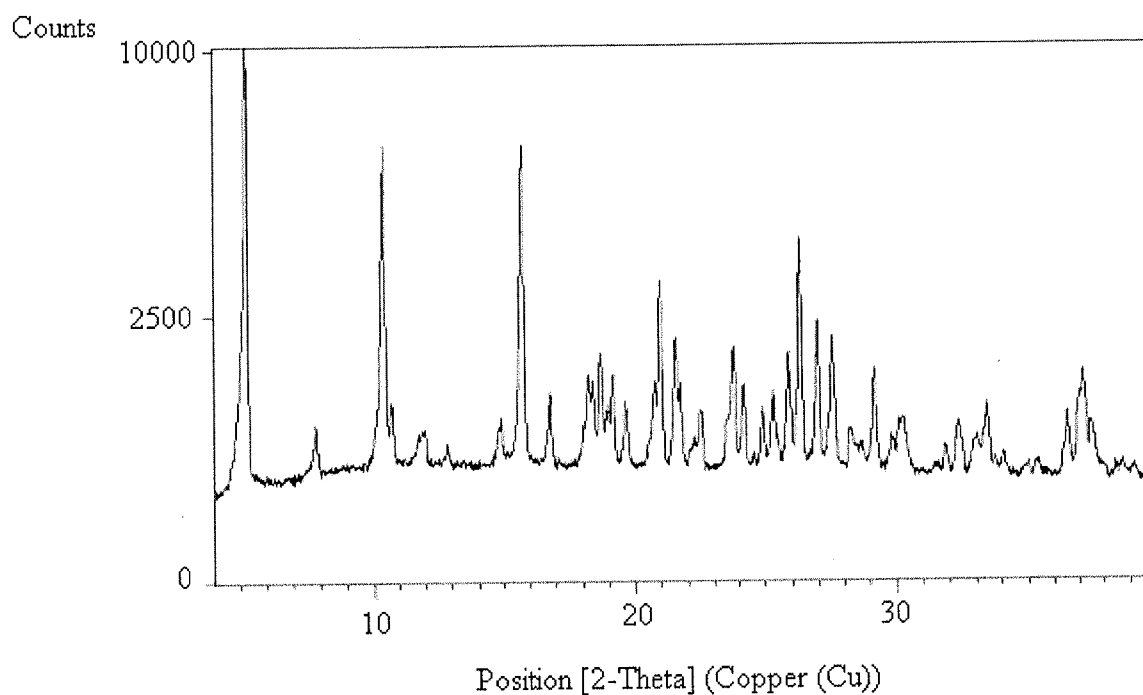
Figure 9**Figure 10**

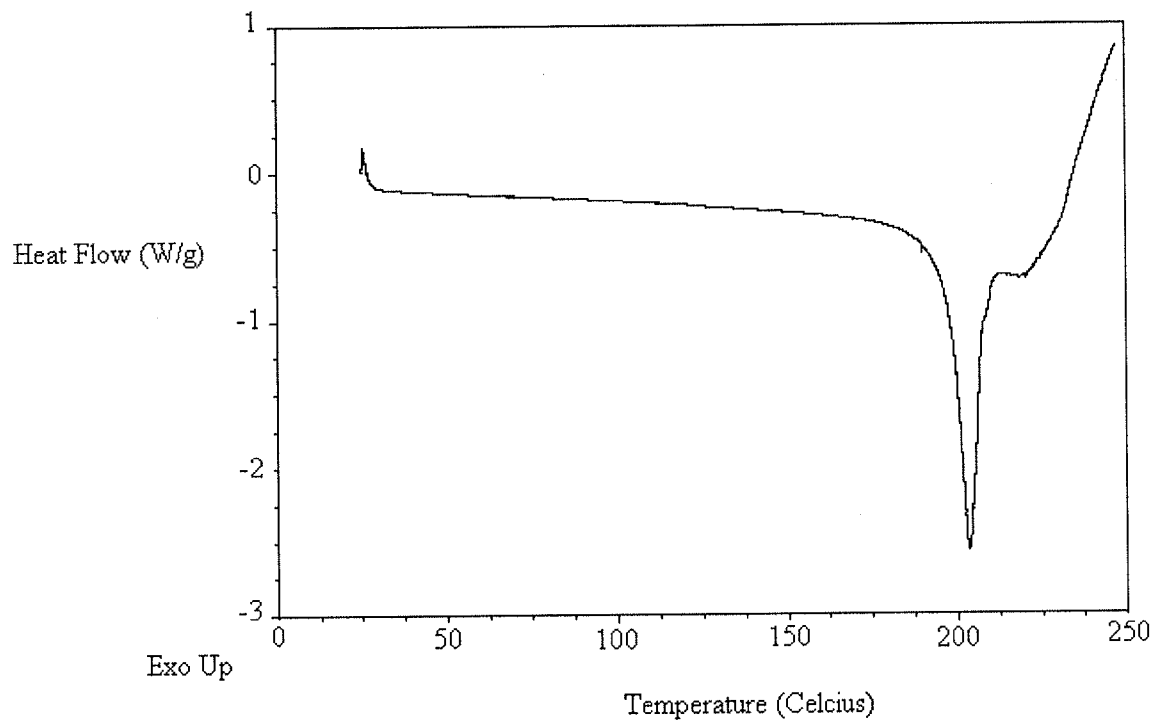
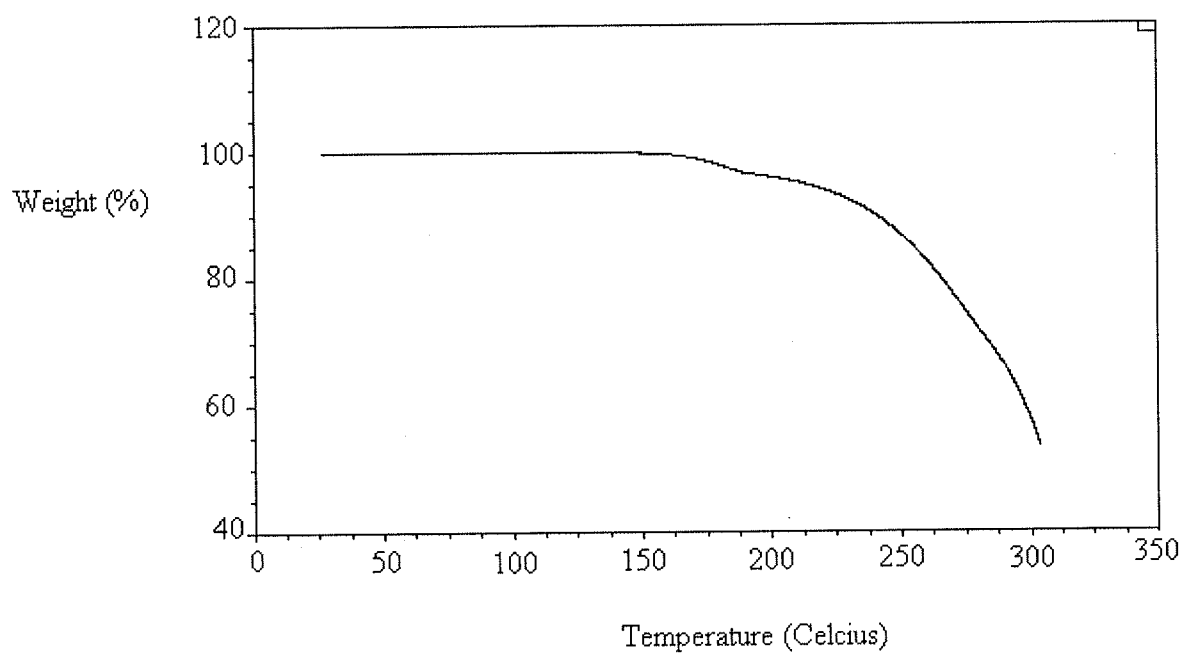
Figure 11**Figure 12**

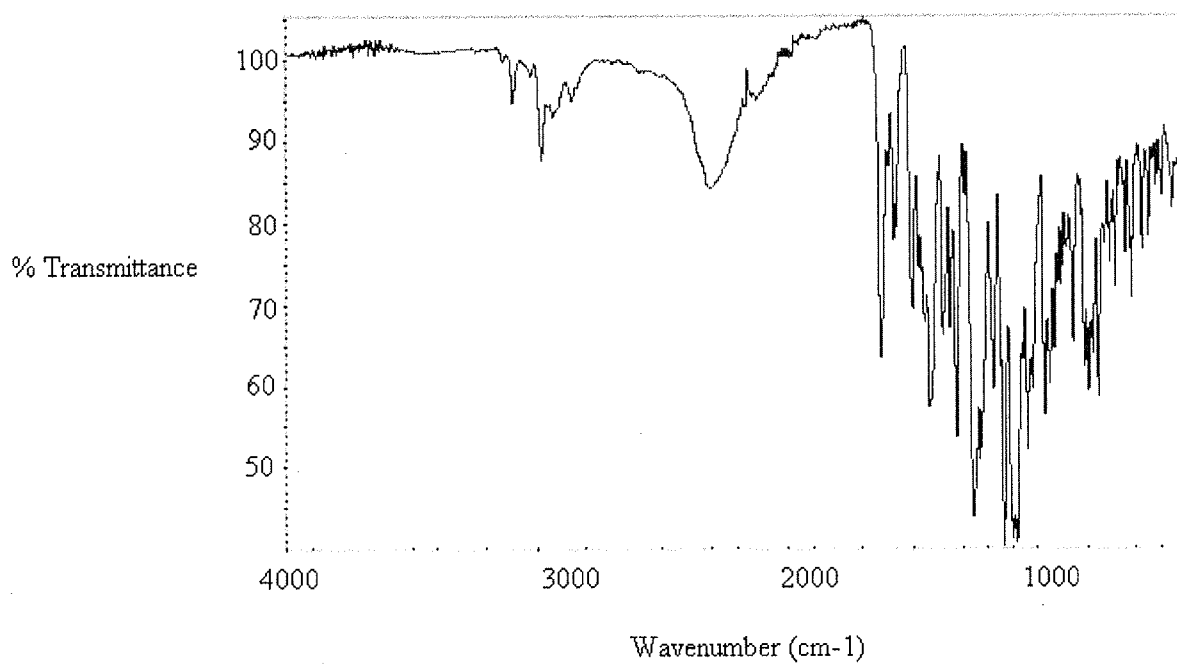
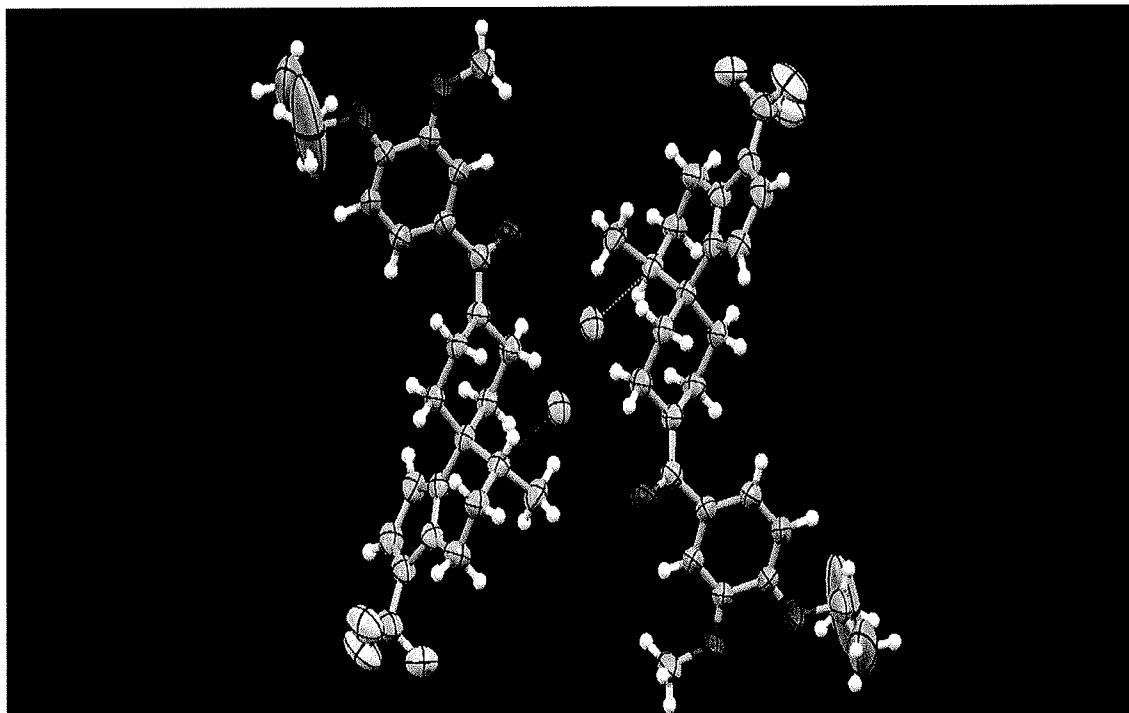
Figure 13**Figure 14**

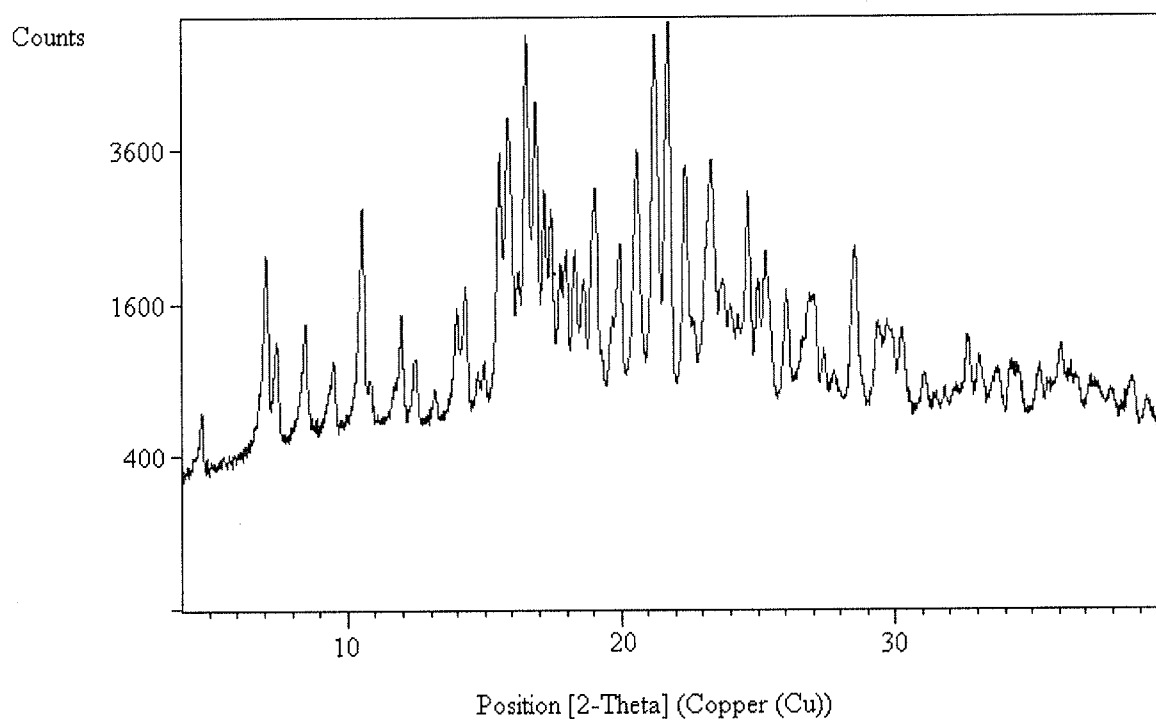
Figure 15

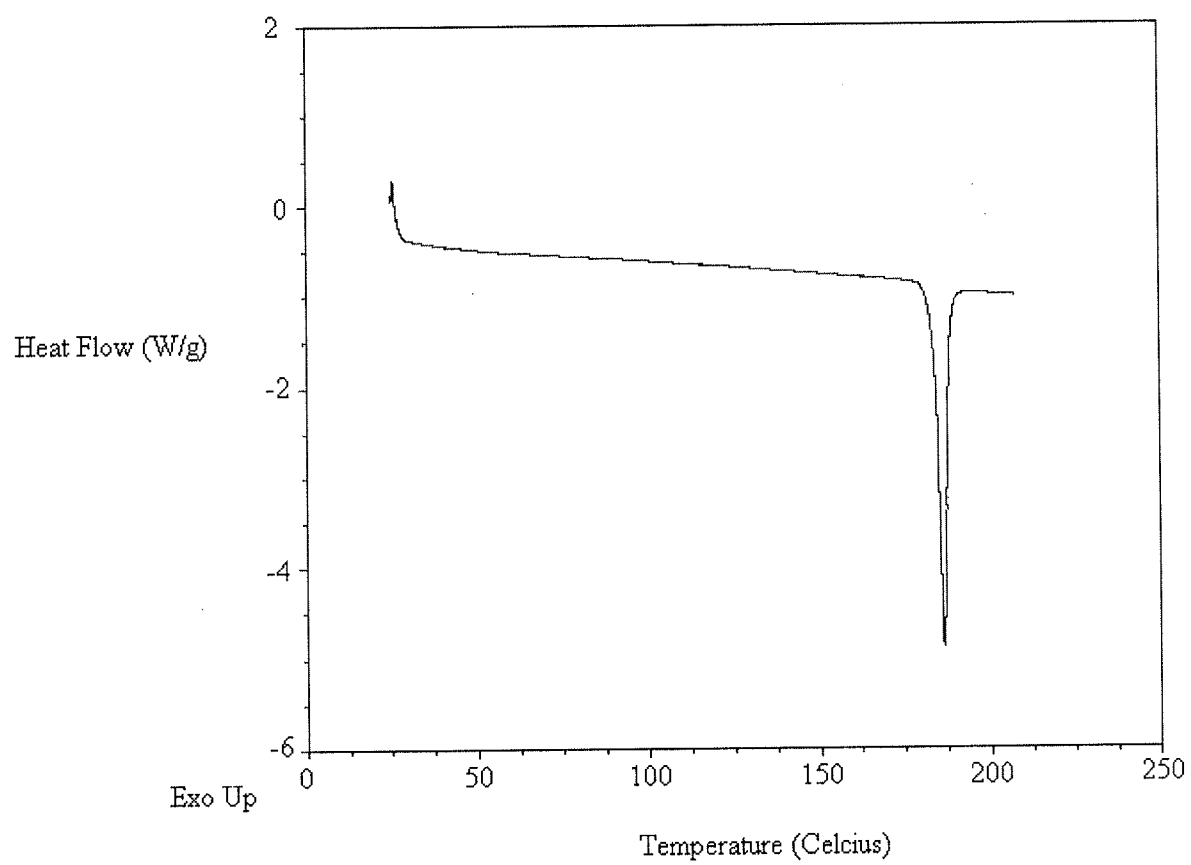
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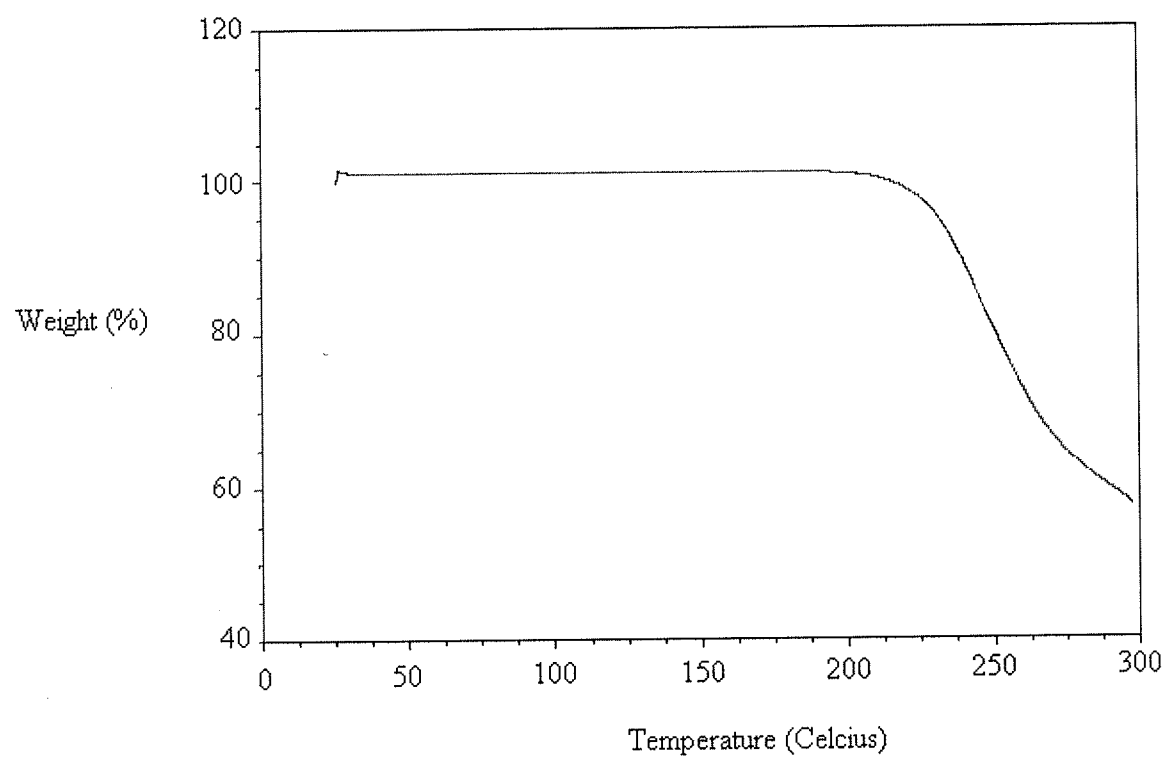
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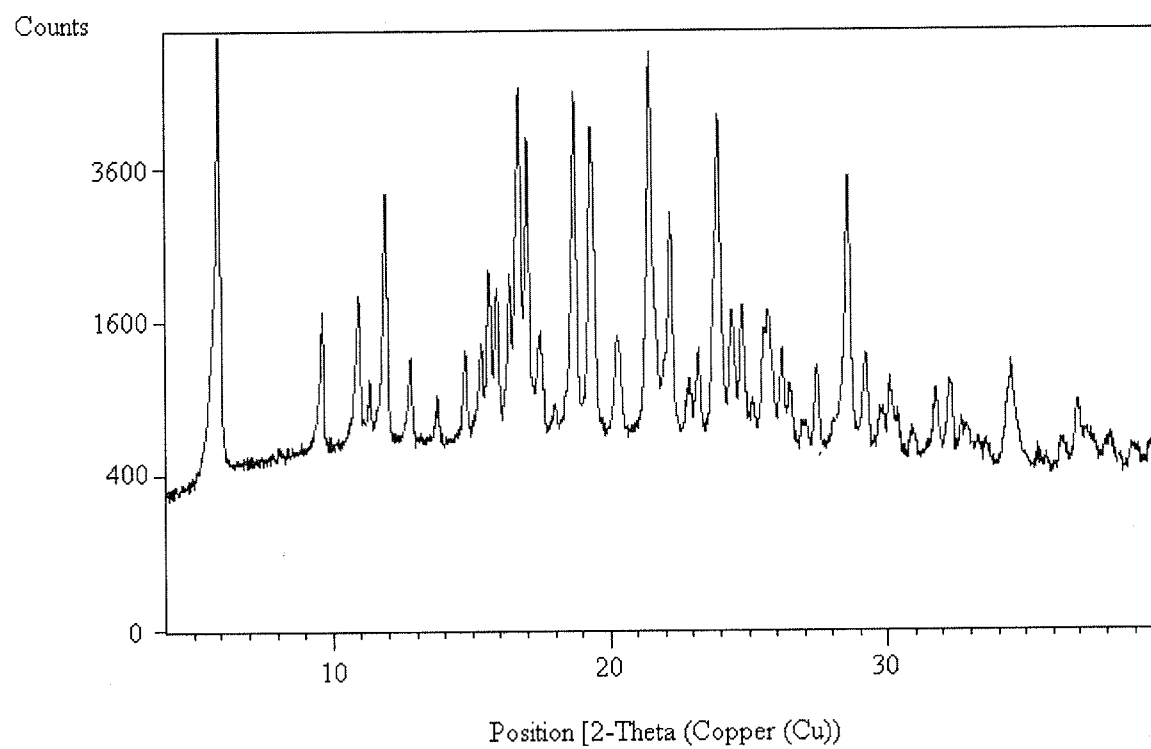
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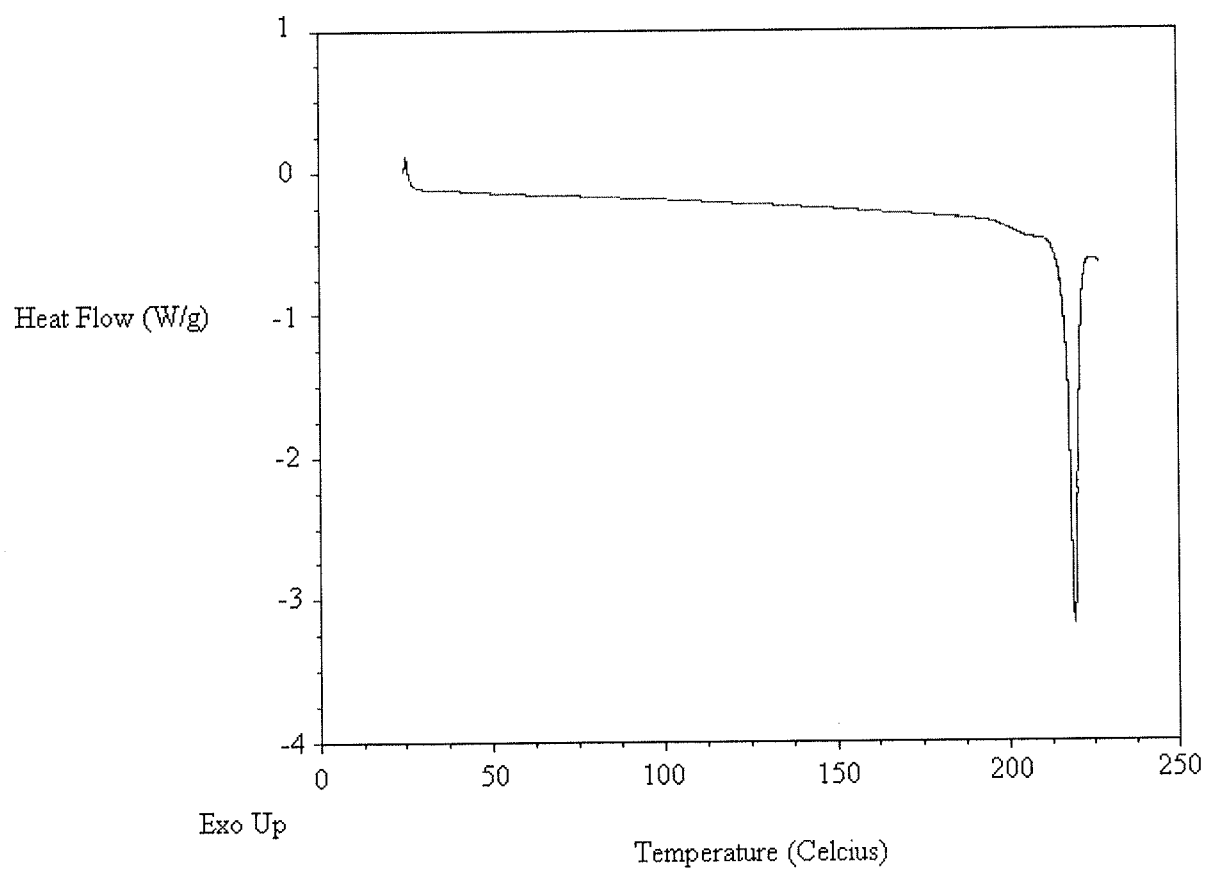
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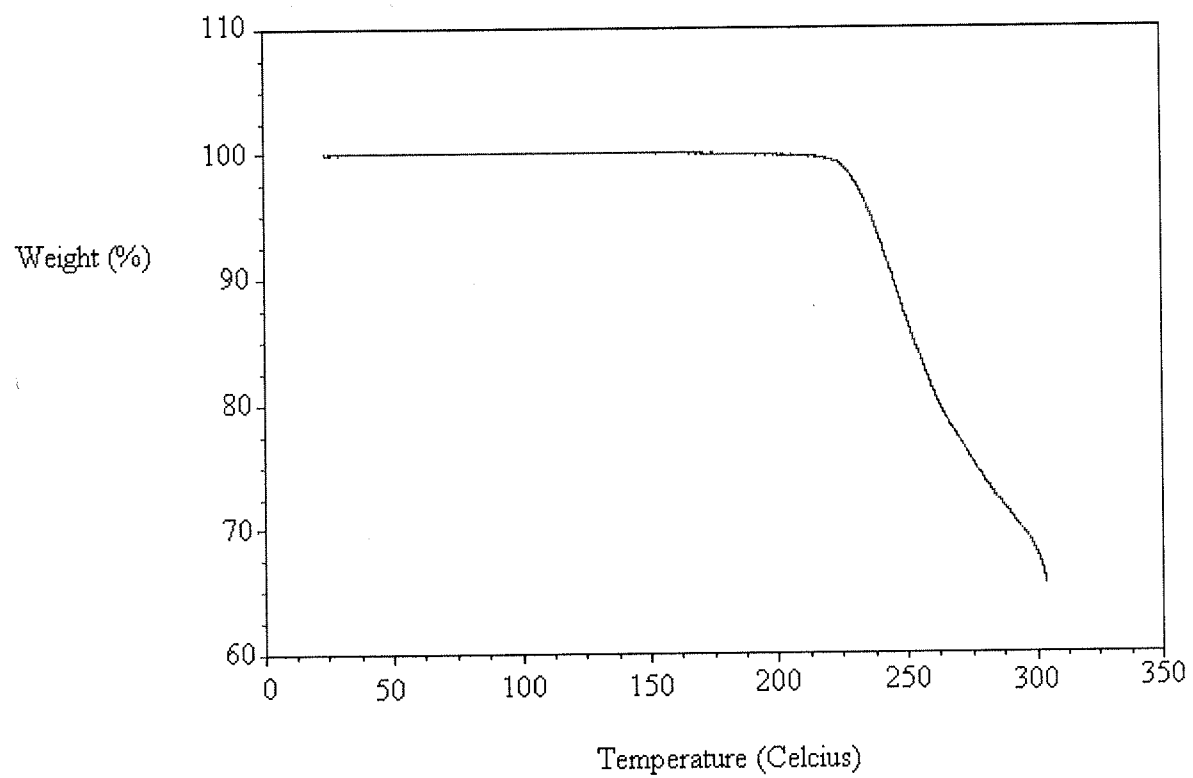
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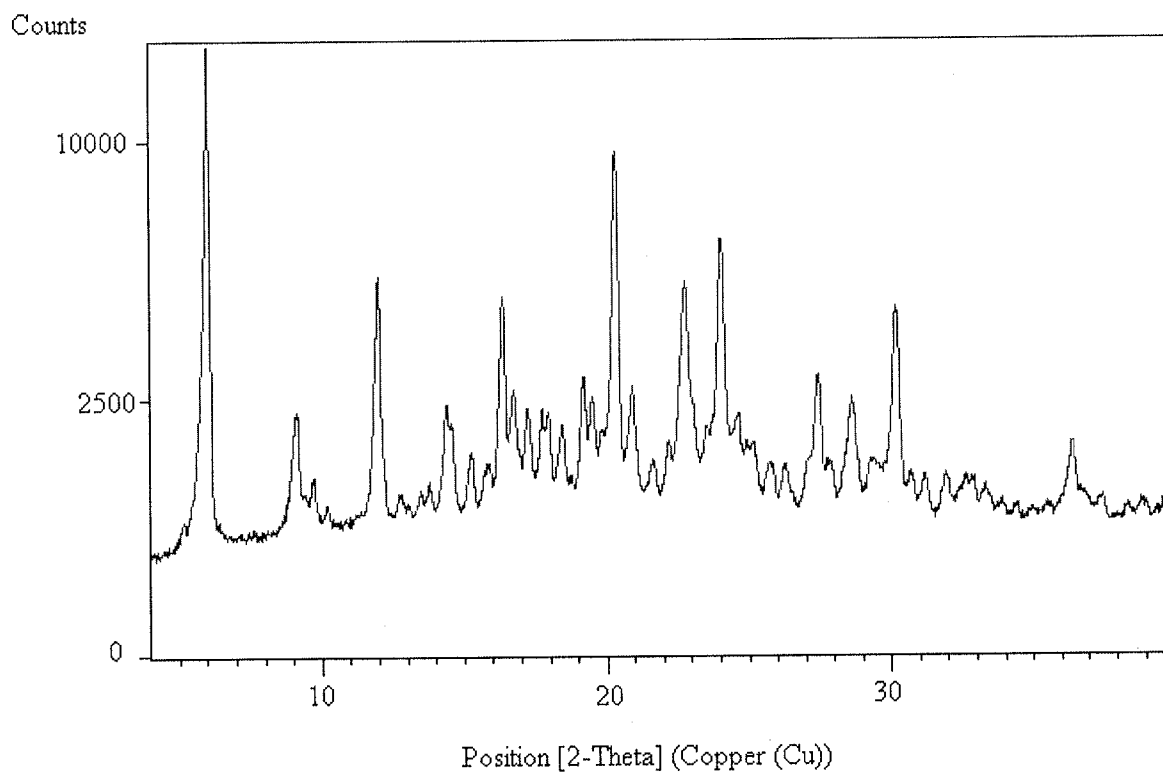
Figure 21

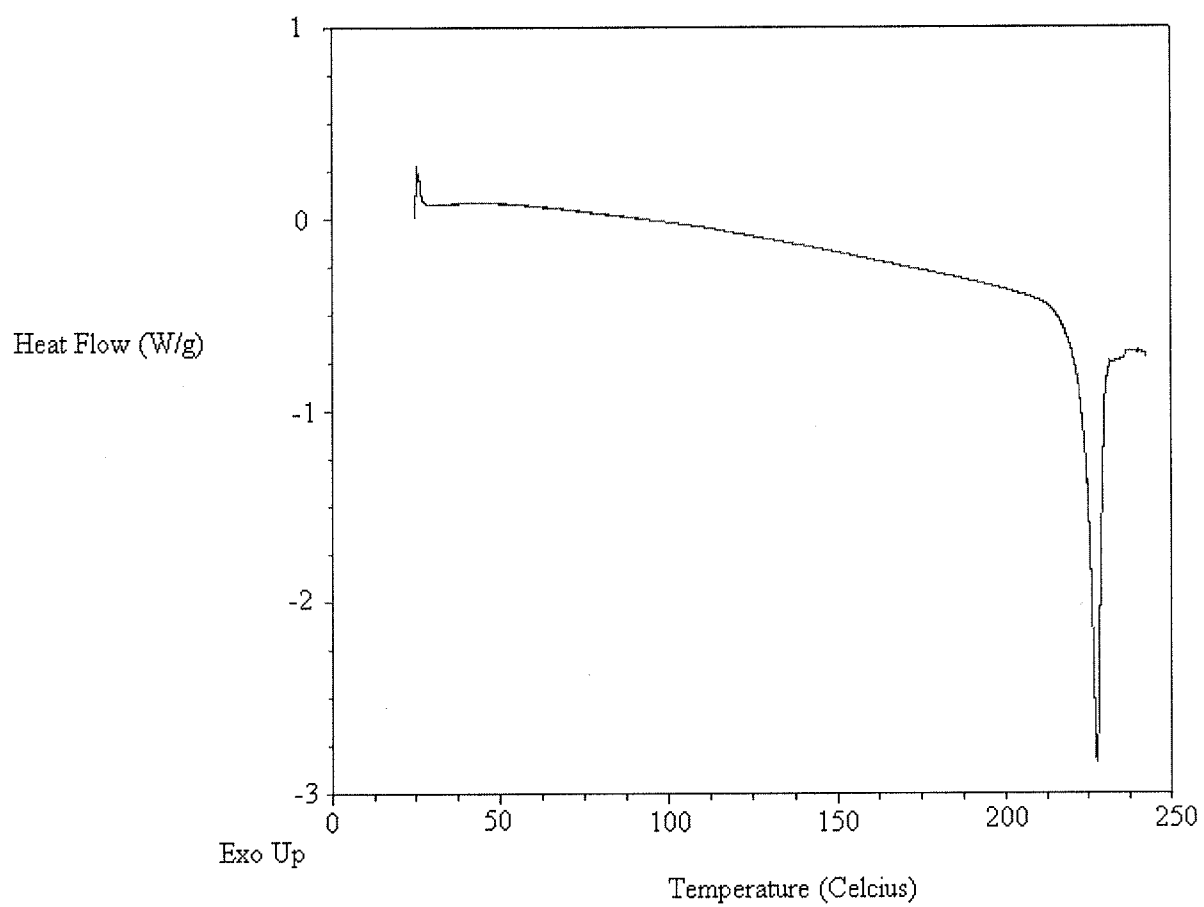
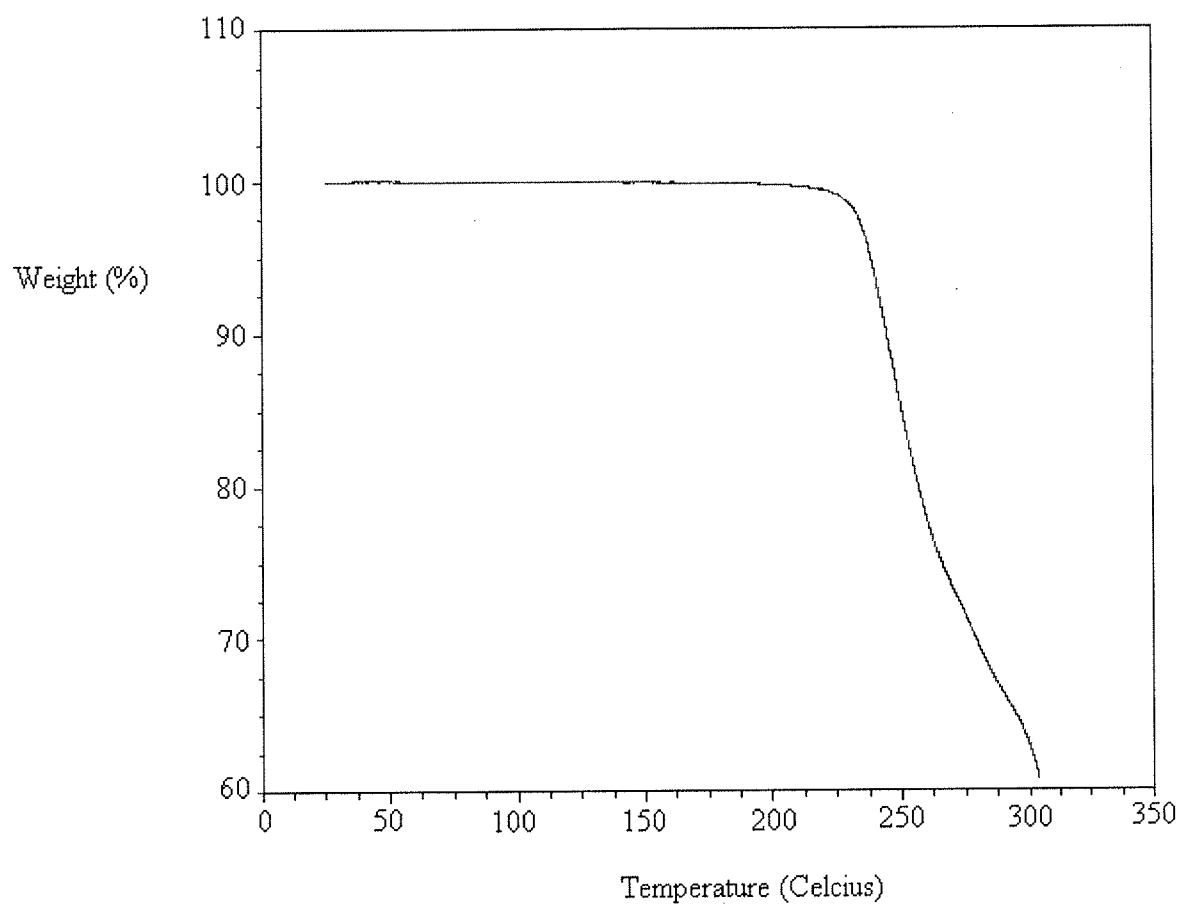
Figure 22

Figure 23

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2013/053176A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D487/22 A61K31/499 A61P29/00
ADD.

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 A61K A61P

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

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

EPO-Internal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2010/151595 A1 (SCHERING CORP [US]; HO GINNY D [US]; TULSHIAN DEEN [US]; HEAP CHARLES) 29 December 2010 (2010-12-29) compounds 4-198 abstract	1-66
X,P	WO 2012/106499 A1 (VERTEX PHARMA [US]; HADIDA RUAH SARA S [US]; KALLEL EDWARD ADAM [US];) 9 August 2012 (2012-08-09) cited in the application page 103 - page 105 page 167 - page 168	1-66



Further documents are listed in the continuation of Box C.



See patent family annex.

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Date of the actual completion of the international search

26 August 2013

Date of mailing of the international search report

02/09/2013

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Authorized officer

Skulj, Primoz

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/US2013/053176

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