Office de la Propriété Intellectuelle du Canada
Un organisme d'Industrie Canada

Canadian Intellectual Property Office
An agency of Industry Canada

CA 2611731 A1 2006/12/14

(21) 2 611 731

(12) DEMANDE DE BREVET CANADIEN
CANADIAN PATENT APPLICATION

(13) A1

(86) Date de dépôt PCT/PCT Filing Date: 2006/06/09
(87) Date publication PCT/PCT Publication Date: 2006/12/14
(85) Entrée phase nationale/National Entry: 2007/12/07
(86) N° demande PCT/PCT Application No.: US 2006/022818
(87) N° publication PCT/PCT Publication No.: 2006/133459
(30) Priorité/Priority: 2005/06/09 (US60/688,919)

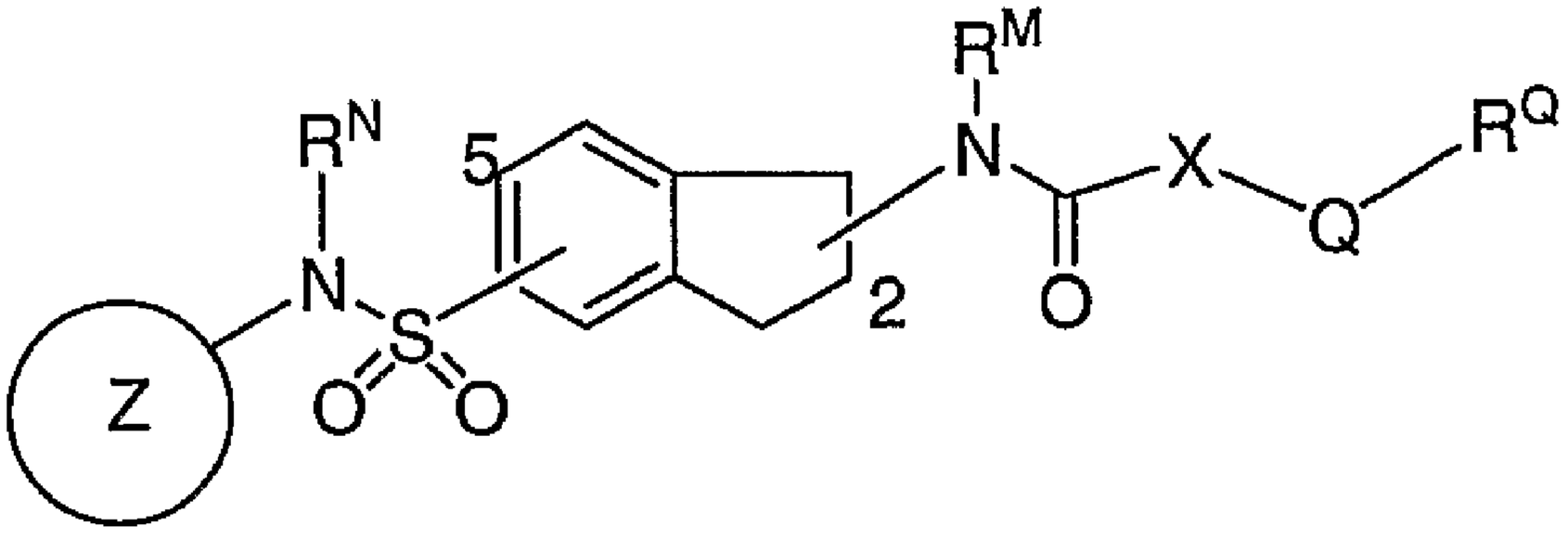
(51) Cl.Int./Int.Cl. *C07D 277/52* (2006.01),
A61K 31/54 (2006.01), *A61P 29/00* (2006.01),
C07D 417/12 (2006.01)

(71) Demandeur/Applicant:
VERTEX PHARMACEUTICALS INCORPORATED, US

(72) Inventeurs/Inventors:
NEUBERT, TIMOTHY, US;
KAWATKAR, AARTI S., US;
MARTINBOROUGH, ESTHER, US;
TERMIN, ANDREAS, US

(74) Agent: SMART & BIGGAR

(54) Titre : DERIVES D'INDANE COMME MODULATEURS DE CANAUX IONIQUES
(54) Title: INDANE DERIVATIVES AS MODULATORS OF ION CHANNELS



(I)

(57) Abrégé/Abstract:
The present invention relates to indane derivatives of formula (I), in which the variables are as defined in the claims, useful as inhibitors of voltage-gated sodium and calcium ion channels. 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.

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
14 December 2006 (14.12.2006)

PCT

(10) International Publication Number
WO 2006/133459 A1

(51) International Patent Classification:
C07D 277/52 (2006.01) *A61K 31/54* (2006.01)
C07D 417/12 (2006.01) *A61P 29/00* (2006.01)

(21) International Application Number:
PCT/US2006/022818

(22) International Filing Date: 9 June 2006 (09.06.2006)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/688,919 9 June 2005 (09.06.2005) US

(71) Applicant *(for all designated States except US)*: **VERTEX PHARMACEUTICALS INCORPORATED** [US/US]; 130 Waverly Street, Cambridge, MA 02139 (US).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **NEUBERT, Timothy** [US/US]; 10721 Ballystock Court, San Diego, CA 92131 (US). **KAWATKAR, Aarti, S.** [IN/US]; 10694 Caminito Alvarez, San Diego, CA 92126 (US). **MARTINBOROUGH, Esther** [US/US]; 11128 Portobelo Drive, San Diego, CA 92124 (US). **TERMIN, Andreas** [US/US]; 2080 Wandering Road, Encinitas, CA 92024 (US).

(74) Agent: **LIU, Yi**; Vertex Pharmaceuticals Incorporated, 130 Waverly Street, Cambridge, MA 02139 (US).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

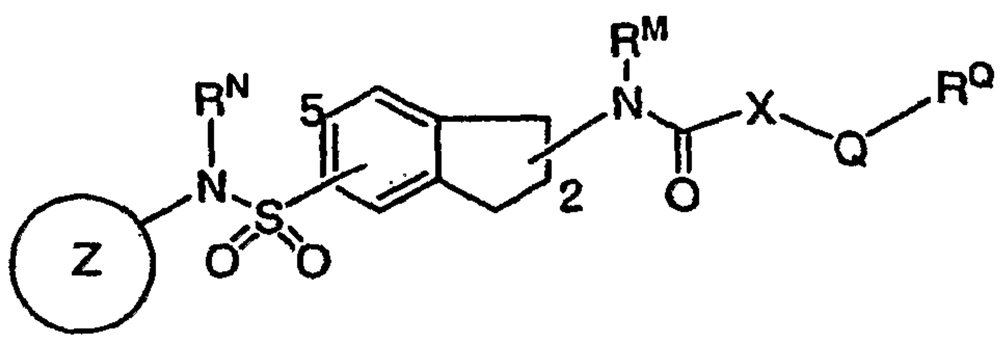
(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*
— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 2006/133459 A1

(54) Title: INDANE DERIVATIVES AS MODULATORS OF ION CHANNELS



(I)

(57) Abstract: The present invention relates to indane derivatives of formula (I), in which the variables are as defined in the claims, useful as inhibitors of voltage-gated sodium and calcium ion channels. 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.

VPI/05-140 WO

INDANE DERIVATIVES AS MODULATORS OF ION CHANNELS

CROSS-REFERENCE TO RELATED APPLICATIONS

[00100] This application claims the benefit under 35 U.S.C. § 119 to United States Provisional application serial no. 60/688,919, filed June 9, 2005 and entitled "INDANE DERIVATIVES AS MODULATORS OF ION CHANNELS". The entire contents of each of the above priority application are incorporated herein by reference.

TECHNICAL FIELD OF THE INVENTION

[00101] The present invention relates to compounds useful as inhibitors of ion channels. 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.

BACKGROUND OF THE INVENTION

[00102] Na channels are central to the generation of action potentials in all excitable cells such as neurons and myocytes. They play key roles in excitable tissue including brain, smooth muscles of the gastrointestinal tract, skeletal muscle, the peripheral nervous system, spinal cord and airway. As such they play key roles in a variety of disease states such as epilepsy (See, Moulard, B. and D. Bertrand (2002) "Epilepsy and sodium channel blockers" Expert Opin. Ther. Patents **12**(1): 85-91)), pain (See, Waxman, S. G., S. Dib-Hajj, et al. (1999) "Sodium channels and pain" Proc Natl Acad Sci U S A **96**(14): 7635-9 and Waxman, S. G., T. R. Cummins, et al. (2000) "Voltage-gated sodium channels and the molecular pathogenesis of pain: a review" J Rehabil Res Dev **37**(5): 517-28), myotonia (See, Meola, G. and V. Sansone (2000) "Therapy in myotonic disorders and in muscle channelopathies" Neurol Sci **21**(5): S953-61 and Mankodi, A. and C. A. Thornton (2002) "Myotonic syndromes" Curr Opin Neurol **15**(5): 545-52), ataxia (See, Meisler, M. H., J. A. Kearney, et al. (2002) "Mutations of voltage-gated sodium channels in movement disorders and epilepsy" Novartis Found Symp **241**: 72-81), multiple sclerosis (See, Black, J. A., S. Dib-Hajj, et al. (2000) "Sensory neuron-specific sodium channel SNS is abnormally expressed in the brains of

mice with experimental allergic encephalomyelitis and humans with multiple sclerosis" Proc Natl Acad Sci U S A **97**(21): 11598-602, and Renganathan, M., M. Gelderblom, et al. (2003) "Expression of Na(v)1.8 sodium channels perturbs the firing patterns of cerebellar purkinje cells" Brain Res **959**(2): 235-42), irritable bowel (See, Su, X., R. E. Wachtel, et al. (1999) "Capsaicin sensitivity and voltage-gated sodium currents in colon sensory neurons from rat dorsal root ganglia" Am J Physiol **277**(6 Pt 1): G1180-8, and Laird, J. M., V. Souslova, et al. (2002) "Deficits in visceral pain and referred hyperalgesia in Nav1.8 (SNS/PN3)- null mice" J Neurosci **22**(19): 8352-6), urinary incontinence and visceral pain (See,Yoshimura, N., S. Seki, et al. (2001) "The involvement of the tetrodotoxin-resistant sodium channel Na(v)1.8 (PN3/SNS) in a rat model of visceral pain" J Neurosci **21**(21): 8690-6), as well as an array of psychiatry dysfunctions such as anxiety and depression (See, Hurley, S. C. (2002) "Lamotrigine update and its use in mood disorders" Ann Pharmacother **36**(5): 860-73).

[00103] Voltage gated Na channels comprise a gene family consisting of 9 different subtypes (NaV1.1-NaV1.9). As shown in Table 1, these subtypes show tissue specific localization and functional differences (See, Goldin, A. L. (2001) "Resurgence of sodium channel research" Annu Rev Physiol **63**: 871-94). Three members of the gene family (NaV1.8, 1.9, 1.5) are resistant to block by the well-known Na channel blocker TTX, demonstrating subtype specificity within this gene family. Mutational analysis has identified glutamate 387 as a critical residue for TTX binding (See, Noda, M., H. Suzuki, et al. (1989) "A single point mutation confers tetrodotoxin and saxitoxin insensitivity on the sodium channel II" FEBS Lett **259**(1): 213-6).

[00104] Table 1 (Abbreviations: CNS = central nervous system, PNS = peripheral nervous sytem, DRG = dorsal root ganglion, TG = Trigeminal ganglion):

Na isoform	Tissue	TTX IC50	Indications
NaV1.1	CNS, PNS soma of neurons	10nM	Pain, Epilepsy, neurodegeneration
NaV1.2	CNS, high in axons	10nM	Neurodegeneration Epilepsy
NaV1.3	CNS, embryonic, injured nerves	15nM	Pain

Na isoform	Tissue	TTX IC50	Indications
NaV1.4	Skeletal muscle	25nM	Myotonia
NaV1.5	Heart	2μM	Arrythmia, long QT
NaV1.6	CNS widespread, most abuntant	6nM	Pain, movement disorders
NaV1.7	PNS, DRG, terminals neuroendocrine	25nM	Pain, Neuroendocrine disorders
NaV1.8	PNS, small neurons in DRG & TG	>50μM	Pain
NaV1.9	PNS, small neurons in DRG & TG	1μM	Pain

[00105] In general, voltage-gated sodium channels (NaVs) are responsible for initiating the rapid upstroke of action potentials in excitable tissue in nervous system, which transmit the electrical signals that compose and encode normal and aberrant pain sensations. Antagonists of NaV channels can attenuate these pain signals and are useful for treating a variety of pain conditions, including but not limited to acute, chronic, inflammatory, and neuropathic pain. Known NaV antagonists, such as TTX, lidocaine (See, Mao, J. and L. L. Chen (2000) "Systemic lidocaine for neuropathic pain relief" Pain **87**(1): 7-17.) bupivacaine, phenytoin (See, Jensen, T. S. (2002) "Anticonvulsants in neuropathic pain: rationale and clinical evidence" Eur J Pain **6** (Suppl A): 61-8), lamotrigine (See, Rozen, T. D. (2001) "Antiepileptic drugs in the management of cluster headache and trigeminal neuralgia" Headache **41 Suppl 1**: S25-32 and Jensen, T. S. (2002) "Anticonvulsants in neuropathic pain: rationale and clinical evidence" Eur J Pain **6** (Suppl A): 61-8.), and carbamazepine (See, Backonja, M. M. (2002) "Use of anticonvulsants for treatment of neuropathic pain" Neurology **59**(5 Suppl 2): S14-7), have been shown to be useful attenuating pain in humans and animal models.

[00106] Hyperalgesia (extreme sensitivity to something painful) that develops in the presence of tissue injury or inflammation reflects, at least in part, an increase in the excitability of high-threshold primary afferent neurons innervating the site

of injury. Voltage sensitive sodium channels activation is critical for the generation and propagation of neuronal action potentials. There is a growing body of evidence indicating that modulation of NaV currents is an endogenous mechanism used to control neuronal excitability (See, Goldin, A. L. (2001) "Resurgence of sodium channel research" Annu Rev Physiol **63**: 871-94.). Several kinetically and pharmacologically distinct voltage-gated sodium channels are found in dorsal root ganglion (DRG) neurons. The TTX-resistant current is insensitive to micromolar concentrations of tetrodotoxin, and displays slow activation and inactivation kinetics and a more depolarized activation threshold when compared to other voltage-gated sodium channels. TTX-resistant sodium currents are primarily restricted to a subpopulation of sensory neurons likely to be involved in nociception. Specifically, TTX-resistant sodium currents are expressed almost exclusively in neurons that have a small cell-body diameter; and give rise to small-diameter slow-conducting axons and that are responsive to capsaicin. A large body of experimental evidence demonstrates that TTX-resistant sodium channels are expressed on C-fibers and are important in the transmission of nociceptive information to the spinal cord.

[00107] Intrathecal administration of antisense oligo-deoxynucleotides targeting a unique region of the TTX-resistant sodium channel (NaV1.8) resulted in a significant reduction in PGE_2-induced hyperalgesia (See, Khasar, S. G., M. S. Gold, et al. (1998) "A tetrodotoxin-resistant sodium current mediates inflammatory pain in the rat" Neurosci Lett **256**(1): 17-20). More recently, a knockout mouse line was generated by Wood and colleagues, which lacks functional NaV1.8. The mutation has an analgesic effect in tests assessing the animal's response to the inflammatory agent carrageenan (See, Akopian, A. N., V. Souslova, et al. (1999) "The tetrodotoxin-resistant sodium channel SNS has a specialized function in pain pathways" Nat Neurosci **2**(6): 541-8.). In addition, deficit in both mechano- and thermoreception were observed in these animals. The analgesia shown by the Nav1.8 knockout mutants is consistent with observations about the role of TTX-resistant currents in nociception.

[00108] Immunohistochemical, in-situ hybridization and in-vitro electrophysiology experiments have all shown that the sodium channel NaV1.8 is selectively localized to the small sensory neurons of the dorsal root ganglion and trigeminal ganglion (See, Akopian, A. N., L. Sivilotti, et al. (1996) "A tetrodotoxin-resistant voltage-gated sodium channel expressed by sensory neurons" Nature **379**(6562):

257-62.). The primary role of these neurons is the detection and transmission of nociceptive stimuli. Antisense and immunohistochemical evidence also supports a role for NaV1.8 in neuropathic pain (See, Lai, J., M. S. Gold, et al. (2002) "Inhibition of neuropathic pain by decreased expression of the tetrodotoxin-resistant sodium channel, NaV1.8" Pain **95**(1-2): 143-52, and Lai, J., J. C. Hunter, et al. (2000) "Blockade of neuropathic pain by antisense targeting of tetrodotoxin- resistant sodium channels in sensory neurons" Methods Enzymol **314**: 201-13.). NaV1.8 protein is upregulated along uninjured C-fibers adjacent to the nerve injury. Antisense treatment prevents the redistribution of NaV1.8 along the nerve and reverses neuropathic pain. Taken together the gene-knockout and antisense data support a role for NaV1.8 in the detection and transmission of inflammatory and neuropathic pain.

[00109] In neuropathic pain states there is a remodeling of Na channel distribution and subtype. In the injured nerve, expression of NaV1.8 and NaV1.9 are greatly reduced whereas expression of the TTX sensitive subunit NaV1.3 is 5-10 fold upregulated (See, Dib-Hajj, S. D., J. Fjell, et al. (1999) "Plasticity of sodium channel expression in DRG neurons in the chronic constriction injury model of neuropathic pain." Pain **83**(3): 591-600.) The timecourse of the increase in NaV1.3 parallels the appearance of allodynia in animal models subsequent to nerve injury. The biophysics of the NaV1.3 channel is distinctive in that it shows very fast repriming after inactivation following an action potential. This allows for sustained rates of high firing as is often seen in the injured nerve (See, Cummins, T. R., F. Aglieco, et al. (2001) "Nav1.3 sodium channels: rapid repriming and slow closed-state inactivation display quantitative differences after expression in a mammalian cell line and in spinal sensory neurons" J Neurosci **21**(16): 5952-61.). NaV1.3 is expressed in the central and peripheral systems of man. NaV1.9 is similar to NaV1.8 as it is selectively localized to small sensory neurons of the dorsal root ganglion and trigeminal ganglion (See, Fang, X., L. Djouhri, et al. (2002). "The presence and role of the tetrodotoxin-resistant sodium channel Na(v)1.9 (NaN) in nociceptive primary afferent neurons." J Neurosci **22**(17): 7425-33.). It has a slow rate of inactivation and left-shifted voltage dependence for activation (See, Dib-Hajj, S., J. A. Black, et al. (2002) "NaN/Nav1.9: a sodium channel with unique properties" Trends Neurosci **25**(5): 253-9.). These two biophysical properties allow NaV1.9 to play a role in establishing the resting membrane potential of nociceptive neurons. The resting membrane potential of

NaV1.9 expressing cells is in the –55 to –50mV range compared to –65mV for most other peripheral and central neurons. This persistent depolarization is in large part due to the sustained low-level activation of NaV1.9 channels. This depolarization allows the neurons to more easily reach the threshold for firing action potentials in response to nociceptive stimuli. Compounds that block the NaV1.9 channel may play an important role in establishing the set point for detection of painful stimuli. In chronic pain states, nerve and nerve ending can become swollen and hypersensitive exhibiting high frequency action potential firing with mild or even no stimulation. These pathologic nerve swellings are termed neuromas and the primary Na channels expressed in them are NaV1.8 and NaV1.7 (See, Kretschmer, T., L. T. Happel, et al. (2002) "Accumulation of PN1 and PN3 sodium channels in painful human neuroma- evidence from immunocytochemistry" Acta Neurochir (Wien) **144**(8): 803-10; discussion 810.). NaV1.6 and NaV1.7 are also expressed in dorsal root ganglion neurons and contribute to the small TTX sensitive component seen in these cells. NaV1.7 in particular my therefore be a potential pain target in addition to it's role in neuroendocrine excitability (See, Klugbauer, N., L. Lacinova, et al. (1995) "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): 1084-90).

[00110] NaV1.1 (See, Sugawara, T., E. Mazaki-Miyazaki, et al. (2001) "Nav1.1 mutations cause febrile seizures associated with afebrile partial seizures." Neurology **57**(4): 703-5.) and NaV1.2 (See, Sugawara, T., Y. Tsurubuchi, et al. (2001) "A missense mutation of the Na+ channel alpha II subunit gene Na(v)1.2 in a patient with febrile and afebrile seizures causes channel dysfunction" Proc Natl Acad Sci U S A **98**(11): 6384-9) have been linked to epilepsy conditions including febrile seizures. There are over 9 genetic mutations in NaV1.1 associated with febrile seizures (See, Meisler, M. H., J. A. Kearney, et al. (2002) "Mutations of voltage-gated sodium channels in movement disorders and epilepsy" Novartis Found Symp **241**: 72-81)

[00111] Antagonists for NaV1.5 have been developed and used to treat cardiac arrhythmias. A gene defect in NaV1.5 that produces a larger noninactivating component to the current has been linked to long QT in man and the orally available local anesthetic mexilitine has been used to treat this condition (See, Wang, D. W., K. Yazawa,

et al. (1997) "Pharmacological targeting of long QT mutant sodium channels." J Clin Invest **99**(7): 1714-20).

[00112] Several Na channel blockers are currently used or being tested in the clinic to treat epilepsy (See, Moulard, B. and D. Bertrand (2002) "Epilepsy and sodium channel blockers" Expert Opin. Ther. Patents **12**(1): 85-91.); acute (See, Wiffen, P., S. Collins, et al. (2000) "Anticonvulsant drugs for acute and chronic pain" Cochrane Database Syst Rev **3**), chronic (See, Wiffen, P., S. Collins, et al. (2000) "Anticonvulsant drugs for acute and chronic pain" Cochrane Database Syst Rev **3**, and Guay, D. R. (2001) "Adjunctive agents in the management of chronic pain" Pharmacotherapy **21**(9): 1070-81), inflammatory (See, Gold, M. S. (1999) "Tetrodotoxin-resistant Na+ currents and inflammatory hyperalgesia." Proc Natl Acad Sci U S A **96**(14): 7645-9), and neuropathic pain (See, Strichartz, G. R., Z. Zhou, et al. (2002) "Therapeutic concentrations of local anaesthetics unveil the potential role of sodium channels in neuropathic pain" Novartis Found Symp **241**: 189-201, and Sandner-Kiesling, A., G. Rumpold Seitlinger, et al. (2002) "Lamotrigine monotherapy for control of neuralgia after nerve section" Acta Anaesthesiol Scand **46**(10): 1261-4); cardiac arrhythmias (See, An, R. H., R. Bangalore, et al. (1996) "Lidocaine block of LQT-3 mutant human Na+ channels" Circ Res **79**(1): 103-8, and Wang, D. W., K. Yazawa, et al. (1997) "Pharmacological targeting of long QT mutant sodium channels" J Clin Invest **99**(7): 1714-20); neuroprotection (See, Taylor, C. P. and L. S. Narasimhan (1997) "Sodium channels and therapy of central nervous system diseases" Adv Pharmacol **39**: 47-98) and as anesthetics (See, Strichartz, G. R., Z. Zhou, et al. (2002) "Therapeutic concentrations of local anaesthetics unveil the potential role of sodium channels in neuropathic pain." Novartis Found Symp **241**: 189-201).

[00113] Various animal models with clinical significance have been developed for the study of sodium channel modulators for numerous different pain indications. E.g., malignant chronic pain, see, Kohase, H., et al., Acta Anaesthesiol Scand. 2004; 48(3):382-3; femur cancer pain (see, Kohase, H., et al., Acta Anaesthesiol Scand. 2004; 48(3):382-3); non-malignant chronic bone pain (see, Ciocon, J. O. et al., J Am Geriatr Soc. 1994; 42(6):593-6); rheumatoid arthritis (see, Calvino, B. et al., Behav Brain Res. 1987; 24(1):11-29); osteoarthritis (see, Guzman, R. E., et al., Toxicol Pathol. 2003; 31(6):619-24); spinal stenosis (see, Takenobu, Y. et al., J Neurosci Methods. 2001;

104(2):191-8); Neuropathic low back pain (see, Hines, R., et al., Pain Med. 2002; 3(4):361-5; Massie, J. B., et al., J Neurosci Methods. 2004; 137(2):283-9;

[00114] neuropathic low back pain (see, Hines, R., et al., Pain Med. 2002; 3(4):361-5; Massie, J. B., et al., J Neurosci Methods. 2004; 137(2):283-9); myofascial pain syndrome (see, Dalpiaz & Dodds, J Pain Palliat Care Pharmacother. 2002; 16(1):99-104; Sluka KA et al., Muscle Nerve. 2001; 24(1):37-46); fibromyalgia (see, Bennet & Tai, Int J Clin Pharmacol Res. 1995;15(3):115-9); temporomandibular joint pain (see, Ime H, Ren K, Brain Res Mol Brain Res. 1999; 67(1):87-97); chronic visceral pain, including, abdominal (see, Al-Chaer, E. D., et al., Gastroenterology. 2000; 119(5):1276-85); pelvic/perineal pain, (see, Wesselmann et al., Neurosci Lett. 1998; 246(2):73-6); pancreatic (see, Vera-Portocarrero, L. B., et al., Anesthesiology. 2003; 98(2):474-84); IBS pain (see, Verne, G. N., et al., Pain. 2003; 105(1-2):223-30; La JH et al., World Gastroenterol. 2003; 9(12):2791-5); chronic headache pain (see, Willimas & Stark, Cephalalgia. 2003; 23(10):963-71); migraine (see, Yamamura, H., et al., J Neurophysiol. 1999; 81(2):479-93); tension headache, including, cluster headaches (see, Costa, A., et al., Cephalalgia. 2000; 20(2):85-91); chronic neuropathic pain, including, post-herpetic neuralgia (see, Attal, N., et al., Neurology. 2004; 62(2):218-25; Kim & Chung 1992, Pain 50:355); diabetic neuropathy (see, Beidoun A et al., Clin J Pain. 2004; 20(3):174-8; Courteix, C., et al., Pain. 1993; 53(1):81-8); HIV- associated neuropathy (see, Portegies & Rosenberg, Ned Tijdschr Geneeskd. 2001; 145(15):731-5; Joseph EK et al., Pain. 2004; 107(1-2):147-58; Oh, S. B., et al., J Neurosci. 2001; 21(14):5027-35); trigeminal neuralgia (see, Sato, J., et al., Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2004; 97(1):18-22; Imamura Y et al., Exp Brain Res. 1997; 116(1):97-103); Charcot-Marie Tooth neuropathy (see, Sereda, M., et al., Neuron. 1996; 16(5):1049-60); hereditary sensory neuropathies (see, Lee, M. J., et al., Hum Mol Genet. 2003; 12(15):1917-25); peripheral nerve injury (see, Attal, N., et al., Neurology. 2004; 62(2):218-25; Kim & Chung 1992, Pain 50:355; Bennett & Xie, 1988, Pain 33:87; Decostered, I. & Woolf, C. J., 2000, Pain 87:149; Shir, Y. & Seltzer, Z. 1990; Neurosci Lett 115:62); painful neuromas (see, Nahabedian & Johnson, Ann Plast Surg. 2001; 46(1):15-22; Devor & Raber, Behav Neural Biol. 1983; 37(2):276-83); ectopic proximal and distal discharges (see, Liu, X. et al., Brain Res. 2001; 900(1):119-27); radiculopathy (see, Devers & Galer, (see, Clin J Pain. 2000; 16(3):205-8; Hayashi N et al., Spine. 1998; 23(8):877-85);

chemotherapy induced neuropathic pain (see, Aley, K. O., et al., Neuroscience. 1996; 73(1):259-65); radiotherapy-induced neuropathic pain;

[00115] post-mastectomy pain (see, Devers & Galer, Clin J Pain. 2000; 16(3):205-8); central pain (Cahana, A., et al., Anesth Analg. 2004; 98(6):1581-4), spinal cord injury pain (see, Hains, B. C., et al., Exp Neurol. 2000; 164(2):426-37); post-stroke pain; thalamic pain (see, LaBuda, C. J., et al., Neurosci Lett. 2000; 290(1):79-83); complex regional pain syndrome (see, Wallace, M. S., et al., Anesthesiology. 2000; 92(1):75-83; Xantos D et al., J Pain. 2004; 5(3 Suppl 2):S1); phanton pain (see, Weber, W. E., Ned Tijdschr Geneeskd. 2001; 145(17):813-7; Levitt & Heyback, Pain. 1981; 10(1):67-73); intractable pain (see, Yokoyama, M., et al., Can J Anaesth. 2002; 49(8):810-3); acute pain, acute post-operative pain (see, Koppert, W., et al., Anesth Analg. 2004; 98(4):1050-5; Brennan, T. J., et al., Pain. 1996; 64(3):493-501); acute musculoskeletal pain; joint pain (see, Gotoh, S., et al., Ann Rheum Dis. 1993; 52(11):817-22); mechanical low back pain (see, Kehl, L. J., et al., Pain. 2000; 85(3):333-43); neck pain; tendonitis; injury/exercise pain (see, Sesay, M., et al., Can J Anaesth. 2002; 49(2):137-43); acute visceral pain, including, abdominal pain; pyelonephritis; appendicitis; cholecystitis; intestinal obstruction; hernias; etc (see, Giambernardino, M. A., et al., Pain. 1995; 61(3):459-69); chest pain, including, cardiac Pain (see, Vergona, R. A., et al., Life Sci. 1984; 35(18):1877-84); pelvic pain, renal colic pain, acute obstetric pain, including, labor pain (see, Segal, S., et al., Anesth Analg. 1998; 87(4):864-9); cesarean section pain; acute inflammatory, burn and trauma pain; acute intermittent pain, including, endometriosis (see, Cason, A. M., et al.,Horm Behav. 2003; 44(2):123-31);

[00116] acute herpes zoster pain; sickle cell anemia; acute pancreatitis (see, Toma, H; Gastroenterology. 2000; 119(5):1373-81); breakthrough pain; orofacial pain, including, sinusitis pain, dental pain (see, Nusstein, J., et al., J Endod. 1998; 24(7):487-91; Chidiac, J. J., et al., Eur J Pain. 2002; 6(1):55-67); multiple sclerosis (MS) pain (see, Sakurai & Kanazawa, J Neurol Sci. 1999; 162(2):162-8); pain in depression (see, Greene B, Curr Med Res Opin. 2003; 19(4):272-7); leprosy pain; behcet's disease pain; adiposis dolorosa (see, Devillers & Oranje, Clin Exp Dermatol. 1999; 24(3):240-1); phlebitic pain; Guillain-Barre pain; painful legs and moving toes; Haglund syndrome; erythromelalgia pain (see, Legroux-Crespel, E., et al., Ann Dermatol Venereol. 2003; 130(4):429-33); Fabry's disease pain (see, Germain, D. P., J Soc Biol. 2002;196(2):183-90); Bladder and

urogenital disease, including, urinary incontinence (see, Berggren, T., et al., J Urol. 1993; 150(5 Pt 1):1540-3); hyperactivity bladder (see, Chuang, Y. C., et al., Urology. 2003; 61(3):664-70); painful bladder syndrome (see, Yoshimura, N., et al., J Neurosci. 2001; 21(21):8690-6); interstitial cyctitis (IC) (see, Giannakopoulos& Campilomatos, Arch Ital Urol Nefrol Androl. 1992; 64(4):337-9; Boucher, M., et al., J Urol. 2000; 164(1):203-8); and prostatitis (see, Mayersak, J. S., Int Surg. 1998; 83(4):347-9; Keith, I. M., et al., J Urol. 2001; 166(1):323-8).

[00117] Voltage-gated calcium channels are membrane-spanning, multi-subunit proteins that open in response to membrane depolarization, allowing Ca entry from the extracellular milieu. Calcium channels were initially classified based on the time and voltage-dependence of channel opening and on the sensitivity to pharmacological block. The categories were low-voltage activated (primarily T-type) and high-voltage activated (L,N,P,Q or R-type). This classification scheme was replaced by a nomenclature based upon the molecular subunit composition, as summarized in Table B (Hockerman GH, Peterson BZ, Johnson BD, Catterall WA. 1997. *Annu Rev Pharmacol Toxicol* 37: 361-96; Striessnig J. 1999. *Cell Physiol Biochem* 9: 242-69). There are four primary subunit types that make up calcium channels - α_1, $\alpha_2\delta$, β and γ (See, e.g., De Waard et al. Structural and functional diversity of voltage-activated calcium channels. In Ion Channels, (ed. T. Narahashi) 41-87, (Plenum Press, New York, 1996)). The α_1 subunit is the primary determinant of the pharmacological properties and contains the channel pore and voltage sensor (Hockerman et al., 1997; Striessnig, 1999). Ten isoforms of the α_1 subunit are known, as indicated in Table I below. The $\alpha_2\delta$ subunit consists of two disulfide linked subunits, α_2, which is primarily extracellular and a transmembrane δ subunit. Four isoforms of $\alpha_2\delta$ are known, $\alpha_2\delta$-1, $\alpha_2\delta$-2, $\alpha_2\delta$-3 and $\alpha_2\delta$-4. The β subunit is a non-glycosylated cytoplasmic protein that binds to the α_1 subunit. Four isoforms are known, termed β_1 to β_4. The γ subunit is a transmembrane protein that has been biochemically isolated as a component of Ca_v1 and Ca_v2 channels. At least 8 isoforms are known (γ_1 to γ_8) [Kang MG, Campbell KP. 2003. *J Biol Chem* 278: 21315-8]. The nomenclature for voltage-gated calcium channels is based upon the content of the α_1 subunit, as indicated in Table I. Each type of α_1 subunit can associate with a variety of β, $\alpha_2\delta$ or γ subunits, so that each Ca_v type corresponds to many different combinations of subunits.

[00118] Table B

Cav Nomenclature	α_1 subunit	Pharmacological name
$Ca_v1.1$	α_{1S}	L-type
$Ca_v1.2$	α_{1C}	L-type
$Ca_v1.3$	α_{1D}	L-type
$Ca_v1.4$	α_{1F}	
$Ca_v2.1$	α_{1A}	P- or Q-type
$Ca_v2.2$	α_{1B}	N-type
$Ca_v2.3$	α_{1E}	R-type
$Ca_v3.1$	α_{1G}	T-type
$Ca_v3.2$	α_{1H}	T-type
$Ca_v3.3$	α_{1I}	T-type

[00119] Ca_v2 currents are found almost exclusively in the central and peripheral nervous system and in neuroendocrine cells and constitute the predominant forms of presynaptic voltage-gated calcium current. Presynaptic action potentials cause channel opening and neurotransmitter release is steeply dependent upon the subsequent calcium entry. Thus, Ca_v2 channels play a central role in mediating neurotransmitter release.

[00120] $Ca_v2.1$ and $Ca_v2.2$ contain high affinity binding sites for the peptide toxins ω-conotoxin-MVIIC and ω-conotoxin-GVIA, respectively, and these peptides have been used to determine the distribution and function of each channel type. $Ca_V2.2$ is highly expressed at the presynaptic nerve terminals of neurons from the dorsal root ganglion and neurons of lamina I and II of the dorsal horn (Westenbroek RE, Hoskins L, Catterall WA. 1998. *J Neurosci* 18: 6319-30; Cizkova D, Marsala J, Lukacova N, Marsala M, Jergova S, et al. 2002. *Exp Brain Res* 147: 456-63). $Ca_V2.2$ channels are also found in presynaptic terminals between second and third order interneurons in the spinal cord. Both sites of neurotransmission are very important in relaying pain information to the brain.

[00121] Pain can be roughly divided into three different types: acute,

inflammatory, and neuropathic. Acute pain serves an important protective function in keeping the organism safe from stimuli that may produce tissue damage. Severe thermal, mechanical, or chemical inputs have the potential to cause severe damage to the organism if unheeded. Acute pain serves to quickly remove the individual from the damaging environment. Acute pain by its very nature generally is short lasting and intense. Inflammatory pain on the other had may last for much longer periods of time and it's intensity is more graded. Inflammation may occur for many reasons including tissue damage, autoimmune response, and pathogen invasion. Inflammatory pain is mediated by an "inflammatory soup" that consists of substance P, histamines, acid, prostaglandin, bradykinin, CGRP, cytokines, ATP, and neurotransmitter release. The third class of pain is neuropathic and involves nerve damage that results in reorganization of neuronal proteins and circuits yielding a pathologic "sensitized" state that can produce chronic pain lasting for years. This type of pain provides no adaptive benefit and is particularly difficult to treat with existing therapies.

[00122] Pain, particularly neuropathic and intractable pain is a large unmet medical need. Millions of individuals suffer from severe pain that is not well controlled by current therapeutics. The current drugs used to treat pain include NSAIDS, COX2 inhibitors, opioids, tricyclic antidepressants, and anticonvulsants. Neuropathic pain has been particularly difficult to treat as it does not respond well to opiods until high doses are reached. Gabapentin is currently the favored therapeutic for the treatment of neuropathic pain although it works in only 60% of patients where it shows modest efficacy. The drug is however very safe and side effects are generally tolerable although sedation is an issue at higher doses.

[00123] Validation of Cav2.2 as a target for the treatment of neuropathic pain is provided by studies with ziconotide (also known as ω-conotoxin-MVIIA), a selective peptide blocker of this channel (Bowersox SS, Gadbois T, Singh T, Pettus M, Wang YX, Luther RR. 1996. *J Pharmacol Exp Ther* 279: 1243-9; Jain KK. 2000. *Exp. Opin. Invest. Drugs* 9: 2403-10; Vanegas H, Schaible H. 2000. *Pain* 85: 9-18) In man, intrathecal infusion of Ziconotide is effective for the treatment of intractable pain, cancer pain, opioid resistant pain, and neuropathic pain. The toxin has an 85% success rate for the treatment of pain in humans with a greater potency than morphine. An orally available antagonist of $Ca_V2.2$ should have similar efficacy without the need for intrathecal infusion. $Ca_V2.1$ and $Ca_V2.3$

are also in neurons of nociceptive pathways and antagonists of these channels could be used to treat pain.

[00124] Antagonists of $Ca_V2.1$, $Ca_V2.2$ or $Ca_V2.3$ should also be useful for treating other pathologies of the central nervous system that apparently involve excessive calcium entry. Cerebral ischaemia and stroke are associated with excessive calcium entry due to depolarization of neurons. The $Ca_V2.2$ antagonist ziconotide is effective in reducing infarct size in a focal ischemia model using laboratory animals, suggesting that $Ca_V2.2$ antagonists could be used for the treatment of stroke. Likewise, reducing excessive calcium influx into neurons may be useful for the treatment of epilepsy, traumatic brain injury, Alzheimer's disease, multi-infarct dementia and other classes of dementia, amyotrophic lateral sclerosis, amnesia, or neuronal damage caused by poison or other toxic substances.

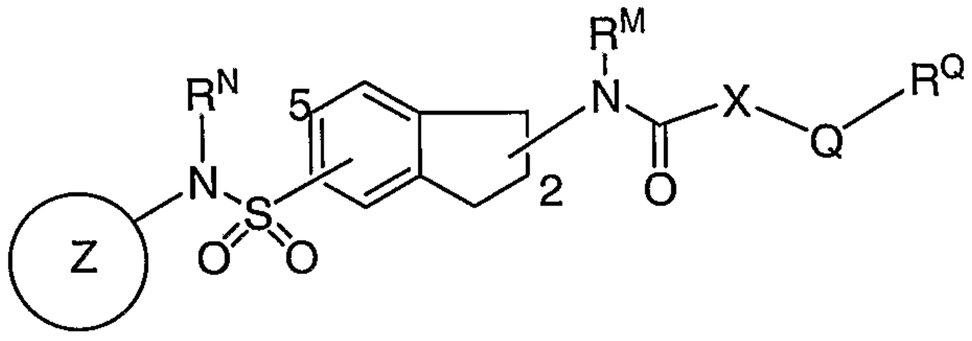
[00125] $Ca_V2.2$ also mediates release of neurotransmitters from neurons of the sympathetic nervous system and antagonists could be used to treat cardiovascular diseases such as hypertension, cardiac arrhythmia, angina pectoris, myocardial infarction, and congestive heart failure.

[00126] Unfortunately, as described above, the efficacy of currently used sodium channel blockers and calcium 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 and Ca channel antagonists, preferably those with higher potency and fewer side effects. Unfortunately, as described above, the efficacy of currently used sodium channel blockers and calcium 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 and Ca channel antagonists, preferably those with higher potency and fewer side effects.

MISSING UPON FILING

SUMMARY OF THE INVENTION

[00127] It has now been found that compounds of this invention, and pharmaceutically acceptable compositions thereof, are useful as inhibitors of voltage-gated sodium channels and calcium channels. These compounds have the general formula **I:**



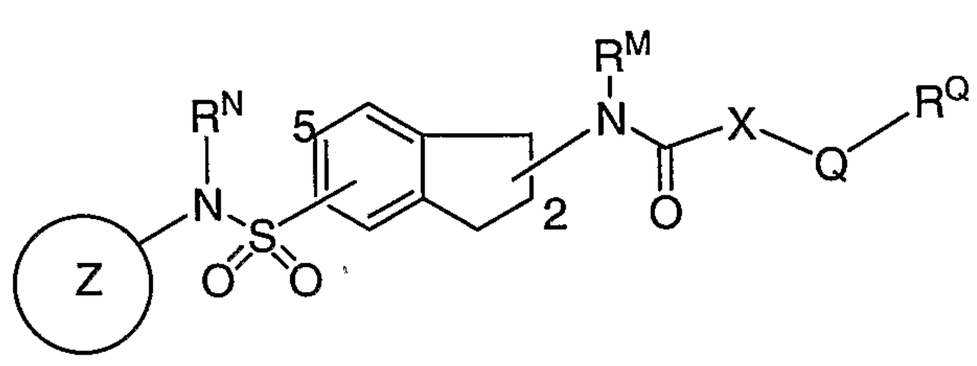
(I);

or a pharmaceutically acceptable salt thereof.

[00128] These compounds and pharmaceutically acceptable compositions are useful for treating or lessening the severity of a variety of diseases, disorders, or conditions, including, but not limited to, acute, chronic, neuropathic, or inflammatory pain, arthritis, migrane, cluster headaches, trigeminal neuralgia, herpetic neuralgia, general neuralgias, epilepsy or epilepsy conditions, neurodegenerative disorders, psychiatric disorders such as anxiety and depression, myotonia, arrythmia, 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.

DETAILED DESCRIPTION OF THE INVENTION

[00129] In one embodiment, the present invention provides compounds of formula **I:**



(I);

or a pharmaceutically acceptable salt thereof;

wherein:

ring Z is a 5-7 membered unsaturated or aromatic ring having at least one ring heteroatom selected from O, S, N, or NH, wherein and said ring Z is optionally substituted with z occurrence of R^Z;

z is 0-4;

R^Z is selected from R^1, R^2, R^3, R^4, or R^5;

X is a bond, O, NR^2, or $C(R^2)_2$;

Q is a bond or a C1-C6 straight or branched alkylidine chain, wherein up to two non-adjacent methylene units of Q are optionally and independently replaced by –CO-, -CS-, -COCO-, -$CONR^2$-, -$CONR^2NR^2$-, -CO_2-, -OCO-, -NR^2CO_2-, -O-, -NR^2CONR^2-, -$OCONR^2$-, -NR^2NR^2, -NR^2NR^2CO-, -NR^2CO-, -S-, -SO, -SO_2-, -NR^2-, -SO_2NR^2-, NR^2SO_2-, -$NR^2SO_2NR^2$-, or a spirocycloalkylene moeity;

R^Q is a C_{1-6} aliphatic group, a 3-8-membered saturated, partially unsaturated, or fully unsaturated monocyclic ring having 0-3 heteroatoms independently selected from O, S, N, or NH, or an 8-12 membered saturated, partially unsaturated, or fully unsaturated bicyclic ring system having 0-5 heteroatoms independently selected from O, S, N, or NH;

wherein R^Q is optionally substituted with up to 5 substituents selected from R^1, R^2, R^3, R^4, or R^5;

R^M and R^N are independently R^2;

R^1 is oxo, $=NN(R^6)_2$, $=NN(R^7)_2$, $=NN(R^6R^7)$, R^6 or $(CH_2)_n$-Y;

n is 0, 1 or 2;

Y is halo, CN, NO_2, CF_3, OCF_3, OH, SR^6, $S(O)R^6$, SO_2R^6, NH_2, NHR^6, $N(R^6)_2$, NR^6R^8, COOH, $COOR^6$ or OR^6; or

two R^1 on adjacent ring atoms, taken together, form 1,2-methylenedioxy or 1,2-ethylenedioxy;

R^2 is hydrogen or C1-C6 aliphatic, wherein each R^2 is optionally substituted with up to 2 substituents independently selected from R^1, R^4, or R^5;

R^3 is a C3-C8 cycloaliphatic, C6-C10 aryl, C3-C8 heterocyclic, or C5-C10 heteroaryl ring, optionally substituted with up to 3 substituents, independently selected from R^1, R^2, R^4 or R^5;

R^4 is OR^5, OR^6, $OC(O)R^6$, $OC(O)R^5$, $OC(O)OR^6$, $OC(O)OR^5$, $OC(O)N(R^6)_2$, $OC(O)N(R^5)_2$, $OC(O)N(R^6R^5)$, $OP(O)(OR^6)_2$, $OP(O)(OR^5)_2$, $OP(O)(OR^6)(OR^5)$, SR^6, SR^5, $S(O)R^6$, $S(O)R^5$, SO_2R^6, SO_2R^5, $SO_2N(R^6)_2$, $SO_2N(R^5)_2$, $SO_2NR^5R^6$, SO_3R^6, SO_3R^5, $C(O)R^5$, $C(O)OR^5$, $C(O)R^6$, $C(O)OR^6$, $C(O)N(R^6)_2$, $C(O)N(R^5)_2$, $C(O)N(R^5R^6)$,

$C(O)N(OR^6)R^6$, $C(O)N(OR^5)R^6$, $C(O)N(OR^6)R^5$, $C(O)N(OR^5)R^5$, $C(NOR^6)R^6$, $C(NOR^6)R^5$, $C(NOR^5)R^6$, $C(NOR^5)R^5$, $N(R^6)_2$, $N(R^5)_2$, $N(R^5R^6)$, $NR^5C(O)R^5$, $NR^6C(O)R^6$, $NR^6C(O)R^5$, $NR^6C(O)OR^6$, $NR^5C(O)OR^6$, $NR^6C(O)OR^5$, $NR^5C(O)OR^5$, $NR^6C(O)N(R^6)_2$, $NR^6C(O)NR^5R^6$, $NR^6C(O)N(R^5)_2$, $NR^5C(O)N(R^6)_2$, $NR^5C(O)NR^5R^6$, $NR^5C(O)N(R^5)_2$, $NR^6SO_2R^6$, $NR^6SO_2R^5$, $NR^5SO_2R^5$, $NR^6SO_2N(R^6)_2$, $NR^6SO_2NR^5R^6$, $NR^6SO_2N(R^5)_2$, $NR^5SO_2NR^5R^6$, $NR^5SO_2N(R^5)_2$, $N(OR^6)R^6$, $N(OR^6)R^5$, $N(OR^5)R^5$, $N(OR^5)R^6$, $P(O)(OR^6)N(R^6)_2$, $P(O)(OR^6)N(R^5R^6)$, $P(O)(OR^6)N(R^5)_2$, $P(O)(OR^5)N(R^5R^6)$, $P(O)(OR^5)N(R^6)_2$, $P(O)(OR^5)N(R^5)_2$, $P(O)(OR^6)_2$, $P(O)(OR^5)_2$, or $P(O)(OR^6)(OR^5)$;

R^5 is a C3-C8 cycloaliphatic, C6-C10 aryl, C3-C8 heterocyclic, or C5-C10 heteroaryl ring, optionally substituted with up to 3 R^1 substituents;

R^6 is H or C1-C6 aliphatic, wherein R^6 is optionally substituted with a R^7 substituent;

R^7 is a C3-C8 cycloaliphatic, C6-C10 aryl, C3-C8 heterocyclic, or C5-C10 heteroaryl ring, and each R^7 is optionally substituted with up to 2 substituents independently chosen from H, C1-C6 aliphatic, or $(CH_2)_m$-Z' wherein m is 0-2;

Z' is selected from halo, CN, NO_2, $C(halo)_3$, $CH(halo)_2$, $CH_2(halo)$, -$OC(halo)_3$, -$OCH(halo)_2$, -$OCH_2(halo)$,OH, S-(C1-C6) aliphatic, S(O)-(C1-C6) aliphatic, SO_2-(C1-C6)aliphatic, NH_2, NH-(C1-C6)aliphatic, $N((C1-C6)aliphatic)_2$, N((C1-C6)aliphatic)R^8, COOH, C(O)O(-(C1-C6)aliphatic), or O-(C1-C6)aliphatic; and

R^8 is acetyl, C6-C10 aryl sulfonyl, or C1-C6 alkyl sulfonyl.

[00130] In one embodiment, the following compound are excluded from compounds of formula **I**:

i) when ring Z is an optionally substituted pyrimidin-2-yl, the sulfonyl group is attached at the 5-position and the $N(R^2)C(O)$ group is attached at the 2-position, R^2 is H, and X and Q each is a bond, then R^Q is not an optionally substituted phenyl or 6-chloro-quinolin-8-yl, fluoren-9-ylethyl, fluoren-9-ylmethyl, indolin-1-yl, cyclohexyl, (phenylthio)methyl, 3-methoxy-thiophen-2-yl, furan-2-yl, (phenoxy)methyl, 3-chloro-thiophen-2-yl, (optionally substituted phenyl)ethyl, butyl, ;

ii) when ring Z is an optionally substituted pyrimidin-2-yl, the sulfonyl group is attached at the 5-position and the $N(R^2)C(O)$ group is attached at the 2-position, R^2 is H,

and X and Q each is a bond, then R^Q is not 2-methyl-5-chloro-2,3-dihydro-benzofuran-7-yl;

iii) when ring Z is an optionally substituted pyrimidin-2-yl, the sulfonyl group is attached at the 5-position and the $N(R^2)C(O)$ group is attached at the 2-position, R^2 is H, and X is -O-, Q is a bond, then R^Q is not ethyl or benzyl; and

iv) when ring Z is an optionally substituted pyrimidin-2-yl, the sulfonyl group is attached at the 5-position and the $N(R^2)C(O)$ group is attached at the 2-position, R^2 is H, and X is -N(Me)-, Q is a bond, then R^Q is not 2-methylphenyl.

[00131] 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.

[00132] As described herein, compounds of the invention may optionally be substituted with one or more substituents, such as are illustrated generally above, or as exemplified by particular classes, subclasses, and species of the invention. It will be appreciated that the phrase "optionally substituted" is used interchangeably with the phrase "substituted or unsubstituted." 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. Unless otherwise indicated, an optionally substituted group may have a substituent at each substitutable (i.e., having the requisite valency available for a given substituent) position of the group, and when more than one position in any given structure may be substituted with more than one substituent selected from a specified group, the substituent may be either the same or different at every position. Combinations of substituents envisioned by this invention are preferably those that result in the formation of stable or chemically feasible compounds. 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.

[00133] The term "aliphatic" or "aliphatic group", 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" means 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 C_3-C_8 hydrocarbon or bicyclic C_8-C_{12} hydrocarbon that is completely saturated or that contains one or more units of 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.

[00134] Unless otherwise specified, the term "heterocycle", "heterocyclyl", "heterocycloaliphatic", 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", 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.

[00135] 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-2*H*-pyrrolyl), NH (as in pyrrolidinyl)

or NR^+ (as in N-substituted pyrrolidinyl)).

[00136] The term "unsaturated", as used herein, means that a moiety has one or more units of unsaturation.

[00137] 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.

[00138] 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".

[00139] 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".

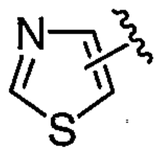
[00140] The term "alkylidene chain" refers to a straight or branched carbon chain that may be fully saturated or have one or more units of unsaturation and has two points of attachment to the rest of the molecule.

[00141] The term "spirocycloalkylene" refers to a cycloaliphatic ring that has two points of attachment from the same carbon atom to the rest of the molecule.

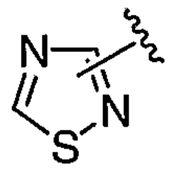
[00142] Unless otherwise stated, structures depicted herein are also meant to include all isomeric (e.g., enantiomeric, diastereomeric, and geometric (or conformational)) forms of the structure; for example, the R and S configurations for each asymmetric center, (Z) and (E) double bond isomers, and (Z) 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. Unless otherwise stated, all tautomeric forms of the

compounds of the invention are within the scope of the invention. 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 having the present structures except for the replacement of hydrogen by deuterium or tritium, or the replacement of a carbon 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 or probes in biological assays.

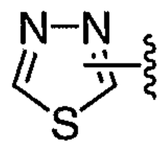
[00143] In one embodiment, Z is an optionally substituted ring selected from:



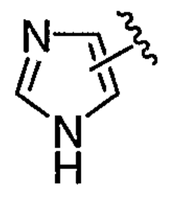
a-i,



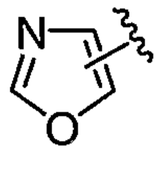
a-ii,



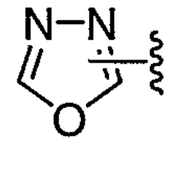
a-iii,



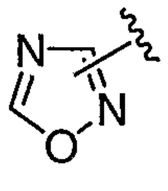
a-iv,



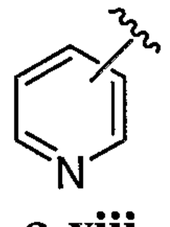
a-v,



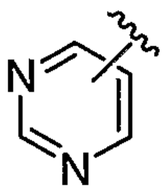
a-vi,



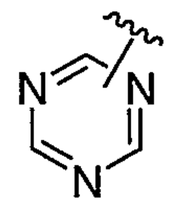
a-vii,



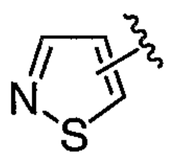
a-viii,



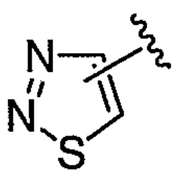
a-ix,



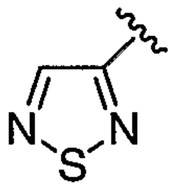
a-x,



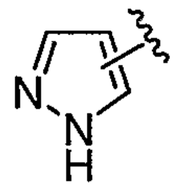
a-xi,



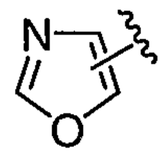
a-xii,



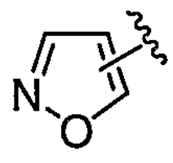
a-xiii,



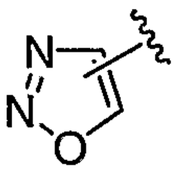
a-xiv,



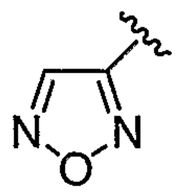
a-xv,



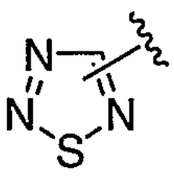
a-xvi,



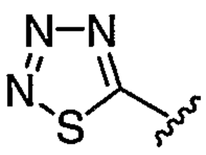
a-xvii,



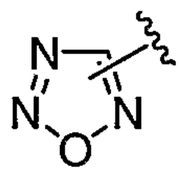
a-xviii,



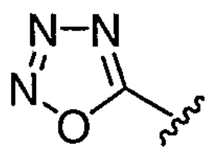
a-xix,



a-xx,



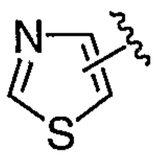
a-xxi,



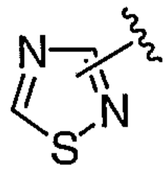
or **a-xxii.**

[00144] In certain embodiments of the compounds of the present invention,

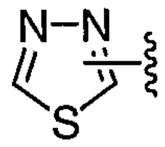
Z is selected from:



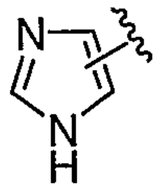
a-i,



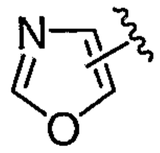
a-ii,



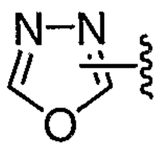
a-iii,



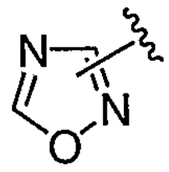
a-iv,



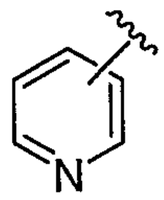
a-v,



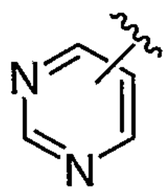
a-vi,



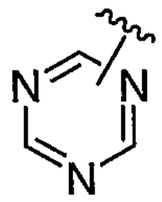
a-vii,



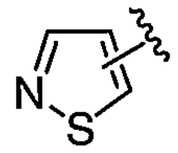
a-viii,



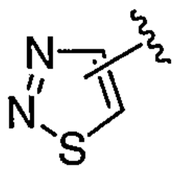
a-ix,



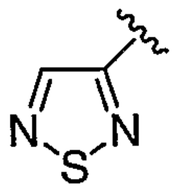
a-x,



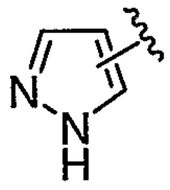
a-xi,



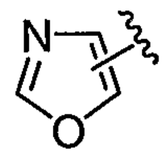
a-xii,



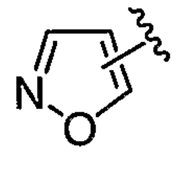
a-xiii,



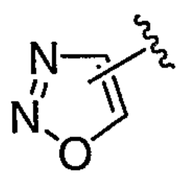
a-xiv,



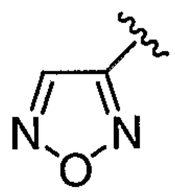
a-xv,



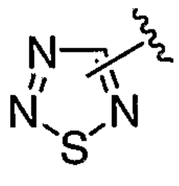
a-xvi,



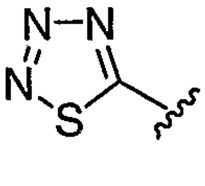
a-xvii,



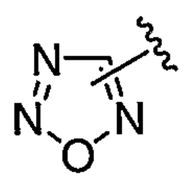
a-xviii,



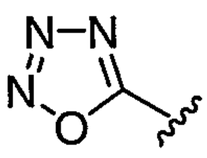
a-xix,



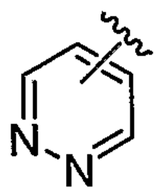
a-xx,



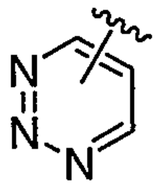
a-xxi,



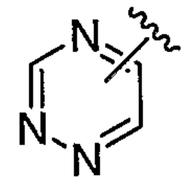
a-xxii,



a-xxiii,



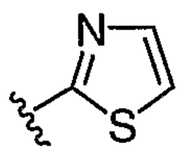
a-xxiv,



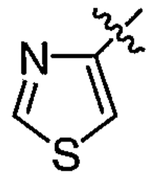
or **a-xxv.**

wherein Z has up to two substituents selected from R^1, R^2, or R^5.

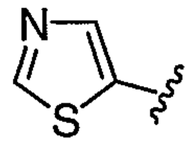
[00145] In other embodiments, Z is selected from:



a-i-a,



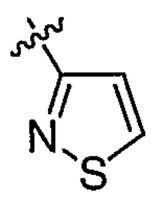
a-i-b,



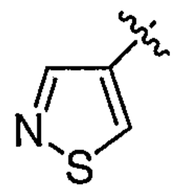
or **a-i-c.**

[00146] Or, Z is formula **a-i-a**.

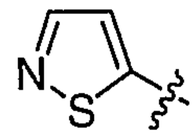
[00147] In other embodiments, Z is selected from:



a-xi-a,

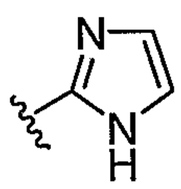


a-xi-b

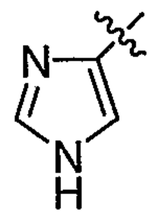


or **a-xi-c.**

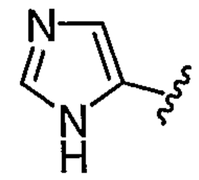
[00148] In certain embodiments of the present invention, Z is selected from:



a-iv-a,

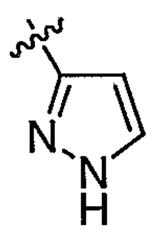


a-iv-b,

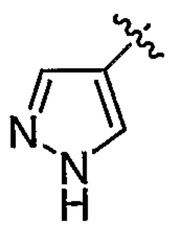


or **a-iv-c.**

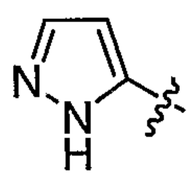
[00149] Or, Z is selected from:



a-xiv-a,

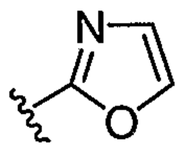


a-xiv-b,

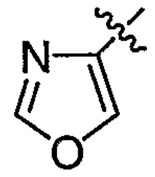


or **a-xiv-c.**

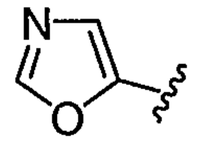
[00150] Or, Z is selected from:



a-xv-a,

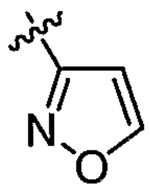


a-xv-b,

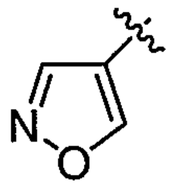


or **a-xv-c.**

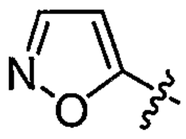
[00151] In certain embodiments, Z is selected from:



a-xvi-a,

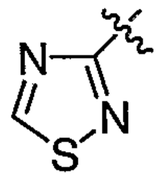


a-xvi-b,

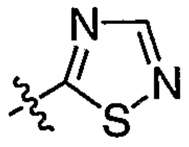


or **a-xvi-c.**

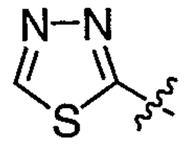
[00152] In certain embodiments, Z is selected from:



a-ii-a,

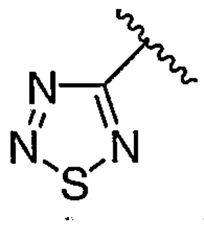


a-ii-b,

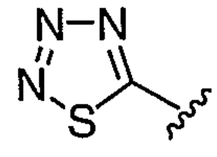


or **a-iii.**

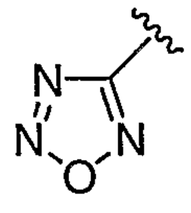
[00153] In certain embodiments, Z is selected from:



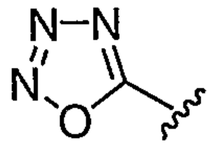
a-xix,



a-xx,

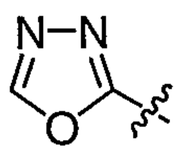


a-xxi,

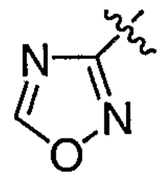


or **a-xxii.**

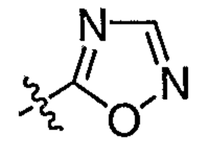
[00154] In other embodiments, Z is selected from:



a-vi,

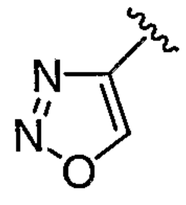


a-vii-a,

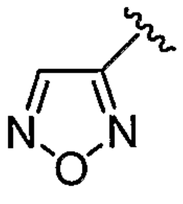


or **a-vii-b**

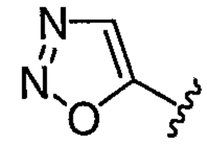
[00155] In other embodiments, Z is selected from:



a-xvii-a,

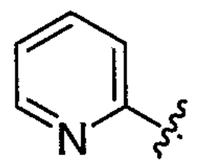


a-xviii,

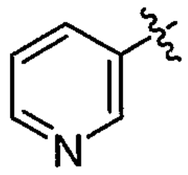


or **a-xvii-b.**

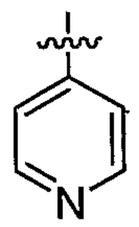
[00156] In certain embodiments, Z is selected from:



a-viii-a,

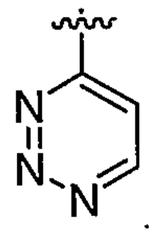


a-viii-b,

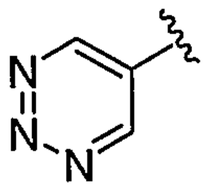


or **a-viii-c.**

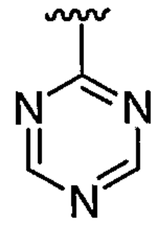
[00157] In certain embodiments, Z is selected from:



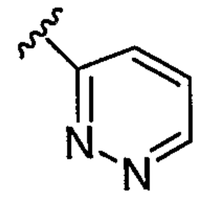
a-xxiv-a,



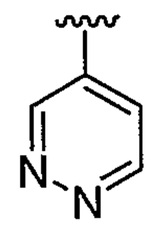
a-xxiv-b



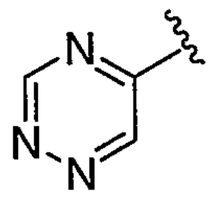
a-x,



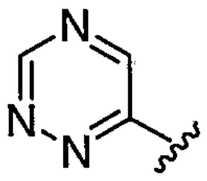
a-xxiii-a,



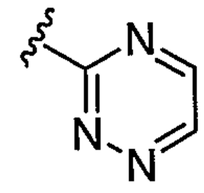
a-xxiii-b,



a-xxv-a,

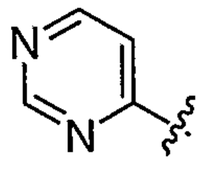


a-xxv-b,

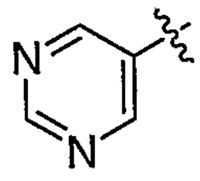


or **a-xxv-c.**

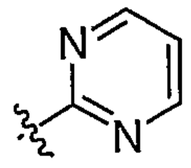
[00158] In other embodiments, Z is selected from:



a-ix-a,



a-ix-b,



or **a-ix-c.**

[00159] According to one embodiment of formula (I), R^Z is selected from R^1, R^2, or R^5.

[00160] According to one embodiment of formula (I), Z is 0-2. According to one embodiment of formula (I), Z is 0. According to another embodiment of formula (I), Z is 1. According to yet another embodiment of formula (I), Z is 2.

[00161] According to one embodiment of formula (I), R^1 is oxo. Or R^1 is $=NN(R^6)_2$, $=NN(R^7)_2$, or $=NN(R^6R^7)$. According to another embodiment, R^1 is R6.

[00162] According to one embodiment, R^1 is (CH_2)n-Y. Or, R^1 is Y.

[00163] Exemplary Y includes halo, CN, NO_2, CF_3, OCF_3, OH, SH, S(C1-4 aliphatic), S(O)(C1-4 aliphatic), SO_2(C1-4 aliphatic), NH_2, NH(C1-4 aliphatic), N(C1-4 aliphatic)2, NR(C1-4 aliphatic)R^8, COOH, COO(C1-4 aliphatic) or O(C1-4 aliphatic). Or, two R^1 on adjacent ring atoms, taken together, form 1,2-methylenedioxy or 1,2-ethylenedioxy. In another embodiment, Y is halo, OH, SH, CN, NO2, CF3, OCF3, COOH, or C(O)O(C1-C4 alkyl). In another embodiment, R^1 is selected from halo, cyano, trifluoromethyl, OH, C_{1-4} alkyl, C_{2-4} alkenyl, C_{1-4} alkoxy, trifluoromethoxy, $C(O)NH_2$, NH_2, NH(C_{1-4} alkyl), N(C_{1-4} alkyl)$_2$, NHC(O)C_{1-4} alkyl, 1-pyrrolidinyl, 1-piperidinyl, 1-morpholinyl, or C(O)C_{1-4} alkyl.

[00164] In another embodiment, R^1 is $(CH_2)_n$-Y. In one embodiment, n is 0 or 1. Or, n is 2. In one embodiment, Y is halo, CN, NO_2, CF_3, OCF_3, OR^6, SR^6, $S(O)R^6$, SO_2R^6, $N(R^6)_2$, NR^6R^8, or $COOR^6$. In another embodiment, Y is halo, OH, SH, CN, NO_2, CF_3, OCF_3, or C(O)O(C1-C4 alkyl).

[00165] In one embodiment, two R^1 on adjacent ring atoms, taken together, form 1,2-methylenedioxy or 1,2-ethylenedioxy.

[00166] According to another embodiment of formula (I), R^2 is a straight or

branched (C1-C6) alkyl or (C2-C6)alkenyl or alkynyl, optionally substituted with up to two R^1 substitutions.

[00167] In one embodiment, R^2 is H. In another embodiment, R^2 is C1-C6 aliphatic. In another embodiment, R^2 is a C1-C6 straight or branched alkyl. In another embodiment, R2 is C1-C4 alkyl. In another embodiment, R^2 is optionally substituted with up to 2 substituents independently selected from R^1 or R^4. Or, R^2 is optionally substituted with up to 2 substituents independently selected from R^1 or R^5.

[00168] In one embodiment, R^3 is a C3-C8 cycloaliphatic optionally substituted with up to 3 substituents independently selected from R^1, R^2, R^4 or R^5. Exemplary cycloaliphatics include cyclopropyl, cyclopentyl, cyclohexyl, or cycloheptyl. In another embodiment, R^3 is a C6-C10 aryl, optionally substituted with up to 3 substituents, independently selected from R^1, R^2, R^4 or R^5. Exemplary aryl rings include phenyl or naphthyl. In another embodiment, R^3 is a C3-C8 heterocyclic, optionally substituted with up to 3 substituents, independently selected from R^1, R^2, R^4 or R^5. Exemplary heterocyclic rings include azetidinyl, pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, or thiomorpholinyl. In another embodiment, R^3 is a C5-C10 heteroaryl ring, optionally substituted with up to 3 substituents, independently selected from R^1, R^2, R^4 or R^5. Exemplary heteroaryl rings include pyridyl, pyrazyl, triazinyl, furanyl, pyrrolyl, thiophenyl, oxazolyl, isoxazolyl, isothiazolyl, oxadiazolyl, imidazolyl, triazolyl, thiadiazolyl, pyrimidinyl. quinolinyl, isoquinolinyl, benzofuranyl, benzothiophenyl, quinolinyl, isoquinolinyl, benzofuranyl, benzothiophenyl, indolizinyl, indolyl, isoindolyl, indolinyl, indazolyl, benzimidazolyl, benzothiazolyl, purinyl, cinnolinyl, phthalazine, quinazolinyl, quinaoxalinyl, naphthylirinyl, or pteridinyl.

[00169] In one embodiment, R^4 is selected from OR^5 or OR^6. Or, R^4 is selected from $OC(O)R^6$ or $OC(O)R^5$. In another embodiment, R^4 is selected from $C(O)R^5$, $C(O)OR^5$, $C(O)R^6$, $C(O)OR^6$, $C(O)N(R^6)_2$, $C(O)N(R^5)_2$ or $C(O)N(R^5R^6)$. In yet another embodiment, R^4 is selected from $N(R^6)_2$, $N(R^5)_2$, or $N(R^5R^6)$. Or, R^4 is selected from $NR^5C(O)R^5$, $NR^6C(O)R^6$, $NR^6C(O)R^5$, $NR^6C(O)N(R^6)_2$, $NR^6C(O)NR^5R^6$, $NR^6C(O)N(R^5)_2$, $NR^5C(O)N(R^6)_2$, $NR^5C(O)NR^5R^6$, or $NR^5C(O)N(R^5)_2$.

[00170] In one embodiment, R^5 is a C3-C8 cycloaliphatic, optionally

substituted with up to 3 R^1 substituents. Exemplary cycloaliphatics include cyclopropyl, cyclopentyl, cyclohexyl, or cycloheptyl. In another embodiment, R^5 is a C6-C10 aryl, optionally substituted with up to 3 R^1 substituents. Exemplary aryl rings include phenyl or naphthyl. In another embodiment, R^5 is a C3-C8 heterocyclic, optionally substituted with up to 3 R^1 substituents. Exemplary heterocyclic rings include azetidinyl, pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, or thiomorpholinyl. In another embodiment, R^5 is a C5-C10 heteroaryl ring, optionally substituted with up to 3 R^1 substituents. Exemplary heteroaryl rings include pyridyl, pyrazyl, triazinyl, furanyl, pyrrolyl, thiophenyl, oxazolyl, isoxazolyl, isothiazolyl, oxadiazolyl, imidazolyl, triazolyl, thiadiazolyl, pyrimidinyl. quinolinyl, isoquinolinyl, benzofuranyl, benzothiophenyl, quinolinyl, isoquinolinyl, benzofuranyl, benzothiophenyl, indolizinyl, indolyl, isoindolyl, indolinyl, indazolyl, benzimidazolyl, benzothiazolyl, purinyl, cinnolinyl, phthalazine, quinazolinyl, quinaoxalinyl, naphthyridinyl, or pteridinyl.

[00171] In one embodiment, R^6 is H. In another embodiment, R^6 is C1-C6 aliphatic, preferably, C1-C6 alkyl. Or, R^6 is C1-C6 aliphatic optionally substituted with a R^7 substituent.

[00172] In one embodiment, R^7 is a C3-C8 cycloaliphatic, optionally substituted with up to 2 substituents independently chosen from H, C1-C6 aliphatic, or $(CH_2)_m$-Z' wherein m is 0-2. Exemplary cycloaliphatics include cyclopropyl, cyclopentyl, cyclohexyl, or cycloheptyl. In another embodiment, R^7 is a C6-C10 aryl, optionally substituted with up to 2 substituents independently chosen from H, C1-C6 aliphatic, or $(CH_2)_m$-Z' wherein m is 0-2. Exemplary aryl rings include phenyl or naphthyl. Or, R^7 is a C3-C8 heterocyclic, optionally substituted with up to 2 substituents independently chosen from H, C1-C6 aliphatic, or $(CH_2)_m$-Z' wherein m is 0-2. Exemplary heterocyclic rings include azetidinyl, pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, or thiomorpholinyl. Or, R^7 is a C5-C10 heteroaryl ring, optionally substituted with up to 2 substituents independently chosen from H, C1-C6 aliphatic, or $(CH_2)_m$-Z' wherein m is 0-2. Exemplary heteroaryl rings include pyridyl, pyrazyl, triazinyl, furanyl, pyrrolyl, thiophenyl, oxazolyl, isoxazolyl, isothiazolyl, oxadiazolyl, imidazolyl, triazolyl, thiadiazolyl, pyrimidinyl. quinolinyl, isoquinolinyl, benzofuranyl, benzothiophenyl, quinolinyl, isoquinolinyl, benzofuranyl, benzothiophenyl, indolizinyl, indolyl, isoindolyl, indolinyl, indazolyl, benzimidazolyl, benzothiazolyl, purinyl,

cinnolinyl, phthalazine, quinazolinyl, quinaoxalinyl, naphthyridinyl, or pteridinyl.

[00173] In one embodiment, Z' is selected from halo, CN, NO_2, $C(halo)_3$, $CH(halo)_2$, $CH_2(halo)$, $-OC(halo)_3$, $-OCH(halo)_2$, $-OCH_2(halo)$,OH, S-(C1-C6) aliphatic, S(O)-(C1-C6) aliphatic, SO_2-(C1-C6)aliphatic, NH_2, NH-(C1-C6)aliphatic, $N((C1-C6)aliphatic)_2$, COOH, C(O)O(-(C1-C6)aliphatic), or O-(C1-C6)aliphatic.

[00174] In one embodiment, R^M is hydrogen. In another embodiment, R^N is hydrogen.

[00175] In one embodiment, X is a bond.

[00176] In another embodiment, X is O. Or, X is $C(R^2)_2$. Or, X is NR^2.

[00177] In one embodiment, X is CH_2. Or, X is CHMe. Or, X is $C(Me)_2$.

[00178] In another embodiment, X is NMe.

[00179] In one embodiment, Q is a bond.

[00180] In another embodiment, Q is O, S, or NR^2. In embodiment, Q is O. Or, Q is S. Or, Q is NR^2. Or, Q is NH or N(C1-C6) alkyl.

[00181] In another embodiment, Q is a C1-C6 straight or branched alkylidine chain, wherein up to one methylene unit of Q is replaced by O, S, NH, or N(C1-C4 alkyl).

[00182] In another embodiment, Q is a C1-C6 alkyl, wherein one methylene group is replaced by a spirocycloalkylene group such as spirocyclopropylene.

[00183] In another embodiment, Q is $-X_2-(X_1)_p-$, wherein:

[00184] X_2 is C1-C6 aliphatic, optionally substituted with up to two substituents independently selected from R^1, R^4, or R^5; and

[00185] p is 0 or 1; and

[00186] X_1 is O, S, or NR^2.

[00187] In one embodiment, X_2 is C1-C6 alkyl or C2-C6 alkylidene. Or, X_2 is C1-C6 alkyl optionally substituted with R^1 or R^4. In one embodiment, X_2 is selected from $-CH_2-$, $-CH_2-CH_2-$, $-(CH_2)_3-$, $-C(Me)_2-$, -CH(Me)-, -C(Me)=CH-, -CH=CH-, -CH(Ph)-, $-CH_2-$CH(Me)-, -CH(Et)-, or -CH(i-Pr)-.

[00188] In certain embodiments, X_1 is NH. Or, X_1 is -N(C1-C4 alkyl)-.

[00189] In one embodiment, p is 0.

[00190] In another embodiment, p is 1 and X_1 is O.

[00191] In another embodiment, p is 1, and X_1 is S.

[00192] In another embodiment, p is 1, and X_1 is NR^2. Preferably, R^2 is hydrogen.

[00193] In one embodiment, R^Q is a C_{1-6} aliphatic group, wherein R^Q is optionally substituted with up to 4 substituents selected from R^1, R^2, R^3, R^4, or R^5.

[00194] In another embodiment, R^Q is a 3-8-membered saturated, partially unsaturated, or aromatic monocyclic ring having 0-3 heteroatoms independently selected from O, S, N, or NH, wherein R^Q is optionally substituted with up to 4 substituents selected from R^1, R^2, R^3, R^4, or R^5. In one embodiment, R^Q is optionally substituted with up to 3 substituents selected from halo, cyano, trifluoromethyl, OH, C_{1-4} alkyl, C_{2-4} alkenyl, C_{1-4} alkoxy, trifluoromethoxy, $C(O)NH_2$, NH_2, $NH(C_{1-4}$ alkyl), $N(C_{1-4}$ alkyl)$_2$, $NHC(O)C_{1-4}$ alkyl, or $C(O)C_{1-4}$ alkyl.

[00195] In one embodiment, R^Q is optionally substituted phenyl, wherein R^Q is optionally substituted with up to 4 substituents selected from R^1, R^2, R^3, R^4, or R^5. In one embodiment, R^Q is phenyl optionally substituted with up to 3 substituents selected from halo, cyano, trifluoromethyl, OH, C_{1-4} alkyl, C_{2-4} alkenyl, C_{1-4} alkoxy, trifluoromethoxy, $C(O)NH_2$, NH_2, $NH(C_{1-4}$ alkyl), $N(C_{1-4}$ alkyl)$_2$, $NHC(O)C_{1-4}$ alkyl, or $C(O)C_{1-4}$ alkyl.

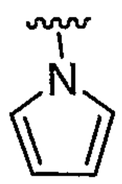
[00196] In one embodiment, R^Q is optionally substituted naphthyl, wherein R^Q is optionally substituted with up to 4 substituents selected from R^1, R^2, R^3, R^4, or R^5. In one embodiment, R^Q is naphthyl optionally substituted with up to 5 substituents

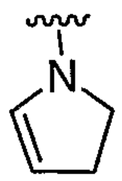
selected from halo, cyano, trifluoromethyl, OH, C_{1-4} alkyl, C_{2-4} alkenyl, C_{1-4} alkoxy, trifluoromethoxy, $C(O)NH_2$, NH_2, $NH(C_{1-4}$ alkyl), $N(C_{1-4}$ alkyl$)_2$, $NHC(O)C_{1-4}$ alkyl, or $C(O)C_{1-4}$ alkyl.

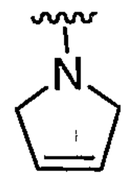
[00197] Or, R^Q is an optionally substituted 3-8 membered cycloaliphatic ring, wherein R^Q is optionally substituted with up to 4 substituents selected from R^1, R^2, R^3, R^4, or R^5. In one embodiment, R^Q is selected from optionally substituted cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl.

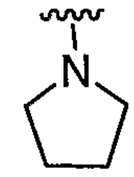
[00198] Or, R^Q is an optionally substituted 5-6 membered monocyclic, unsaturated, partically saturated, or aromatic ring containing up to 3 heteroatoms independently selected from O, S, N, or NH. Or, R^Q is a 3-7 membered monocyclic, heterocyclic ring.

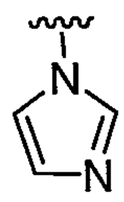
[00199] In one embodiment, R^Q is selected from an optionally substituted ring selected from:

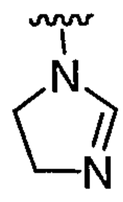

i,

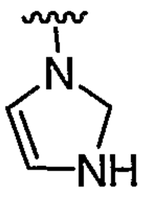

ii,

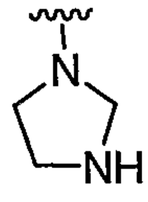

iii,

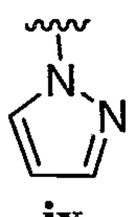

iv,

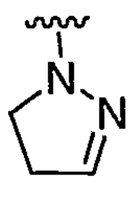

v,

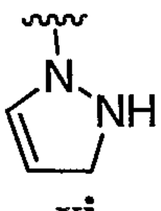

vi,

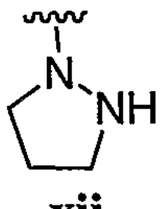

vii,


viii,


ix,


x,

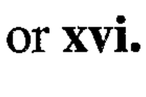

xi,


xii,

xiii,

xiv,

xv,

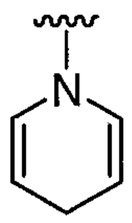

or **xvi.**

[00200] In another embodiment, R^Q is selected from any of rings **i** - **xiv** or **xvi**, wherein said ring is fused to an optionally substituted phenyl ring.

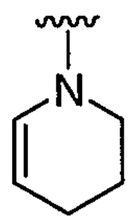
[00201] In another embodiment, R^Q is selected from an optionally

substituted ring selected from pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl.

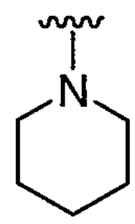
[00202] In another embodiment, R^Q is an optionally substituted ring selected from:



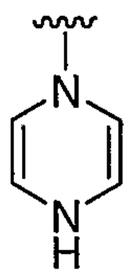
xvii,



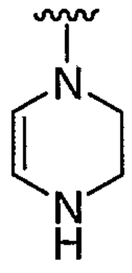
xviii,



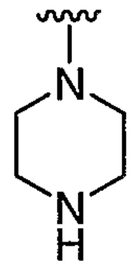
xix,



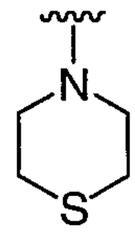
xx,



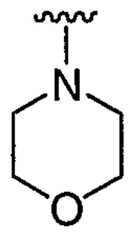
xxi,



xxii,



xxiii,

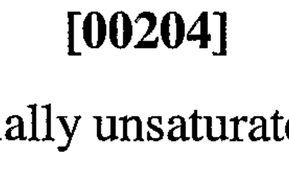


or **xxiv.**

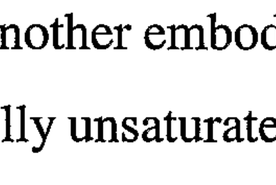
[00203] In another embodiment, R^Q is any one of the above rings **xvii** - **xxiv**, wherein said ring is fused to an optionally substituted phenyl ring.

[00204] In another embodiment, R^Q is an 8-12 membered saturated, partially unsaturated, or fully unsaturated bicyclic ring system having 0-5 heteroatoms independently selected from O, S, N, or NH, wherein R^Q is optionally substituted with up to 4 substituents selected from R^1, R^2, R^3, R^4, or R^5. In one embodiment, R^Q is optionally substituted naphthyl. Or, RQ is an optionally substituted 8-10 membered, bicyclic, heteroaromatic ring. Or, RQ is an optionally substituted, 8-10 membered, bicyclic, heterocyclic ring.

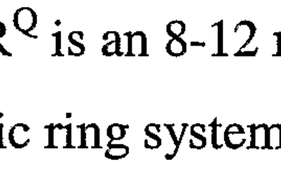
[00205] In one embodiment, R^Q is an optionally substituted ring selected from:



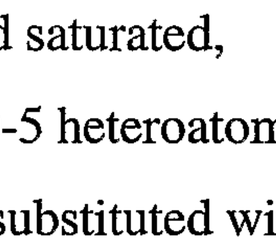
xxv,



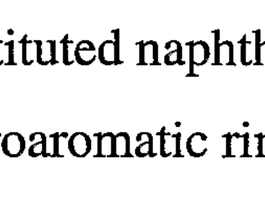
xxvi,



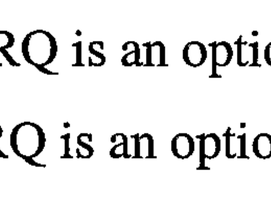
xxvii,



xxviii,

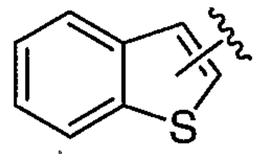


xxix,

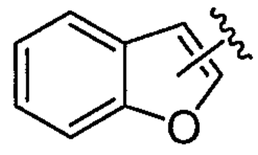


or **xxx.**

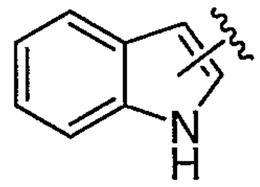
[00206] In another embodiment, R^Q is an optionally substituted ring selected from:



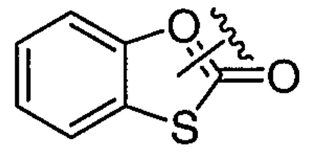
xxxi,



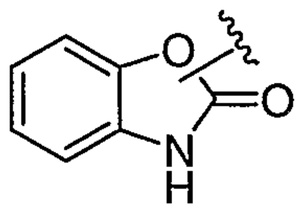
xxxii,



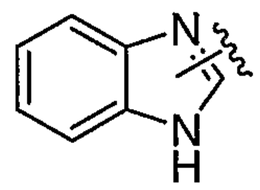
xxxiii,



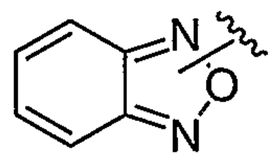
xxxiv,



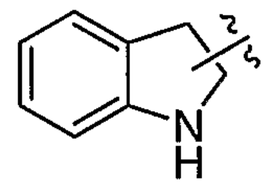
xxxv,



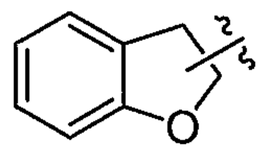
xxxvi,



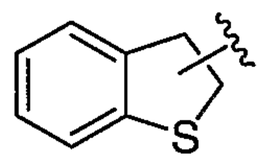
xxxvii,



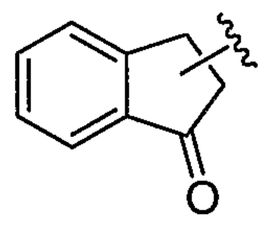
xxxviii,



xxxix,

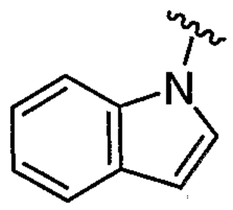


xl,

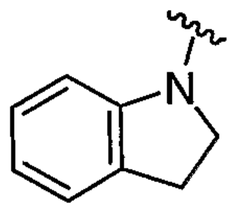


or **xli.**

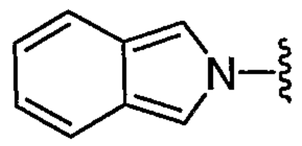
[00207] In another embodiment, R^Q is an optionally substituted ring selected from:



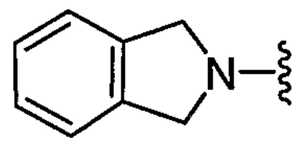
xlii,



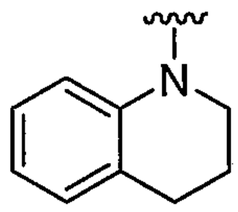
xliii,



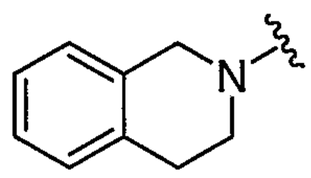
xliv,



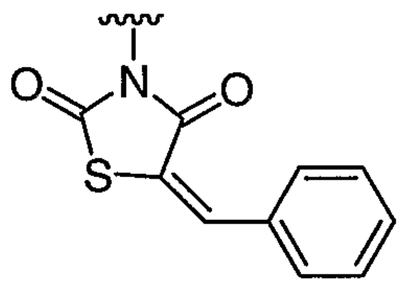
xlv,



xlvi,

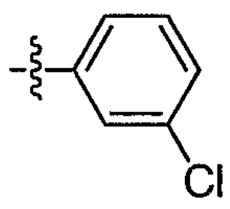


xlvii,

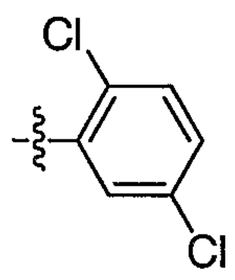


or, **xlviii.**

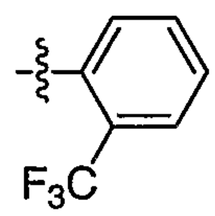
[00208] In another embodiment, R^Q is selected from the following:



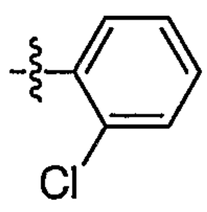
xlix,



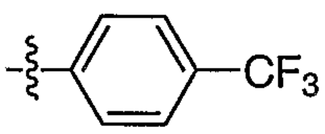
l,



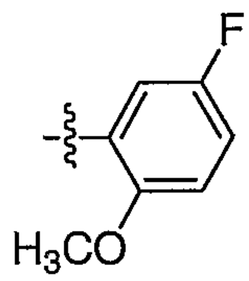
li,



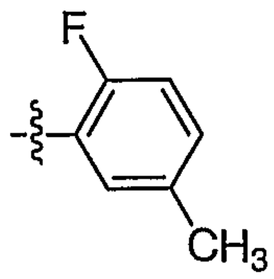
lii,



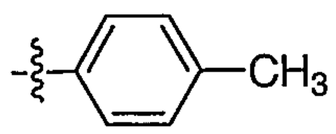
liii,



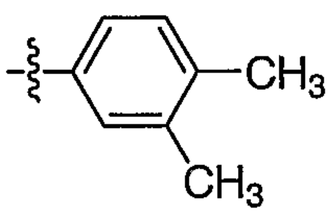
liv,



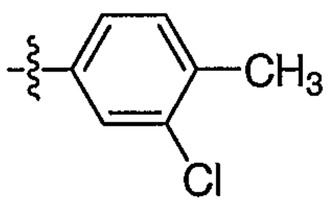
lv,



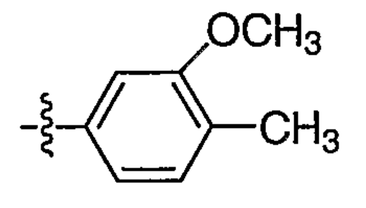
lvi,



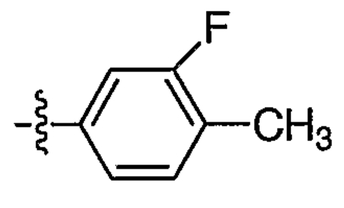
lvii,



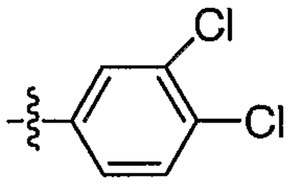
lviii,



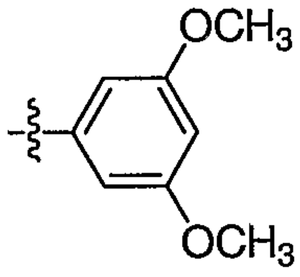
lvix,



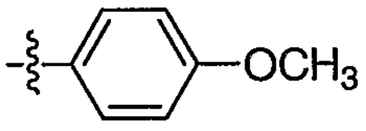
lx,



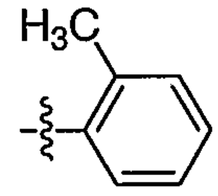
lxi,



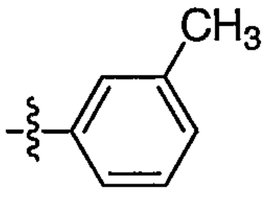
lxii,



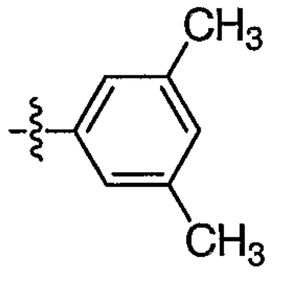
lxiii,



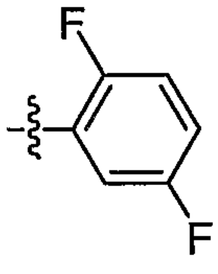
lxiv,



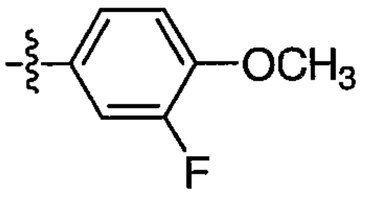
lxv,



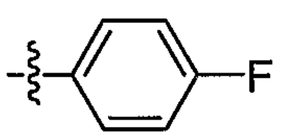
lxvi,



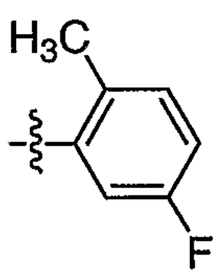
lxvii,



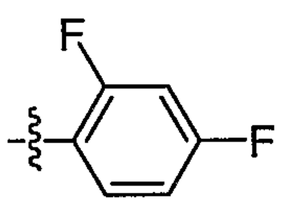
lxviii,



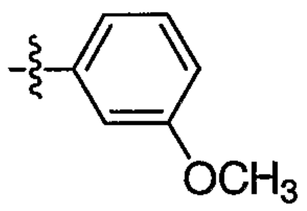
lxix,



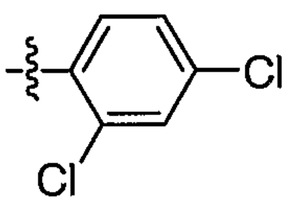
lxx,



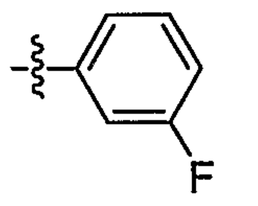
lxxi,



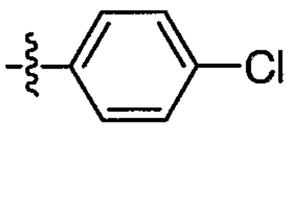
lxxii,



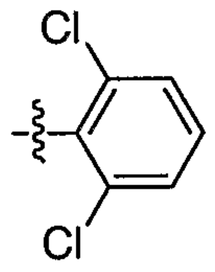
lxxiii



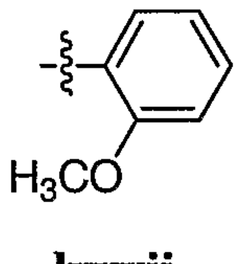
lxxiv,



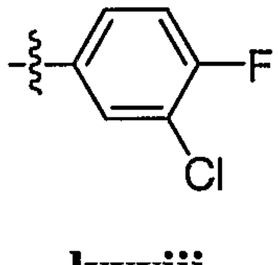
lxxv,



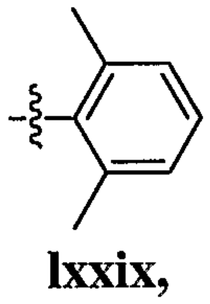
lxxvi,



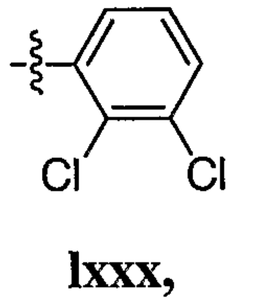
lxxvii,



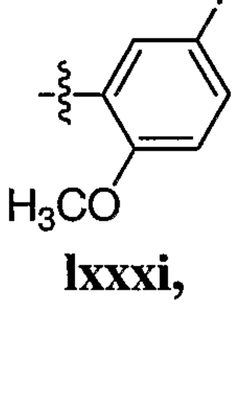
lxxviii,



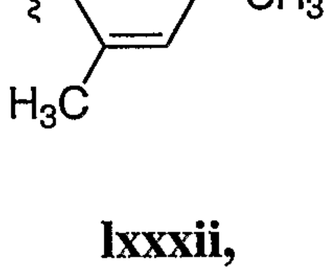
lxxix,



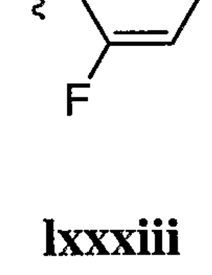
lxxx,



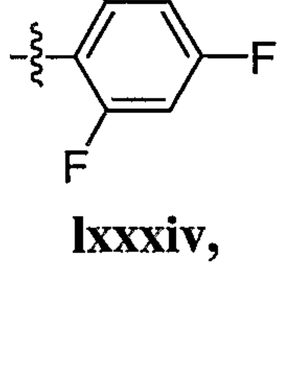
lxxxi,



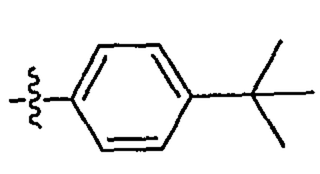
lxxxii,



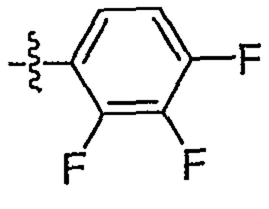
lxxxiii



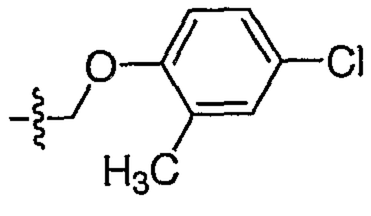
lxxxiv,



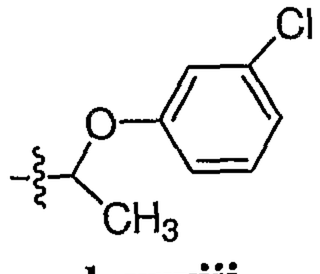
lxxxv



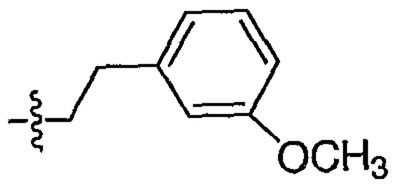
lxxxvi,



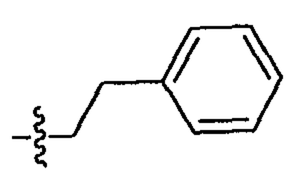
lxxxvii,



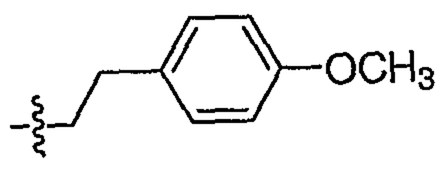
lxxxviii,



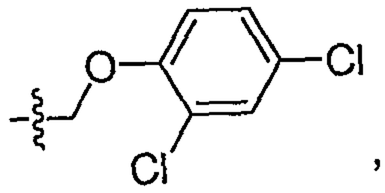
lxxxix,



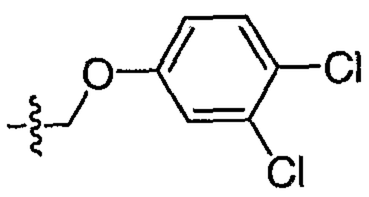
xc,



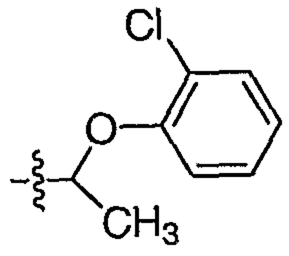
xci,



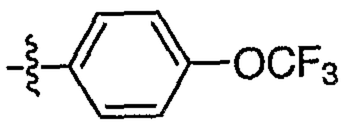
xcii,



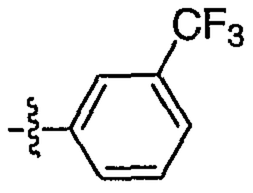
xciii,



xciv,



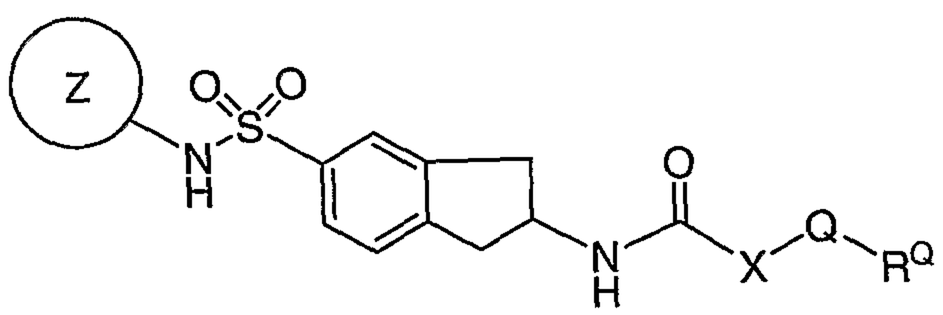
xcv,



or xcvi.

[00209] In another embodiment, R^Q is selected from pyrrolidin-1-yl, 3,3-difluoropyrrolidin-1-yl, piperidin-1-yl, 3-methyl-piperidin-1-yl, 4-methyl-piperidin-1-yl, 4,4-difluoropiperidin-1-yl, 4,5-dimethyl-4-morpholin-1-yl, indol-1-yl, 5-chloro-indol-1-yl, tetrahydro-isoquinolin-2-yl, 7-chloro-tetrahydro-isoquinolin-2-yl, 7-trifluoromethyl-tetrahydro-isoquinolin-2-yl, 7-fluoro-tetrahydro-isoquinolin-2-yl, 6-methyl-tetrahydro-isoquinolin-2-yl, 8-trifluoromethyl-quinolin-4-yl, pyridine-3-yl, or pyridine-4-yl.

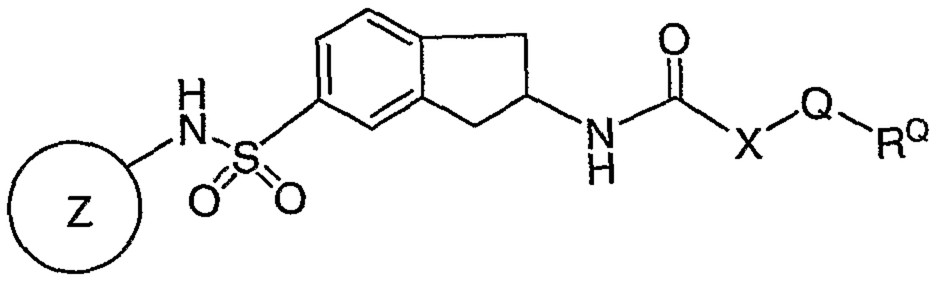
[00210] In one embodiment, the present invention provides compounds of formula I-A:



I-A;

wherein ring Z, X, Q, and R^Q are as defined above.

[00211] In one embodiment, the present invention provides compounds of formula I-B:

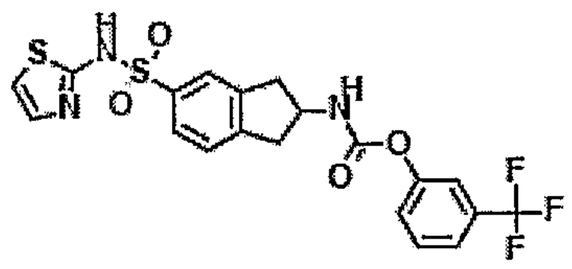
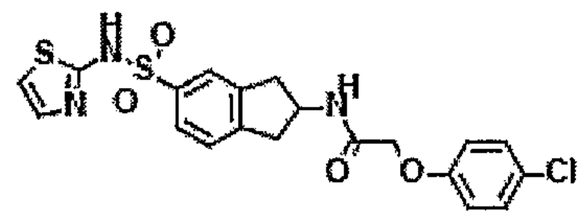
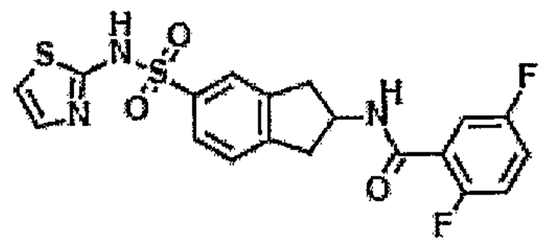
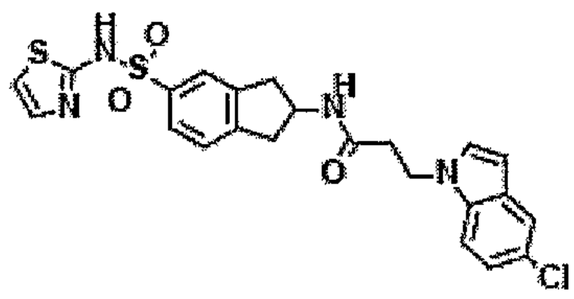
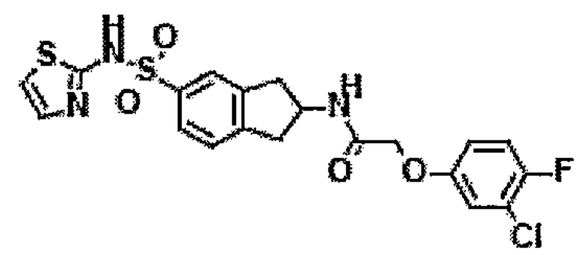
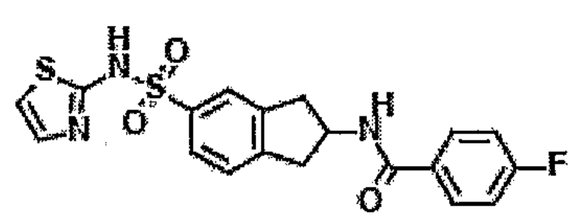
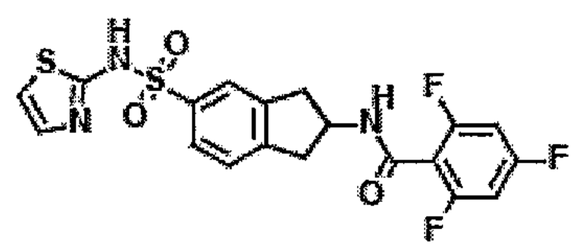
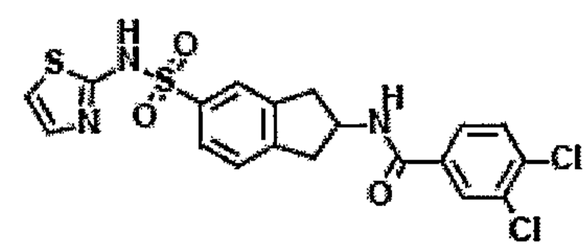
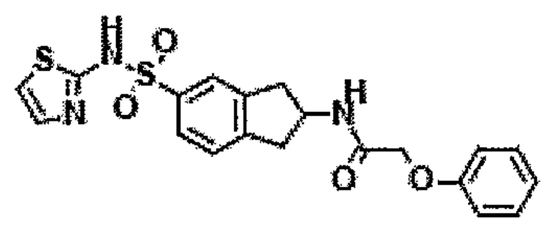
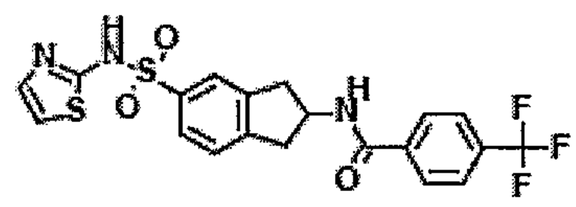
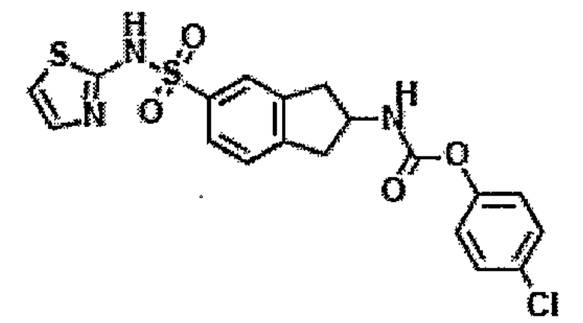
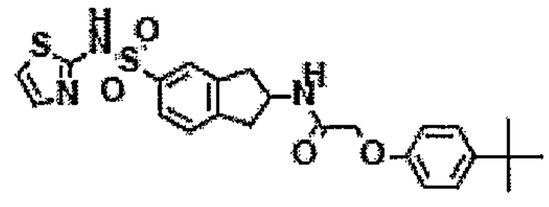


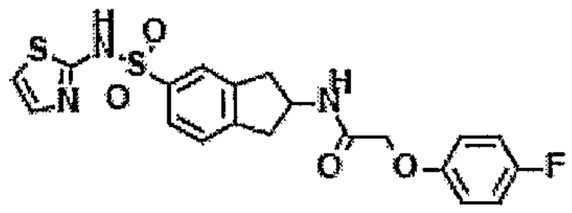
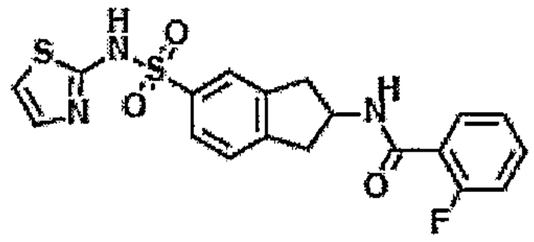
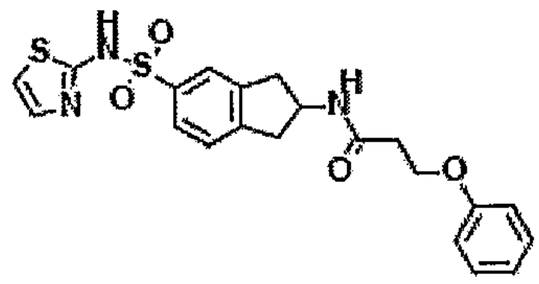
I-B;

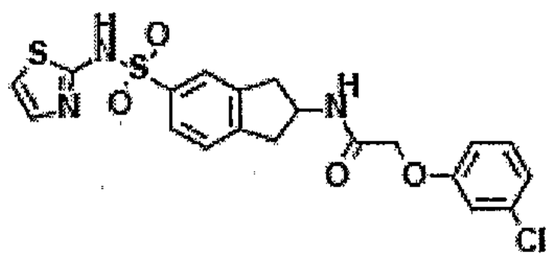
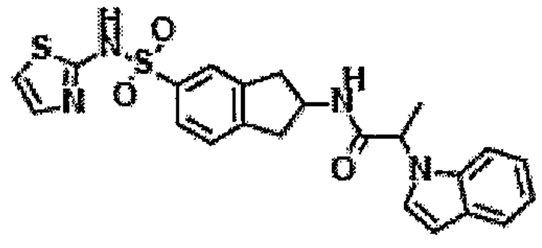
wherein ring Z, X, Q, and R^Q are as defined above.

[00212] In another embodiment, the present invention provides compounds of **Table 2** below.

[00213] Table 2

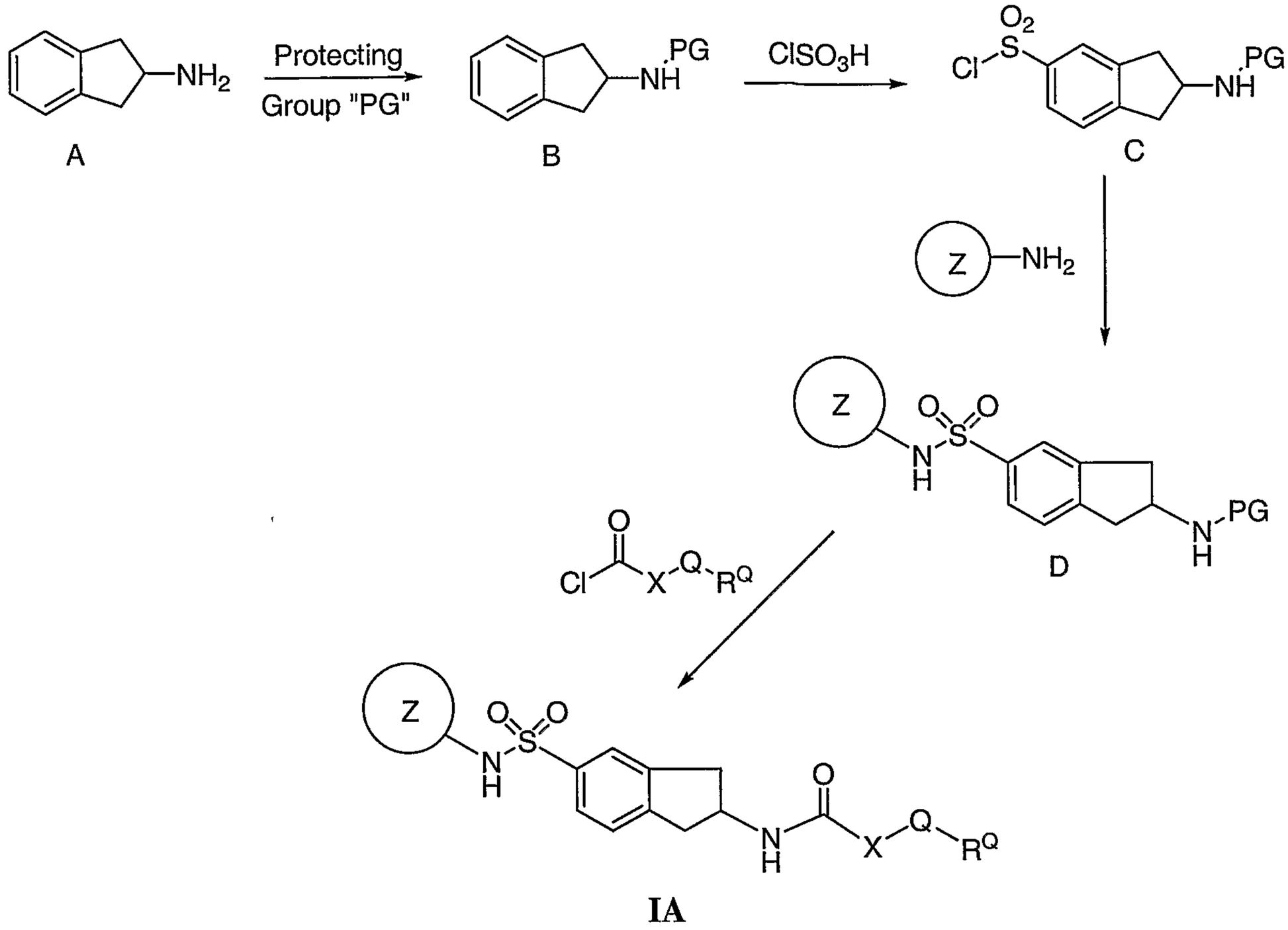
1	2	3
		
4	5	6
		
7	8	9
		
10	11	12
		

13	14	15
		

16	17
	

[00214] The compounds of the present invention may be prepared readily using methods known in the art. Illustrated below in **Scheme 1** is one such method for preparing the compounds of the present invention.

[00215] **Scheme 1**:



Uses, Formulation and Administration

Pharmaceutically acceptable compositions

[00216] As discussed above, the present invention provides compounds that are inhibitors of voltage-gated sodium ion channels and/or calcium channels, and thus the present compounds are useful for the treatment of diseases, disorders, and conditions including, but not limited to acute, chronic, neuropathic, or inflammatory pain, arthritis, migrane, cluster headaches, trigeminal neuralgia, herpetic neuralgia, general neuralgias, epilepsy or epilepsy conditions, neurodegenerative disorders, psychiatric disorders such as anxiety and depression, myotonia, arrythmia, movement disorders, neuroendocrine disorders, ataxia, multiple sclerosis, irritable bowel syndrome, and incontinence. Accordingly, in another aspect of the present invention, pharmaceutically acceptable compositions are provided, wherein these compositions comprise any of the compounds 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.

[00217] It will also be appreciated that certain of the compounds of present invention can exist in free form for treatment, or where appropriate, as a pharmaceutically acceptable derivative thereof. According to the present 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 patient in need is capable of providing, directly or indirectly, a compound as otherwise described herein, or a metabolite or residue thereof.

[00218] 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, 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 metabolite or residue thereof" means that a metabolite or residue thereof is also an inhibitor of a voltage-gated sodium ion channel or calcium channel.

[00219] 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. 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 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, 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 dispersable 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.

[00220] As described above, the pharmaceutically acceptable compositions of the present 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; 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; 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.

[00221] *Uses of Compounds and Pharmaceutically Acceptable Compositions*

[00222] In yet another aspect, a method for the treatment or lessening the severity of acute, chronic, neuropathic, or inflammatory pain, arthritis, migrane, cluster headaches, trigeminal neuralgia, herpetic neuralgia, general neuralgias, epilepsy or epilepsy conditions, neurodegenerative disorders, psychiatric disorders such as anxiety and depression, myotonia, arrythmia, 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 comprising administering an effective amount of a compound, or a pharmaceutically acceptable composition comprising a compound to a subject in need thereof. In certain embodiments, a method for the treatment or lessening the severity of acute, chronic, neuropathic, or inflammatory pain is provided comprising 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 embodiments, a method for the treatment or lessening the severity of severe or intractable pain, acute pain, postsurgical pain, back pain, tinnitis or cancer pain is provided comprising administering an effective amount of a compound or a pharmaceutically acceptable composition to a subject in need thereof.

[00223] In certain embodiments of the present invention an "effective amount" of the compound or pharmaceutically acceptable composition is that amount effective for treating or lessening the severity of one or more of acute, chronic, neuropathic, or inflammatory pain, arthritis, migrane, cluster headaches, trigeminal neuralgia, herpetic neuralgia, general neuralgias, epilepsy or epilepsy conditions, neurodegenerative disorders, psychiatric disorders such as anxiety and depression, myotonia, arrythmia, 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, tinnitis or cancer pain.

[00224] The compounds and compositions, according to the method of the present 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, chronic, neuropathic, or inflammatory pain, arthritis, migrane, cluster headaches, trigeminal neuralgia, herpetic neuralgia, general neuralgias, epilepsy or epilepsy conditions, neurodegenerative disorders, psychiatric disorders such as anxiety and depression, myotonia, arrythmia, 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, tinnitis 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 compounds of the invention are preferably formulated in dosage unit 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 patient to be treated. It will be understood, however, that the total daily usage of the compounds and compositions of the

present invention will be decided by the attending physician within the scope of sound medical judgment. The specific effective dose level for any particular patient 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 patient; the time of administration, route of administration, and rate of excretion of the specific compound employed; the duration 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 "patient", as used herein, means an animal, preferably a mammal, and most preferably a human.

[00225] The pharmaceutically acceptable compositions of this invention can be administered to humans and other animals orally, rectally, parenterally, intracisternally, intravaginally, intraperitoneally, topically (as by powders, ointments, or drops), bucally, 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 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.

[00226] 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 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, the oral compositions can also include adjuvants such as wetting agents, emulsifying and suspending agents, sweetening, flavoring, and perfuming agents.

[00227] 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 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 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.

[00228] 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 sterile injectable medium prior to use.

[00229] In order to prolong the effect of a compound of the present 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 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 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.

[00230] Compositions for rectal or vaginal administration are preferably 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.

[00231] 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, 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 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.

[00232] 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. 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 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 polethylene glycols and the like.

[00233] The active compounds 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 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 a 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 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.

[00234] Dosage forms for topical or transdermal administration of a compound 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 present invention 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 the compound in a polymer matrix or gel.

[00235] As described generally above, the compounds of the invention are useful as inhibitors of voltage-gated sodium ion channels or calcium channels, preferably N-type calcium channels. In one embodiment, the compounds and compositions of the invention are inhibitors of one or more of NaV1.1, NaV1.2, NaV1.3, NaV1.4, NaV1.5, NaV1.6, NaV1.7, NaV1.8, NaV1.9, or CaV2.2, and thus, without wishing to be bound by any particular theory, the compounds and compositions 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, NaV1.9, or CaV2.2 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, NaV1.9, or CaV2.2, 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" or a "CaV2.2-mediated condition or disorder". Accordingly, in another aspect, the present 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, NaV1.9, or CaV2.2 is implicated in the disease state.

[00236] The activity of a compound utilized in this invention as an inhibitor of NaV1.1, NaV1.2, NaV1.3, NaV1.4, NaV1.5, NaV1.6, NaV1.7, NaV1.8, NaV1.9, or CaV2.2 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.

[00237] In certain exemplary embodiments, compounds of the invention are useful as inhibitors of NaV1.3. In other embodiments, compounds of the invention are useful as inhibitors of NaV1.3 and CaV2.2. In still other embodiments, compounds of the invention are useful as inhibitors of CaV2.2.

[00238] It will also be appreciated that the compounds and pharmaceutically acceptable compositions of the present invention can be employed in combination therapies, that is, the compounds and pharmaceutically acceptable compositions 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 sa 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 Asprin, 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 (intraspinal infusion, neural blocade), 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.

[00239] 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.

[00240] The compounds 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 present invention, in another aspect, includes a composition for coating an implantable device comprising a compound of the present 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 present invention includes an implantable device coated with a composition comprising a compound of the present 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, polysaccarides, polyethylene glycol, phospholipids or combinations thereof to impart controlled release characteristics in the composition.

[00241] 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, NaV1.9, or CaV2.2 activity in a biological sample or a patient, which method comprises administering to the patient, 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.

[00242] Inhibition of one or more of NaV1.1, NaV1.2, NaV1.3, NaV1.4, NaV1.5, NaV1.6, NaV1.7, NaV1.8, NaV1.9, or CaV2.2 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.

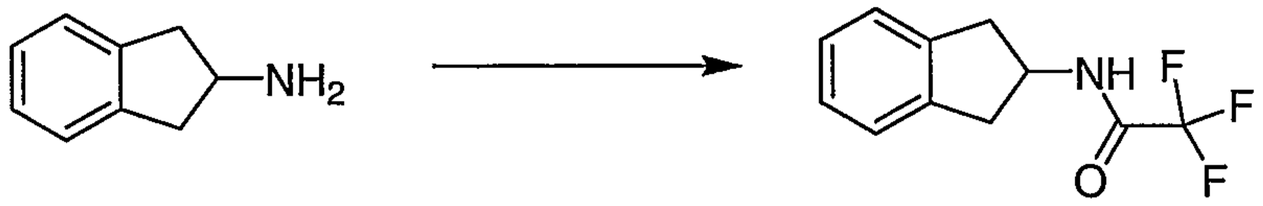
EXAMPLES

[00243] **General methods.** ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were obtained as solutions in deuteriochloroform ($CDCl_3$) 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□ C18 column. The LC/MS eluting system was 10-99% acetonitrile in H_2O with 0.035% v/v trifluoroacetic acid using a 4.5 minute linear gradient and a flow rate of 4.0 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), were from Aldrich Sure-Seal bottles kept under dry nitrogen. All reactions were stirred magnetically unless otherwise

noted. Unless specified otherwise, all temperatures refer to internal reaction temperatures.

[00244] Example 1

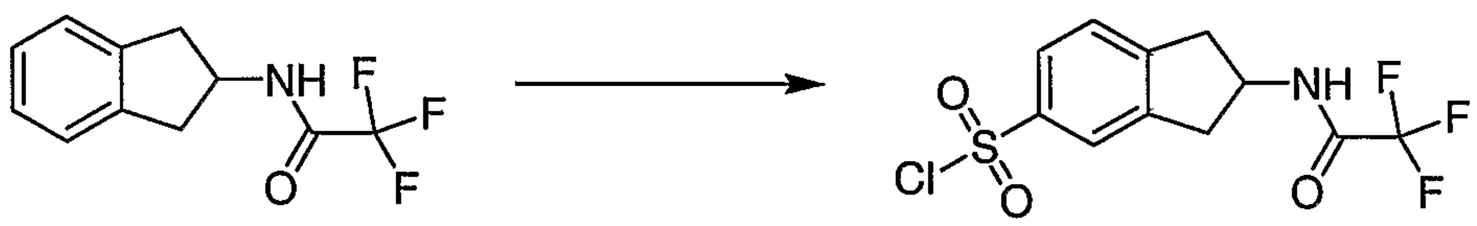
[00245] **2,2,2-trifluoro-N-(2,3-dihydro-1H-inden-2-yl)acetamide**



Under N_2 at -75 °C, trifluoroacetic acid was added to a stirring solution of 2,3-dihydro-1H-inden-2-amine (HCl salt, 8.0 g, 47.2 mmol), Et_3N (14.9 ml, 106.7 mmol) and THF (160 ml). After the solution was allowed to warm up to rt, it was partitioned between H_2O and DCM. The organic layer was dried over $MgSO_4$ and evaporated *in vacuo*. The residue was triturated with hexanes: Et_2O (1:1) to obtain the product as a white solid (8.9 g, 82 % yield). ^{1}H-NMR (400 MHz, CDCl3) δ 7.28-7.20 (m, 4H), 6.50 (s, 1H), 4.81-4.74 (m, 1H), 3.38 (dd, J = 16.4, 7.1 Hz, 2H), 2.89 (dd, J = 16.3, 4.2 Hz, 2H).

[00246] Example 2

[00247] **2-(2,2,2-trifluoroacetamido)-2,3-dihydro-1H-indene-5-sulfonyl chloride**

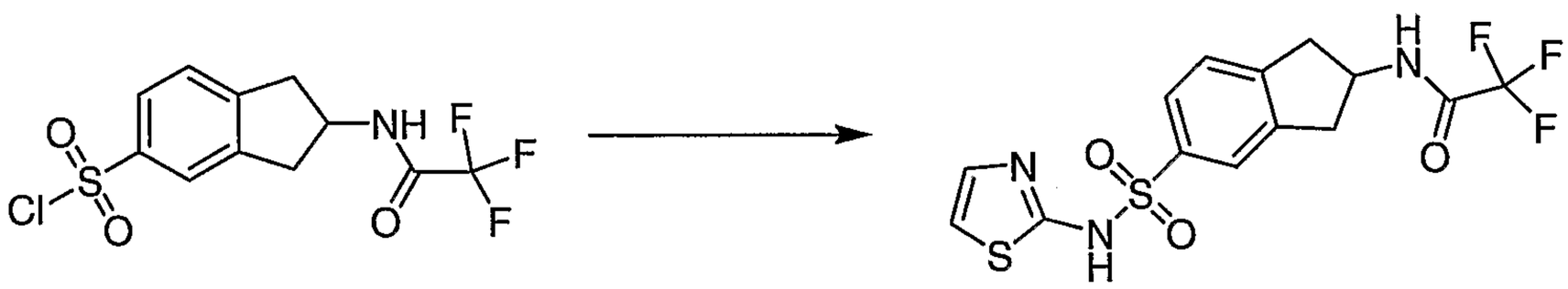


After cooling chlorosulfonic acid (3.0 ml) to –78 °C under nitrogen, 2,2,2-trifluoro-N-(2,3-dihydro-1H-inden-2-yl)acetamide (500.0 mg, 2.2 mmol) was added and then allowed to warm up to rt. The solution was poured into an ice-water mixture (100.0 ml), followed by an extraction with EtOAc. The organic layer was dried over $MgSO_4$ and evaporated *in vacuo*. The residue was triturated with Et_2O to obtain the product as a white solid (510.0 mg, 71 % yield). ^{1}H-NMR (400 MHz, DMSO-d6) δ 7.93-7.91 (m, 2H), 7.51-

7.49 (m, 1H), 6.50 (s, 1H), 4.91-4.83 (m, 1H), 3.52 (dd, J = 16.8, 7.3 Hz, 2H), 3.05 (dd, J = 17.0, 4.8 Hz, 2H).

[00248] Example 3

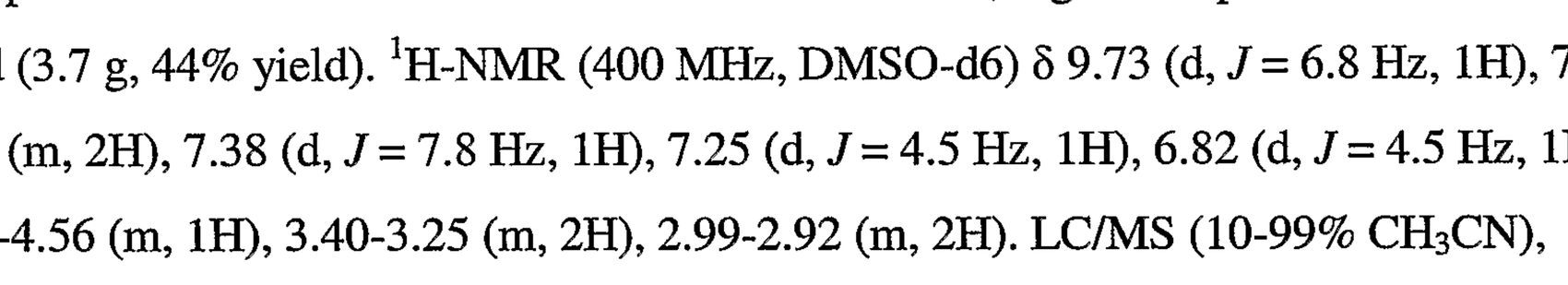
[00249] **2,2,2-Trifluoro-N-[5-(thiazol-2-ylsulfamoyl)-indan-2-yl]-acetamide**



2-(2,2,2-trifluoroacetamido)-2,3-dihydro-1H-indene-5-sulfonyl chloride (7.0 g, 21.4 mmol) and 2-aminothiazole (2.2 g, 21.4 mmol) were stirred in pyridine at rt for 2 h. The solution was partitioned between 1N HCl and DCM. The organic layer was dried over $MgSO_4$ and evaporated *in vacuo*. After dissolving the residue in DCM: Et_2O (4:1), a precipitate formed which was filtered and vacuum dried to give the product as a white solid (3.7 g, 44% yield). ^{1}H-NMR (400 MHz, DMSO-d6) δ 9.73 (d, J = 6.8 Hz, 1H), 7.65-7.62 (m, 2H), 7.38 (d, J = 7.8 Hz, 1H), 7.25 (d, J = 4.5 Hz, 1H), 6.82 (d, J = 4.5 Hz, 1H), 4.64-4.56 (m, 1H), 3.40-3.25 (m, 2H), 2.99-2.92 (m, 2H). LC/MS (10-99% CH_3CN), M/Z: M+1 *obs* = 392.1; t_R = 2.64 min.

[00250] Example 3

[00251] **2-Amino-indan-5-sulfonic acid thiazol-2-ylamide**

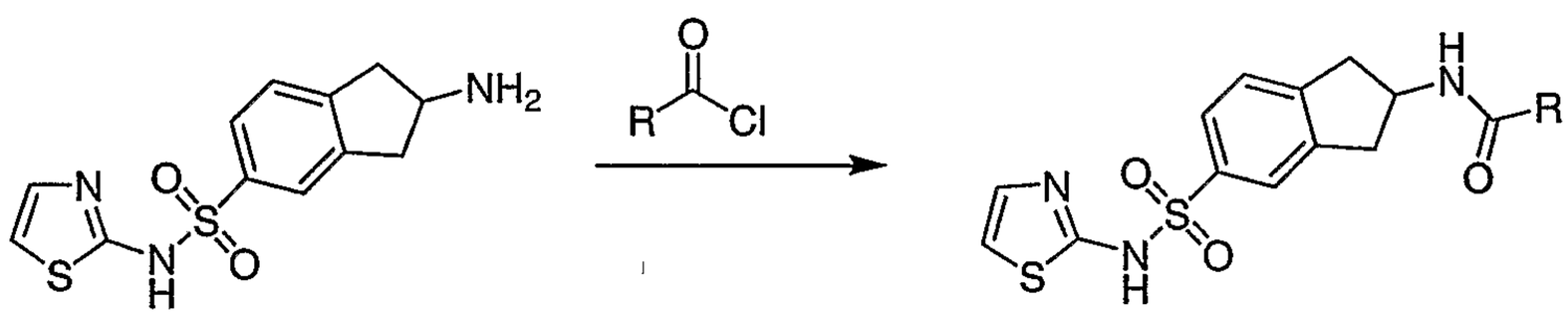


A solution of 2,2,2-Trifluoro-N-[5-(thiazol-2-ylsulfamoyl)-indan-2-yl]-acetamide (1.0 g, 2.6 mmol), KOH (430.0 mg, 7.7 mmol), EtOH (10.0 ml) and H_2O (2.0 ml) was stirred at rt for 3 h. While adding AcOH dropwise to obtain a pH of 7, a

precipitate formed quickly which was filtered, washed with MeOH, and dried under vacuum to give product as a white solid (710.0 mg, 94 % yield). ^{1}H-NMR (400 MHz, DMSO-d6) δ 7.60 (d, *J* = 4.7 Hz, 2H), 7.27-7.25 (m, 1H), 6.94 (d, *J* = 3.9 Hz, 1H), 6.48 (d, *J* = 3.9 Hz, 1H), 4.02-3.96 (m, 1H), 3.27-3.20 (m, 2H), 2.92-2.86 (m, 2H). LC/MS (10-99% CH_3CN), M/Z: M+1 *obs* = 296.2; t_R = 0.55 min.

[00252] Example 4

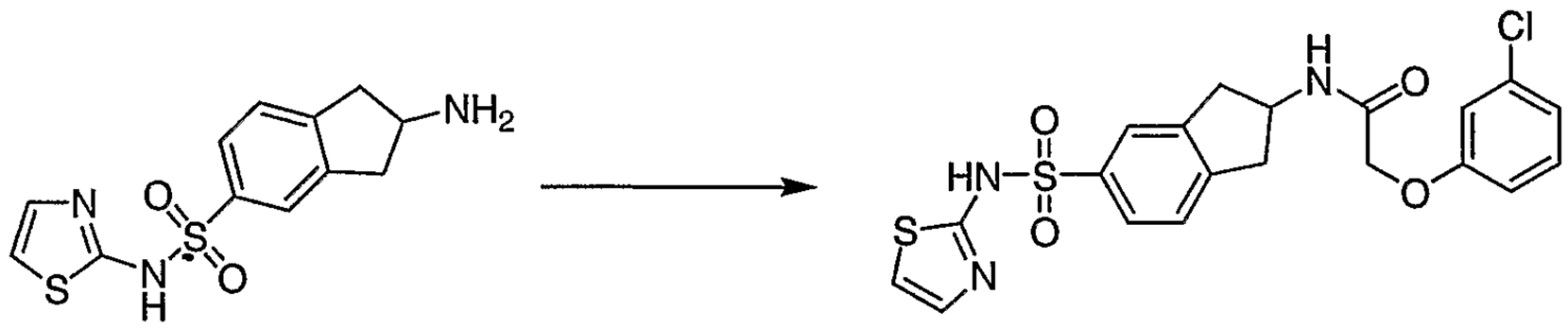
[00253] **General procedure 1:**



Under N_2 at –78 °C, the acid chloride (0.17 mmol) was added to a solution of 2-Amino-indan-5-sulfonic acid thiazol-2-ylamide (50 mg, 0.17 mmol), Et_3N (47 µl, 0.33 mmol) and DCM (0.20 ml). The solution was allowed to warm up to rt over a period of 15 min. The reaction mixture was purified with Gilson preparative HPLC (10-99 % CH_3CN-H_2O) to give the desired product.

[00254] Example 5

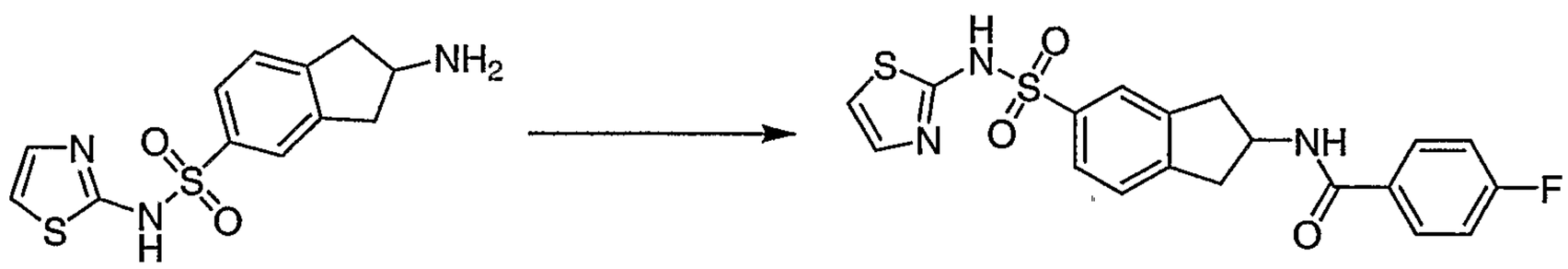
[00255] **2-(3-Chloro-phenoxy)-N-[5-(thiazol-2-ylsulfamoyl)-indan-2-yl]-acetamide**



Synthesized according to **General procedure 1.** LC/MS (10-99% CH_3CN), M/Z: M+1 *obs* = 464.3; t_R = 2.98 min.

[00256] Example 6

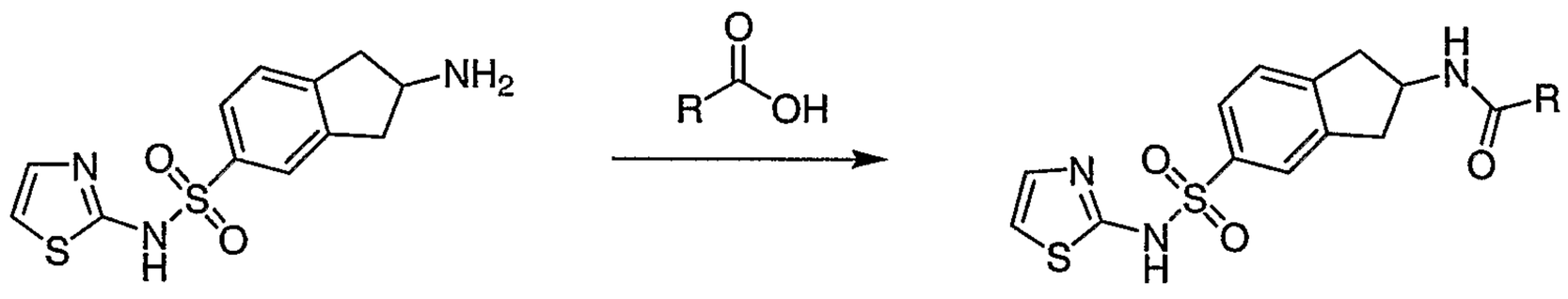
[00257] **4-Fluoro-N-[5-(thiazol-2-ylsulfamoyl)-indan-2-yl]-benzamide**



Synthesized according to **General procedure 1.** LC/MS (10-99% CH_3CN), M/Z: M+1 *obs* = 418.2; t_R = 2.67 min.

[00258] Example 7

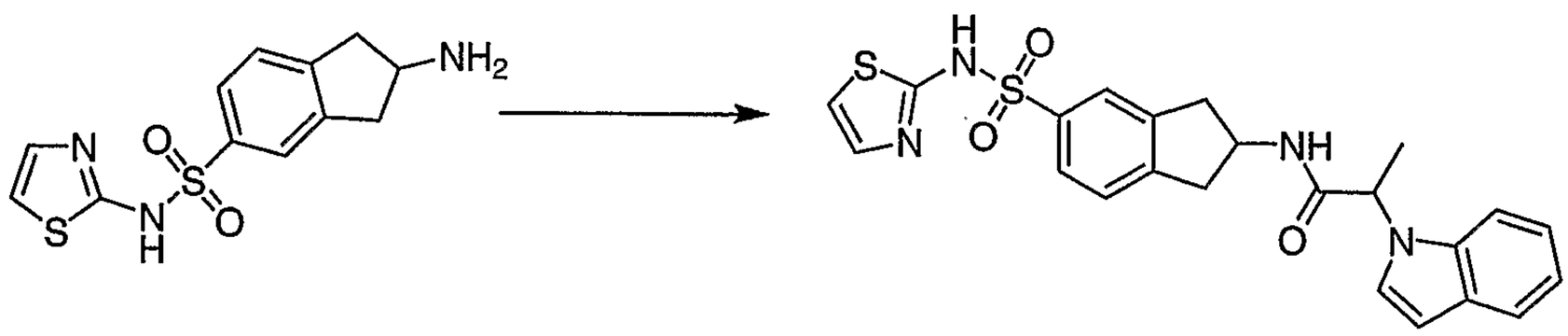
[00259] **General procedure 2:**



The carboxylic acid (0.17 mmol), 2-Amino-indan-5-sulfonic acid thiazol-2-ylamide (50 mg, 0.17 mmol), BOP (75 mg, 0.17 mmol), Et_3N (25 μl) and DMF (0.3 ml) were stirred at rt for 19 h. The reaction mixture was purified by Gilson preparative HPLC (10-99 % CH_3CN-H_2O) to obtain product.

[00260] Example 8

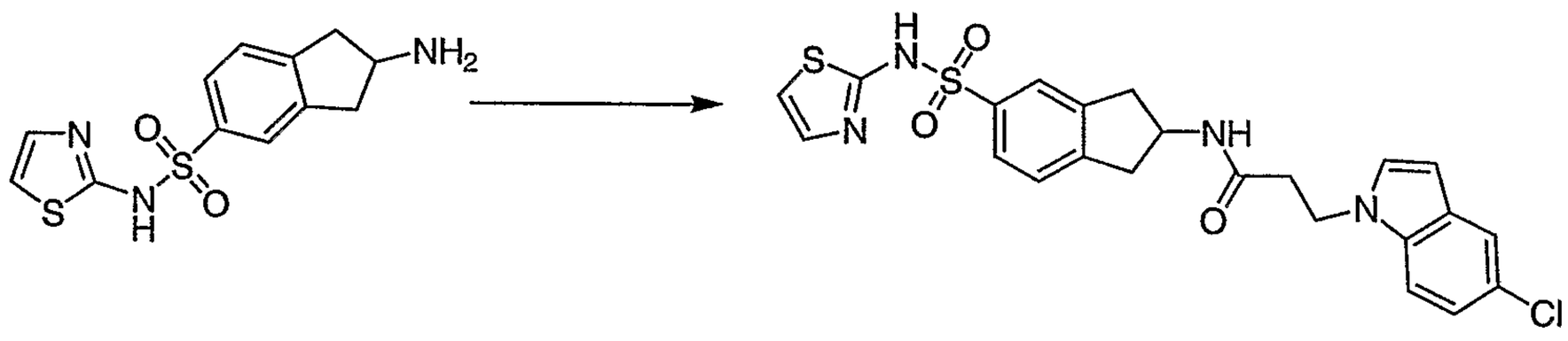
[00261] **2-Indol-1-yl-N-[5-(thiazol-2-ylsulfamoyl)-indan-2-yl]-propionamide**



Synthesized according to **general procedure 2.** LC/MS (10-99% CH_3CN), M/Z: M+1 *obs* = 467; t_R = 2.92 min.

[00262] Example 9

[00263] **3-(5-Chloro-indol-1-yl)-N-[5-(thiazol-2-ylsulfamoyl)-indan-2-yl]-propionamide**



Synthesized according to **General procedure 2.** LC/MS (10-99% CH_3CN), M/Z: M+1 *obs* = 501.2; t_R = 2.99 min.

[00264] Analytical data for exemplary compounds of the present invention are shown below in Table 3.

[00265] Table 3

Cmpd No.	LC-MS M+1	LC-RT min
1	484.3	3.22
2	464.3	2.99
3	436.1	2.78
4	501.2	2.99
5	482.3	3.03
6	418.2	2.67
7	454.3	2.75
8	468.1	3.16
9	430.2	2.7
10	468.1	3.06
11	450.1	3.11
12	486.3	3.31
13	448.3	2.83
14	418.3	2.67
15	444.3	2.84
16	464.3	2.98
17	467.	2.92

ASSAYS FOR DETECTING AND MEASURING NaV INHIBITION PROPERTIES OF COMPOUND

Optical methods for assaying NaV inhibition properties of compounds:

[00266] Compounds of the invention are useful as antagonists of voltage-gated sodium ion channels. Antagonist properties of test compounds were assessed as follows. Cells expressing the NaV of interest were placed into microtiter plates. After an incubation period, the cells were stained with fluorescent dyes sensitive to the transmembrane potential. The test compounds were added to the microtiter plate. The cells were stimulated with either a chemical or electrical means to evoke a NaV dependent membrane potential change from unblocked channels, which was detected and measured

with trans-membrane potential-sensitive dyes. Antagonists were detected as a decreased membrane potential response to the stimulus. The optical membrane potential assay utilized voltage-sensitive FRET sensors described by Gonzalez and Tsien (See, Gonzalez, J. E. and R. Y. Tsien (1995) "Voltage sensing by fluorescence resonance energy transfer in single cells" Biophys J **69**(4): 1272-80, and Gonzalez, J. E. and R. Y. Tsien (1997) "Improved indicators of cell membrane potential that use fluorescence resonance energy transfer" Chem Biol **4**(4): 269-77) in combination with instrumentation for measuring fluorescence changes such as the Voltage/Ion Probe Reader (VIPR®) (See, Gonzalez, J. E., K. Oades, et al. (1999) "Cell-based assays and instrumentation for screening ion-channel targets" Drug Discov Today **4**(9): 431-439).

B) VIPR® optical membrane potential assay method with chemical stimulation

Cell Handling and Dye Loading

[00267] 24 hours before the assay on VIPR, CHO cells endogenously expressing a NaV1.2 type voltage-gated NaV are seeded in 96-well poly-lysine coated plates at 60,000 cells per well. Other subtypes are performed in an analogous mode in a cell line expressing the NaV of interest.

1) On the day of the assay, medium is aspirated and cells are washed twice with 225 µL of Bath Solution #2 (BS#2).
2) A 15 uM CC2-DMPE solution is prepared by mixing 5 mM coumarin stock solution with 10% Pluronic 127 1:1 and then dissolving the mix in the appropriate volume of BS#2.
3) After bath solution is removed from the 96-well plates, the cells are loaded with 80 µL of the CC2-DMPE solution. Plates are incubated in the dark for 30 minutes at room temperature.
4) While the cells are being stained with coumarin, a 15 µL oxonol solution in BS#2 is prepared. In addition to $DiSBAC_2(3)$, this solution should contain 0.75 mM ABSC1 and 30 µL veratridine (prepared from 10 mM EtOH stock, Sigma #V-5754).
5) After 30 minutes, CC2-DMPE is removed and the cells are washed twice with 225 µL of BS#2. As before, the residual volume should be 40 µL.

6) Upon removing the bath, the cells are loaded with 80 μL of the DiSBAC$_2$(3) solution, after which test compound, dissolved in DMSO, is added to achieve the desired test concentration to each well from the drug addition plate and mixed thoroughly. The volume in the well should be roughly 121 μL. The cells are then incubated for 20-30 minutes.
7) Once the incubation is complete, the cells are ready to be assayed on VIPR® with a sodium addback protocol. 120 μL of Bath solution #1 is added to stimulate the NaV dependent depolarization. 200 μL tetracaine was used as an antagonist positive control for block of the NaV channel.

Analysis of VIPR® Data:

[00268] 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 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:

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

[00269] 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 $R = R_f/R_i$ is then calculated. For the Na^+ addback analysis time windows, baseline is 2-7 sec and final response is sampled at 15-24 sec.

[00270] 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

Solutions [mM]

Bath Solution #1: NaOH	NaCl 160, KCl 4.5, $CaCl_2$ 2, $MgCl_2$ 1, HEPES 10, pH 7.4 with
Bath Solution #2	TMA-Cl 160, $CaCl_2$ 0.1, $MgCl_2$ 1, HEPES 10, pH 7.4 with KOH (final K concentration ~ 5 mM)
CC2-DMPE:	prepared as a 5 mM stock solution in DMSO and stored at -20°C
$DiSBAC_2(3)$:	prepared as a 12 mM stock in DMSO and stored at -20°C
ABSC1:	prepared as a 200 mM stock in distilled H_2O and stored at room temperature

Cell Culture

[00271] **[0220]** CHO cells are grown in DMEM (Dulbecco's Modified Eagle Medium; GibcoBRL #10569-010) 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% CO_2, to 100% confluence. They are usually split by trypsinization 1:10 or 1:20, depending on scheduling needs, and grown for 2-3 days before the next split.

C) VIPR® optical membrane potential assay method with electrical stimulation

[00272] The following is an example of how NaV1.3 inhibition activity is measured using the optical membrane potential method#2. Other subtypes are performed in an analogous mode in a cell line expressing the NaV of interest.

[00273] HEK293 cells stably expressing NaV1.3 are plated into 96-well

microtiter plates. After an appropriate incubation period, the cells are stained with the voltage sensitive dyes CC2-DMPE/DiSBAC2(3) as follows.

Reagents:

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

10 mM $DiSBAC_2(3)$ (Aurora #00-100-010) in dry DMSO

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

200 mM ABSC1 in H_20

Hank's Balanced Salt Solution (Hyclone #SH30268.02) supplemented with 10 mM HEPES (Gibco #15630-080)

Loading protocol:

[00274] 2X CC2-DMPE = 20 μM CC2-DMPE: 10 mM CC2-DMPE is vortexed with an equivalent volume of 10% pluronic, followed by vortexing in required amount of HBSS containing 10 mM HEPES. Each cell plate will require 5 mL of 2X CC2-DMPE. 50 μL of 2X CC2-DMPE is to wells containing washed cells, resulting in a 10 μM final staining concentration. The cells are stained for 30 minutes in the dark at RT.

[00275] 2X $DISBAC_2(3)$ with ABSC1 = 6μM $DISBAC_2(3)$ and 1 mM ABSC1: The required amount of 10 mM $DISBAC_2(3)$ is added to a 50 ml conical tube and mixed with 1 μL 10% pluronic for each mL of solution to be made and vortexed together. Then HBSS/HEPES is added to make up 2X solution. Finally, the ABSC1 is added .

[00276] The 2X $DiSBAC_2(3)$ solution can be used to solvate compound plates. Note that compound plates are made at 2X drug concentration. Wash stained plate again, leaving residual volume of 50 μL. Add 50 uL/well of the 2X $DiSBAC_2(3)$ w/ ABSC1. Stain for 30 minutes in the dark at RT.

[00277] The electrical stimulation instrument and methods of use are described in ION Channel Assay Methods PCT/US01/21652, herein incorporated by reference. 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 instrument passes user-programmed electrical stimulus protocols to cells within the wells of the microtiter plate.

Reagents

[00278] Assay buffer #1

140 mM NaCl, 4.5 mM KCl, 2 mM $CaCl_2$, 1 mM $MgCl_2$, 10 mM HEPES, 10 mM glucose, pH 7.40, 330 mOsm

Pluronic stock (1000X): 100 mg/mL pluronic 127 in dry DMSO
Oxonol stock (3333X): 10 mM $DiSBAC_2(3)$ in dry DMSO
Coumarin stock (1000X): 10 mM CC2-DMPE in dry DMSO
ABSC1 stock (400X): 200 mM ABSC1 in water

Assay Protocol

1. Insert or use electrodes into each well to be assayed.
2. Use the current-controlled amplifier to deliver stimulation wave pulses for 3 s. Two seconds of pre-stimulus recording are performed to obtain the un-stimulated intensities. Five seconds of post-stimulation recording are performed to examine the relaxation to the resting state.

Data Analysis

[00279] 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

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:

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

[00280] 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 $R = R_f/R_i$ is then calculated.

[00281] 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

[00282] 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.

VOLTAGE-CLAMP assay in DRG neurons

[00283] TTX-resistant sodium currents were recorded from DRG somata using the whole-cell variation of the patch clamp technique. Recordings were made at room temperature (~22o C) with thick walled borosilicate glass electrodes (WPI; resistance 3-4 MΩ) using an Axopatch 200B amplifier (Axon Instruments). After establishing the whole-cell configuration, approximately 15 minutes were allowed for the pipette solution to equilibrate within the cell before beginning recording. Currents were lowpass filtered between 2-5 kHz and digitally sampled at 10 kHz. Series resistance was compensated 60-70% and was monitored continuously throughout the experiment. The liquid junction potential (-7 mV) between the intracellular pipette solution and the external recording solution was not accounted for in the data analysis. Test solutions were applied to the cells with a gravity driven fast perfusion system (SF-77; Warner Instruments).

[00284] Dose-response relationships were determined in voltage clamp mode by repeatedly depolarizing the cell from the experiment specific holding potential to a test potential of +10mV once every 60 seconds. Blocking effects were allowed to plateau before proceeding to the next test concentration.

Solutions

[00285] Intracellular solution (in mM): Cs-F (130), NaCl (10), MgCl2 (1), EGTA (1.5), CaCl2 (0.1), HEPES (10), glucose (2), pH = 7.42, 290 mOsm.

[00286] Extracellular solution (in mM): NaCl (138), CaCl2 (1.26), KCl (5.33), KH2PO4 (0.44), MgCl2 (0.5), MgSO4 (0.41), NaHCO3 (4), Na2HPO4 (0.3), glucose (5.6), HEPES (10), CdCl2 (0.4), NiCl2 (0.1), TTX (0.25 x 10^{-3}).

CURRENT-CLAMP assay for NaV channel inhibition activity of compounds

[00287] Cells were current-clamped in whole-cell configuration with a Multiplamp 700A amplifier (Axon Inst). Borosilicate pipettes (4-5 MOhm) were filled

with (in mM):150 K-gluconate, 10 NaCl, 0.1 EGTA, 10 Hepes, 2 $MgCl_2$, (buffered to pH 7.34 with KOH). Cells were bathed in (in mM): 140 NaCl, 3 KCl, 1 MgCl , 1 CaCl , and 10 Hepes). Pipette potential was zeroed before seal formation; liquid junction potentials were not corrected during acquisition. Recordings were made at room temperature.

[00288] Activity data for selected compounds against NaV 1.3 channel is displayed below in Table 4. The activity range is as follows:

"+++" < 2 μM < "++" 5 μM < "+"

Table 4.

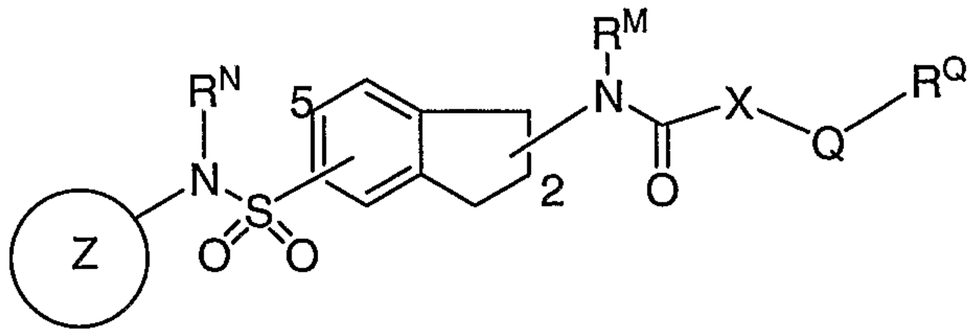
Cmpd No.	IC50
1	+++
2	+++
3	+
4	+++
5	+++
6	+
7	+
8	++
9	+

Cmpd No.	IC50
10	+
11	+++
12	+++
13	++
14	+
15	+
16	+++
17	++

[00289] 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.

CLAIMS

1. A compound of formula **I:**



(I);

or a pharmaceutically acceptable salt thereof;

wherein:

ring Z is a 5-7 membered unsaturated or aromatic ring having at least one ring heteroatom selected from O, S, N, or NH, wherein and said ring Z is optionally substituted with z occurrence of R^Z;

z is 0-4;

R^Z is selected from R^1, R^2, R^3, R^4, or R^5;

X is a bond, O, NR^2, or $C(R^2)_2$;

Q is a bond or a C1-C6 straight or branched alkylidine chain, wherein up to two non-adjacent methylene units of Q are optionally and independently replaced by –CO-, -CS-, -COCO-, -$CONR^2$-, -$CONR^2NR^2$-, -CO_2-, -OCO-, -NR^2CO_2-, -O-, -NR^2CONR^2-, -$OCONR^2$-, -NR^2NR^2, -NR^2NR^2CO-, -NR^2CO-, -S-, -SO, -SO_2-, -NR^2-, -SO_2NR^2-, NR^2SO_2-, -$NR^2SO_2NR^2$-, or a spirocycloalkylene moeity;

R^Q is a C_{1-6} aliphatic group, a 3-8-membered saturated, partially unsaturated, or fully unsaturated monocyclic ring having 0-3 heteroatoms independently selected from O, S, N, or NH, or an 8-12 membered saturated, partially unsaturated, or fully unsaturated bicyclic ring system having 0-5 heteroatoms independently selected from O, S, N, or NH;

wherein R^Q is optionally substituted with up to 5 substituents selected from R^1, R^2, R^3, R^4, or R^5;

R^M and R^N are independently R^2;

R^1 is oxo, $=NN(R^6)_2$, $=NN(R^7)_2$, $=NN(R^6R^7)$, R^6 or $(CH_2)_n$-Y;

n is 0, 1 or 2;

Y is halo, CN, NO_2, CF_3, OCF_3, OH, SR^6, $S(O)R^6$, SO_2R^6, NH_2, NHR^6, $N(R^6)_2$, NR^6R^8, COOH, $COOR^6$ or OR^6; or

two R^1 on adjacent ring atoms, taken together, form 1,2-methylenedioxy or 1,2-ethylenedioxy;

R^2 is hydrogen or C1-C6 aliphatic, wherein each R^2 is optionally substituted with up to 2 substituents independently selected from R^1, R^4, or R^5;

R^3 is a C3-C8 cycloaliphatic, C6-C10 aryl, C3-C8 heterocyclic, or C5-C10 heteroaryl ring, optionally substituted with up to 3 substituents, independently selected from R^1, R^2, R^4 or R^5;

R^4 is OR^5, OR^6, $OC(O)R^6$, $OC(O)R^5$, $OC(O)OR^6$, $OC(O)OR^5$, $OC(O)N(R^6)_2$, $OC(O)N(R^5)_2$, $OC(O)N(R^6R^5)$, $OP(O)(OR^6)_2$, $OP(O)(OR^5)_2$, $OP(O)(OR^6)(OR^5)$, SR^6, SR^5, $S(O)R^6$, $S(O)R^5$, SO_2R^6, SO_2R^5, $SO_2N(R^6)_2$, $SO_2N(R^5)_2$, $SO_2NR^5R^6$, SO_3R^6, SO_3R^5, $C(O)R^5$, $C(O)OR^5$, $C(O)R^6$, $C(O)OR^6$, $C(O)N(R^6)_2$, $C(O)N(R^5)_2$, $C(O)N(R^5R^6)$, $C(O)N(OR^6)R^6$, $C(O)N(OR^5)R^6$, $C(O)N(OR^6)R^5$, $C(O)N(OR^5)R^5$, $C(NOR^6)R^6$, $C(NOR^6)R^5$, $C(NOR^5)R^6$, $C(NOR^5)R^5$, $N(R^6)_2$, $N(R^5)_2$, $N(R^5R^6)$, $NR^5C(O)R^5$, $NR^6C(O)R^6$, $NR^6C(O)R^5$, $NR^6C(O)OR^6$, $NR^5C(O)OR^6$, $NR^6C(O)OR^5$, $NR^5C(O)OR^5$, $NR^6C(O)N(R^6)_2$, $NR^6C(O)NR^5R^6$, $NR^6C(O)N(R^5)_2$, $NR^5C(O)N(R^6)_2$, $NR^5C(O)NR^5R^6$, $NR^5C(O)N(R^5)_2$, $NR^6SO_2R^6$, $NR^6SO_2R^5$, $NR^5SO_2R^5$, $NR^6SO_2N(R^6)_2$, $NR^6SO_2NR^5R^6$, $NR^6SO_2N(R^5)_2$, $NR^5SO_2NR^5R^6$, $NR^5SO_2N(R^5)_2$, $N(OR^6)R^6$, $N(OR^6)R^5$, $N(OR^5)R^5$, $N(OR^5)R^6$, $P(O)(OR^6)N(R^6)_2$, $P(O)(OR^6)N(R^5R^6)$, $P(O)(OR^6)N(R^5)_2$, $P(O)(OR^5)N(R^5R^6)$, $P(O)(OR^5)N(R^6)_2$, $P(O)(OR^5)N(R^5)_2$, $P(O)(OR^6)_2$, $P(O)(OR^5)_2$, or $P(O)(OR^6)(OR^5)$;

R^5 is a C3-C8 cycloaliphatic, C6-C10 aryl, C3-C8 heterocyclic, or C5-C10 heteroaryl ring, optionally substituted with up to 3 R^1 substituents;

R^6 is H or C1-C6 aliphatic, wherein R^6 is optionally substituted with a R^7 substituent;

R^7 is a C3-C8 cycloaliphatic, C6-C10 aryl, C3-C8 heterocyclic, or C5-C10 heteroaryl ring, and each R^7 is optionally substituted with up to 2 substituents independently chosen from H, C1-C6 aliphatic, or $(CH_2)_m$-Z' wherein m is 0-2;

Z' is selected from halo, CN, NO_2, $C(halo)_3$, $CH(halo)_2$, $CH_2(halo)$, -$OC(halo)_3$, -$OCH(halo)_2$, -$OCH_2(halo)$,OH, S-(C1-C6) aliphatic, S(O)-(C1-C6) aliphatic, SO_2-(C1-C6)aliphatic, NH_2, NH-(C1-C6)aliphatic, N((C1-C6)aliphatic)$_2$, N((C1-C6)aliphatic)R^8, COOH, C(O)O(-(C1-C6)aliphatic), or O-(C1-C6)aliphatic; and

R^8 is acetyl, C6-C10 aryl sulfonyl, or C1-C6 alkyl sulfonyl;

provided that:

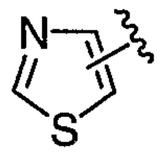
(i) when ring Z is an optionally substituted pyrimidin-2-yl, the sulfonyl group is attached at the 5-position and the $N(R^2)C(O)$ group is attached at the 2-position, R^2 is H, and X and Q each is a bond, then R^Q is not an optionally substituted phenyl or 6-chloro-quinolin-8-yl, fluoren-9-ylethyl, fluoren-9-ylmethyl, indolin-1-yl, cyclohexyl, (phenylthio)methyl, 3-methoxy-thiophen-2-yl, furan-2-yl, (phenoxy)methyl, 3-chloro-thiophen-2-yl, (optionally substituted phenyl)ethyl, or butyl;

(ii) when ring Z is an optionally substituted pyrimidin-2-yl, the sulfonyl group is attached at the 5-position and the $N(R^2)C(O)$ group is attached at the 2-position, R^2 is H, and X and Q each is a bond, then R^Q is not 2-methyl-5-chloro-2,3-dihydro-benzofuran-7-yl;

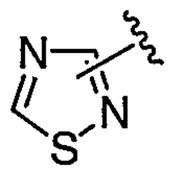
(iii) when ring Z is an optionally substituted pyrimidin-2-yl, the sulfonyl group is attached at the 5-position and the $N(R^2)C(O)$ group is attached at the 2-position, R^2 is H, and X is -O-, Q is a bond, then R^Q is not ethyl or benzyl; and

(iv) when ring Z is an optionally substituted pyrimidin-2-yl, the sulfonyl group is attached at the 5-position and the $N(R^2)C(O)$ group is attached at the 2-position, R^2 is H, and X is -N(Me)-, Q is a bond, then R^Q is not 2-methylphenyl.

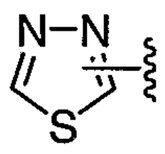
2. The compound according to claim 1, Z is selected from:



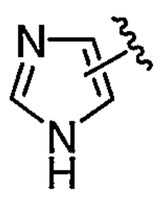
a-i,



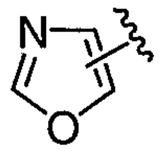
a-ii,



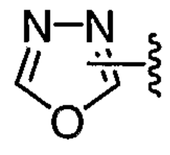
a-iii,



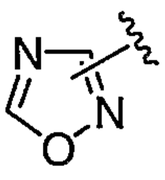
a-iv,



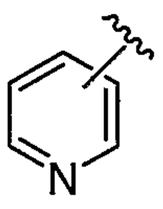
a-v,



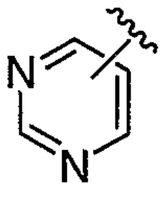
a-vi,



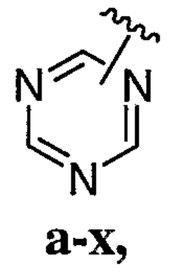
a-vii,



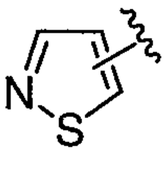
a-viii,



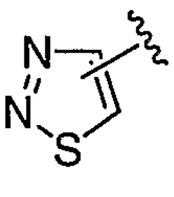
a-ix,



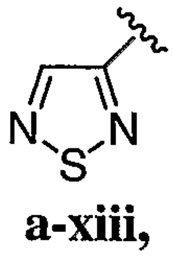
a-x,



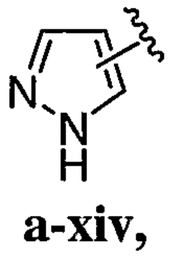
a-xi,



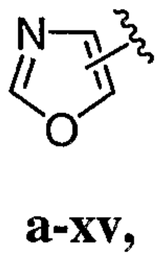
a-xii,



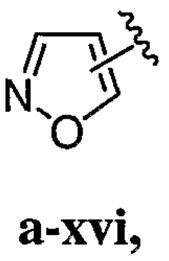
a-xiii,



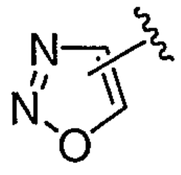
a-xiv,



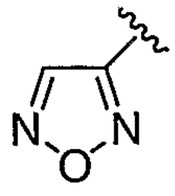
a-xv,



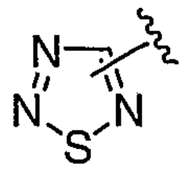
a-xvi,



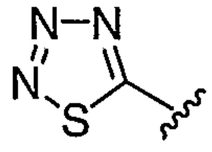
a-xvii,



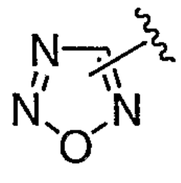
a-xviii,



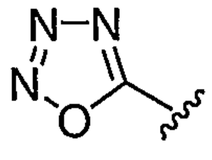
a-xix,



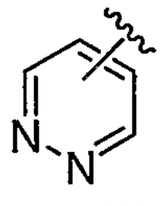
a-xx,



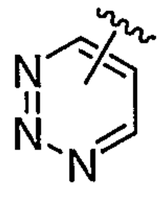
a-xxi,



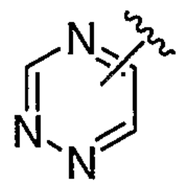
a-xxii,



a-xxiii,



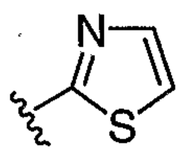
a-xxiv,



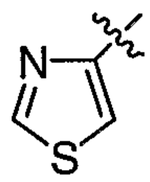
or **a-xxv.**

3. The compound according to claim 1, wherein z is 0-2.

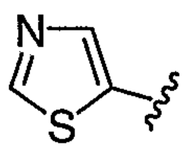
4. The compound according to claim 2, wherein Z is selected from:



a-i-a,

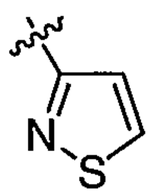


a-i-b,

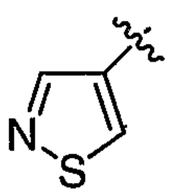


or **a-i-c.**

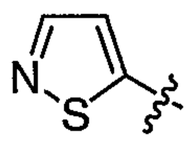
5. The compound according to claim 2, wherein Z is selected from:



a-xi-a,

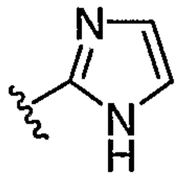


a-xi-b

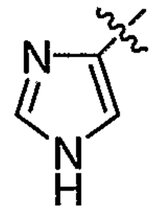


or **a-xi-c.**

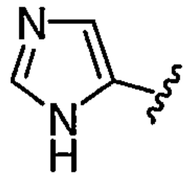
6. The compound according to claim 2, wherein Z is selected from:



a-iv-a,

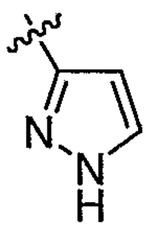


a-iv-b,

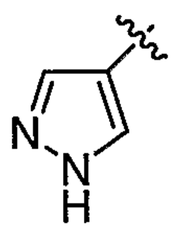


or **a-iv-c.**

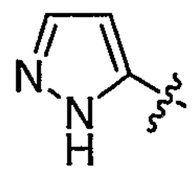
7. The compound according to claim 2, wherein Z is selected from:



a-xiv-a,

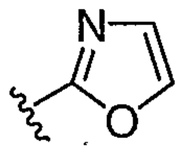


a-xiv-b,

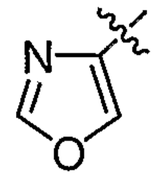


or **a-xiv-c.**

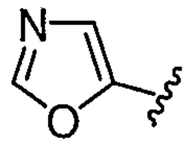
8. The compound according to claim 2, wherein Z is selected from:



a-xv-a,

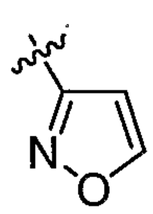


a-xv-b,

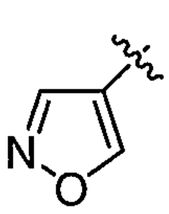


or **a-xv-c.**

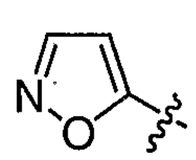
9. The compound according to claim 2, wherein Z is selected from:



a-xvi-a,

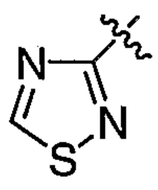


a-xvi-b,

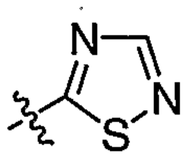


or **a-xvi-c.**

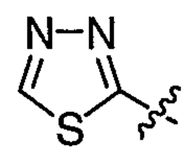
10. The compound according to claim 2, wherein Z is selected from:



a-ii-a,

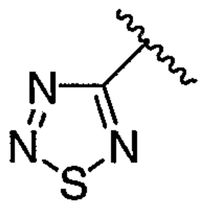


a-ii-b,

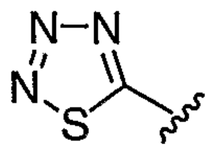


or **a-iii.**

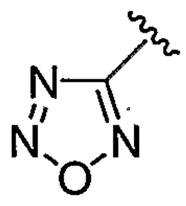
11. The compound according to claim 2, wherein Z is selected from:



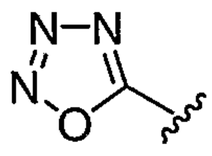
a-xix,



a-xx,

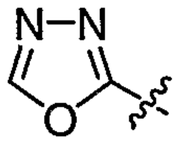


a-xxi,

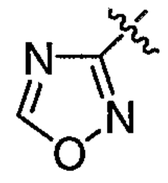


or **a-xxii.**

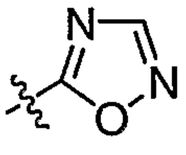
12. The compound according to claim 2, wherein Z is selected from:



a-vi,

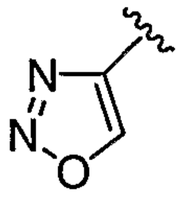


a-vii-a,

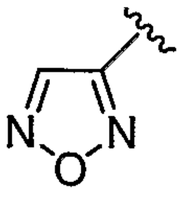


or **a-vii-b**

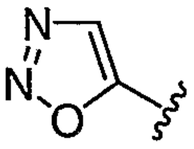
13. The compound according to claim 2, wherein Z is selected from:



a-xvii-a,

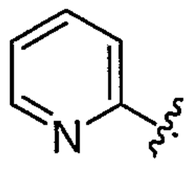


a-xviii,

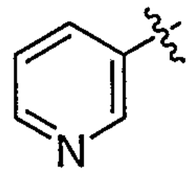


or **a-xvii-b.**

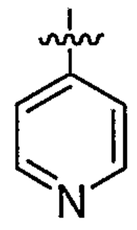
14. The compound according to claim 2, wherein Z is selected from:



a-viii-a,

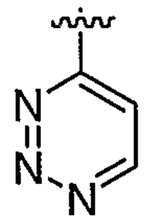


a-viii-b,

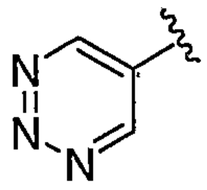


or **a-viii-c.**

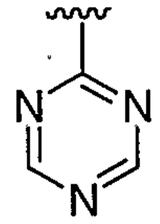
15. The compound according to claim 2, wherein Z is selected from:



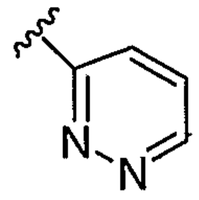
a-xxiv-a,



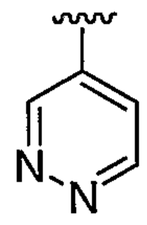
a-xxiv-b



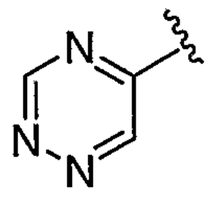
a-x,



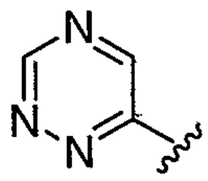
a-xxiii-a,



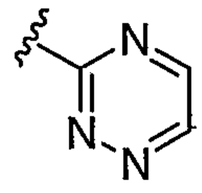
a-xxiii-b,



a-xxv-a,

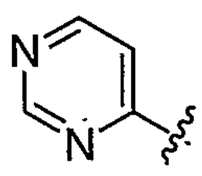


a-xxv-b,

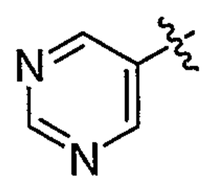


or **a-xxv-c.**

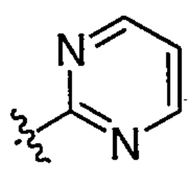
16. The compound according to claim 2, wherein Z is selected from:



a-ix-a,



a-ix-b,



or **a-ix-c.**

17. The compound according to claim 1, wherein R^Z is selected from R^1, R^2, or R^5.

18. The compound according to claim 17, wherein R^Z is selected from a hydrogen, halo, a C1-C6 aliphatic, or an optionally substituted group independently selected from C3-C8 cycloaliphatic, C6-C10 aryl, C3-C8 heterocyclic, or C5-C10 heteroaryl ring; wherein said cycloaliphatic, said aryl, said heterocyclic, or said heteroaryl is optionally substituted with up to 3 substituents selected from R^1, R^2, R^4, or R^5.

19. The compound according to claim 18, wherein R^Z is selected from hydrogen, Cl, C1-C6 straight or branched alkyl, C2-C6 straight or branched alkenyl, or C2-C6 straight or branched alkynyl.

20. The compound according to claim 1, wherein R^M is hydrogen.

21. The compound according to claim 1, wherein R^N is hydrogen.

22. The compound according to claim 1, wherein X is selected from a bond, CH_2, or O.

23. The compound according to claim 1, wherein Q is selected from a bond or a C1-C6 straight or branched alkylidene chain, wherein up to two methylene units of said alkylidene is independently replaced by O, S, OCO, NH, $N(R^2)$, or a spirocycloalkylene group.

24. The compound according to claim 23, wherein Q is $-X_2-(X_1)_p-$,

wherein:

X_2 is a bond or C1-C6 aliphatic, optionally substituted with up to two substituents independently selected from R^1, R^4, or R^5;

p is 0 or 1; and

X_1 is O, S, or NR^2.

25. The compound according to claim 24, wherein X_2 is a bond, C1-C6 alkyl, or C2-C6 alkylidene, and said alkyl and alkylidene are independently and optionally substituted with R^1 or R^4.

26. The compound according to claim 25, wherein X_2 is selected from a bond, $-CH_2-$, $-CH_2-CH_2-$, $-(CH_2)_3-$, $-C(Me)_2-$, -CH(Me)-, -C(Me)=CH-, -CH=CH-, -CH(Ph)-, $-CH_2-$CH(Me)-, -CH(Et)-, or -CH(i-Pr)-.

27. The compound according to claim 24, wherein X_1 is NH or -N(C1-C6 alkyl)-.

28. The compound according to claim 1, wherein R^Q is optionally substituted with up to 4 substituents selected from halo, cyano, trifluoromethyl, OH, C_{1-4} alkyl, C_{2-4} alkenyl, C_{1-4} alkoxy, trifluoromethoxy, $C(O)NH_2$, NH_2, $NH(C_{1-4}$ alkyl), $N(C_{1-4}$ alkyl$)_2$, $NHC(O)C_{1-4}$ alkyl, or $C(O)C_{1-4}$ alkyl.

29. The compound according to claim 1, wherein R^Q is an optionally substituted C1-C6 aliphatic group.

30. The compound according to claim 1, wherein R^Q is an optionally substituted 3-8 membered saturated, partially unsaturated, or aromatic monocyclic ring having 0-3 heteratoms independently selected from O, S, N, or NH.

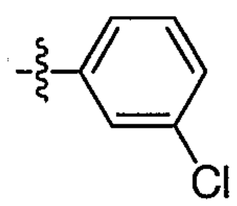
31. The compound according to claim 30, wherein R^Q is an optionally substituted 3-8 membered cycloaliphatic ring.

32. The compound according to claim 31, wherein R^Q is an optionally substituted ring selected from cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl.

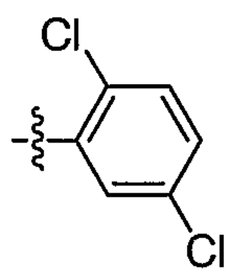
33. The compound according to claim 30, wherein R^Q is an optionally substituted phenyl.

34. The compound according to claim 33, wherein said phenyl is optionally substituted with up to 3 substituents selected from halo, cyano, trifluoromethyl, OH, C_{1-4} alkyl, C_{2-4} alkenyl, C_{1-4} alkoxy, trifluoromethoxy, $C(O)NH_2$, NH_2, $NH(C_{1-4}$ alkyl), $N(C_{1-4}$ alkyl)$_2$, $NHC(O)C_{1-4}$ alkyl, or $C(O)C_{1-4}$ alkyl.

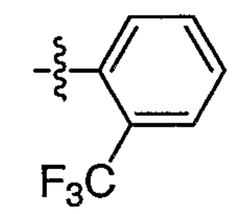
35. The compound according to claim 33, wherein R^Q is selected from:



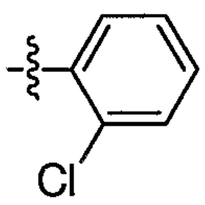
xlix,



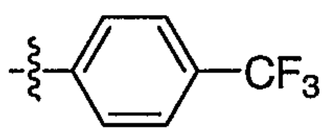
l,



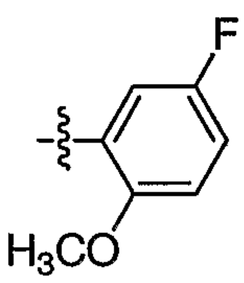
li,



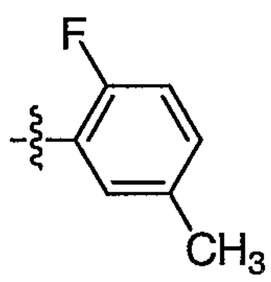
lii,



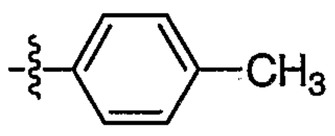
liii,



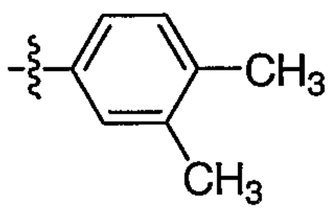
liv,



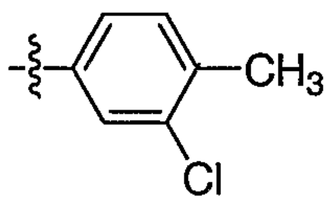
lv,



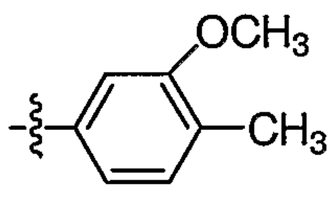
lvi,



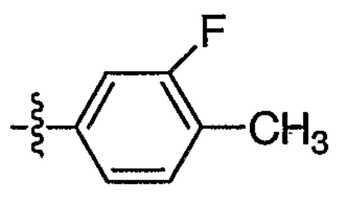
lvii,



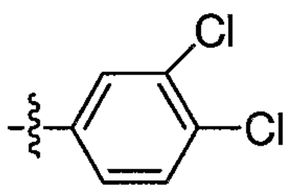
lviii,



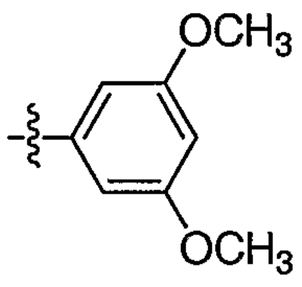
lvix,



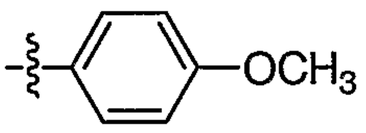
lx,



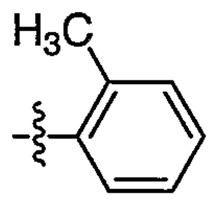
lxi,



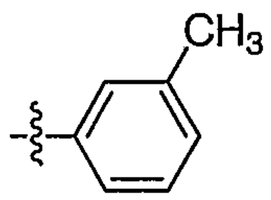
lxii,



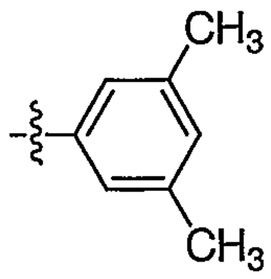
lxiii,



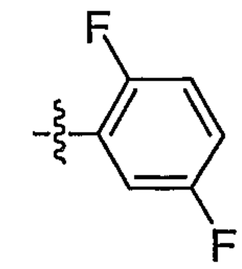
lxiv,



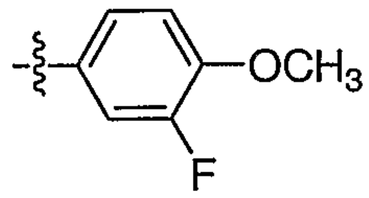
lxv,



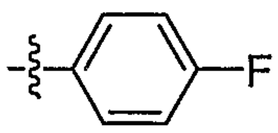
lxvi,



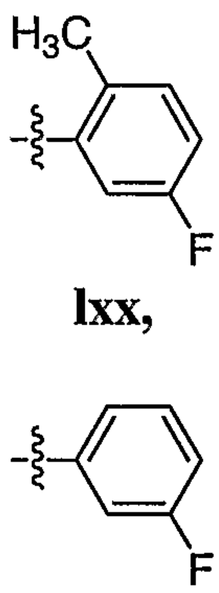
lxvii,



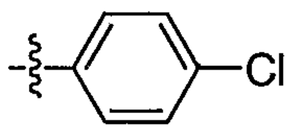
lxviii,



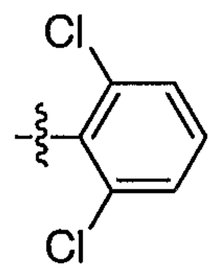
lxix,



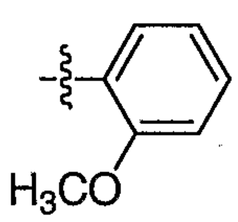
lxx,



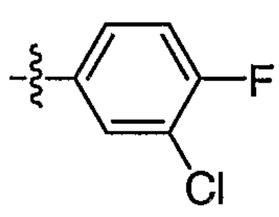
lxxi,



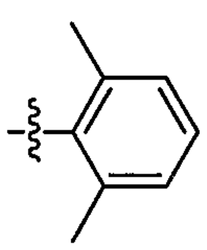
lxxii,



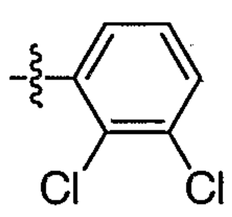
lxxiii



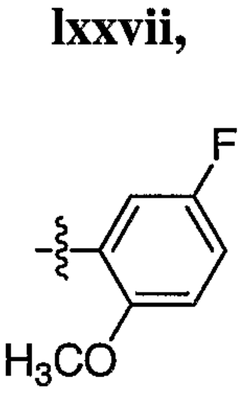
lxxiv,



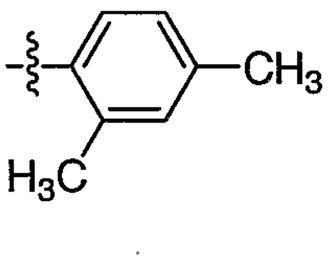
lxxv,



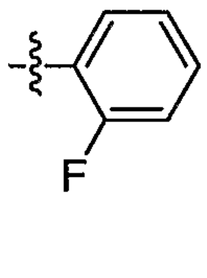
lxxvi,



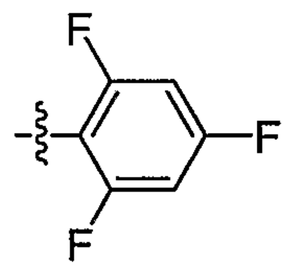
lxxvii,



lxxviii,



lxxix,



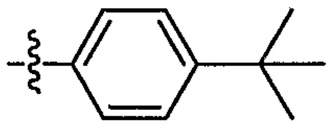
lxxx,

lxxxi,

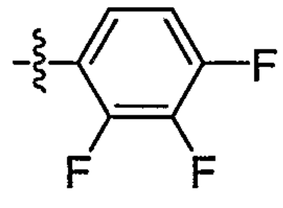
lxxxii,

lxxxiii

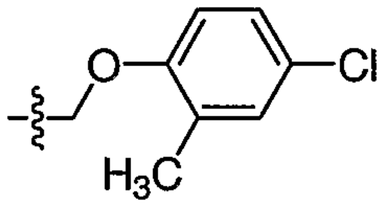
lxxxiv,



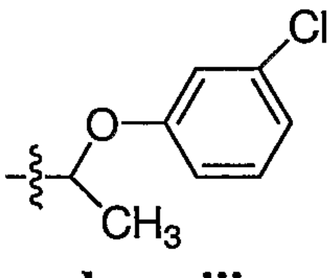
lxxxv



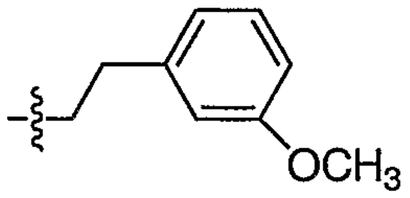
lxxxvi,



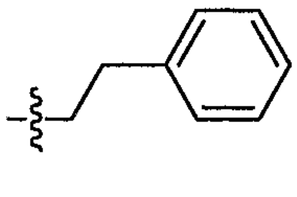
lxxxvii,



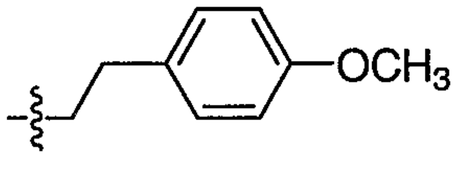
lxxxviii,



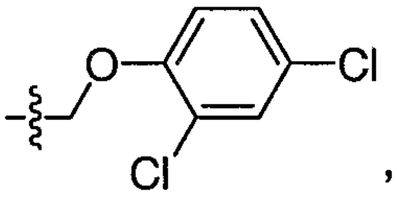
lxxxix,



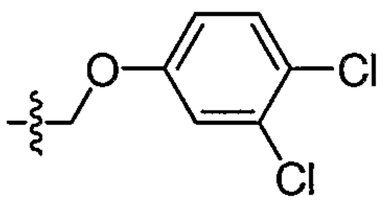
xc,



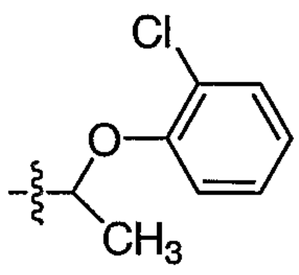
xci,



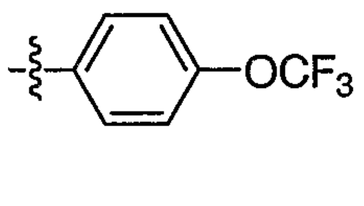
xcii,



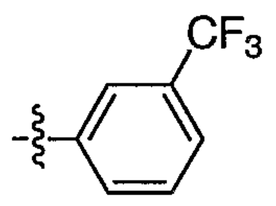
xciii,



xciv,



xcv,



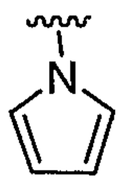
or xcvi.

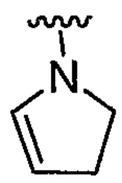
36. The compound according to claim 30, wherein R^Q is an optionally substituted 3-7 membered monocyclic heterocyclic ring.

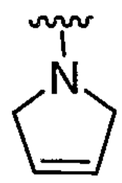
37. The compound according to claim 30, wherein R^Q is an optionally substituted 5-6 membered saturated, partially unsaturated, or aromatic monocyclic ring having 0-3 heteratoms independently selected from O, S, N, or NH.

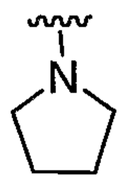
38. The compound according to claim 37, wherein R^Q is an optionally substituted ring selected from pyridyl, pyrimidinyl, pyrazinyl, or pyridazinyl.

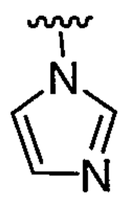
39. The compound according to claim 37, wherein R^Q is an optionally substituted ring selected from:

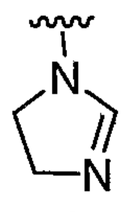

i,

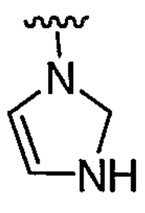

ii,

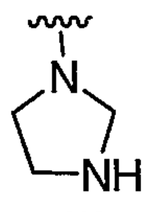

iii,

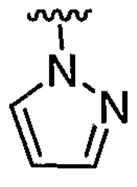

iv,

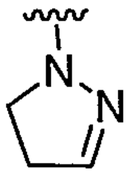

v,

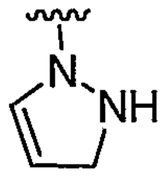

vi,

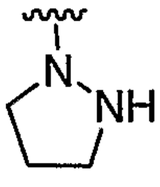

vii,

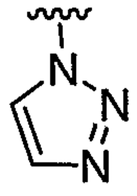

viii,

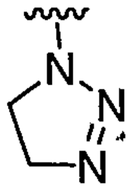

ix,

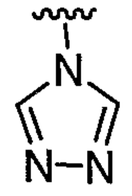

x,

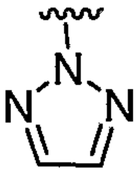

xi,

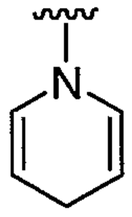

xii,

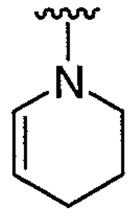

xiii,

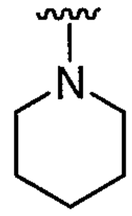

xiv,

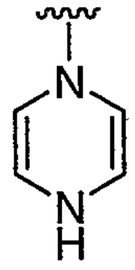

xv,

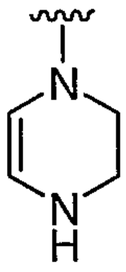

xvi,

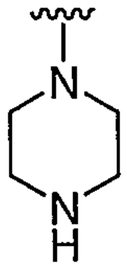

xvii,

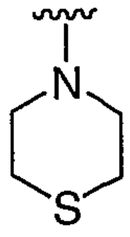

xviii,

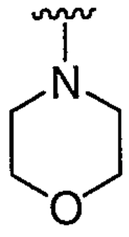

xix,


xx,


xxi,


xxii,


xxiii,


or **xxiv.**

40. The compound according to claim 39, wherein R^Q is optionally fused to an optionally substituted phenyl ring.

41. The compound according to claim 1, wherein R^Q is an optionally substituted 8-12 membered saturated, partially unsaturated, or fully unsaturated bicyclic ring system having 0-5 heteroatoms independently selected from O, S, N, or NH.

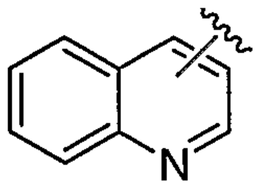
42. The compound according to claim 41, wherein R^Q is an optionally substituted naphthyl.

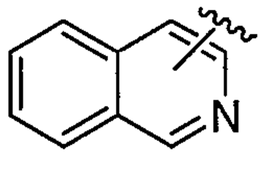
43. The compound according to claim 42, wherein said naphthyl is optionally substituted with up to 5 substituents selected from halo, cyano, trifluoromethyl, OH, C_{1-4} alkyl, C_{2-4} alkenyl, C_{1-4} alkoxy, trifluoromethoxy, $C(O)NH_2$, NH_2, $NH(C_{1-4}$ alkyl), $N(C_{1-4}$ alkyl)$_2$, $NHC(O)C_{1-4}$ alkyl, or $C(O)C_{1-4}$ alkyl.

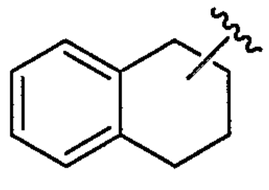
44. The compound according to claim 41, wherein R^Q is an optionally substituted 8-10 membered, bicyclic, heteroaromatic ring.

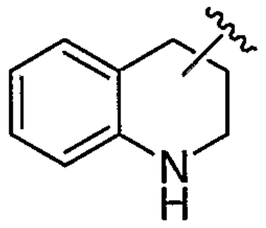
45. The compound according to claim 41, wherein R^Q is an optionally substituted 8-10 membered, bicyclic, heterocyclic ring.

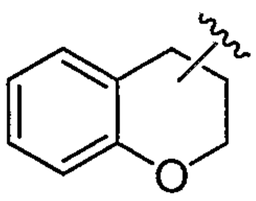
46. The compound according to claim 41, wherein R^Q is an optionally substituted ring selected from:

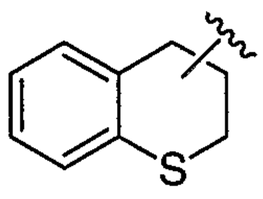

xxv,

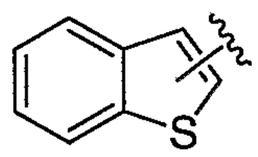

xxvi,

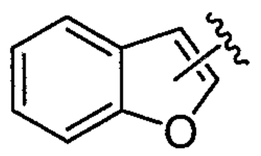

xxvii,

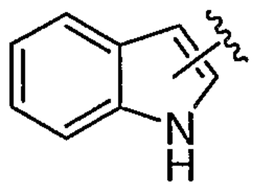

xxviii,


xxix,

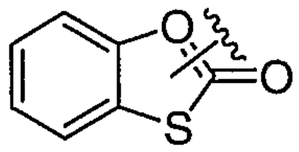

xxx,


xxxi,

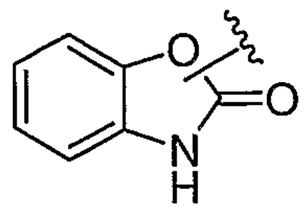

xxxii,



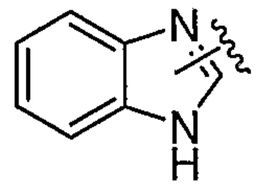
xxxiii,



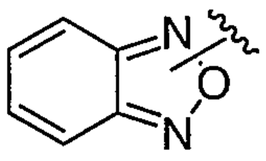
xxxiv,



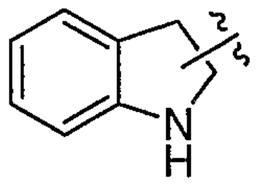
xxxv,



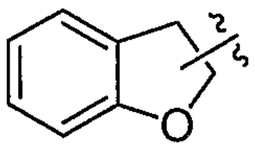
xxxvi,



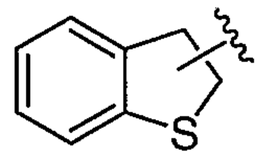
xxxvii,



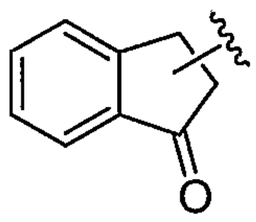
xxxviii,



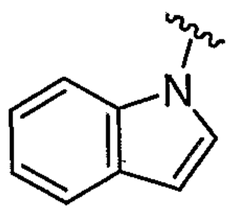
xxxix,



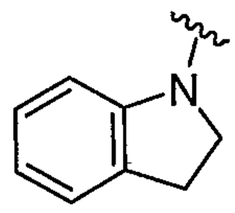
xl,



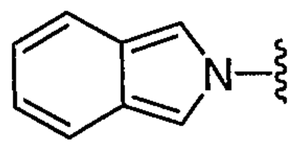
xli,



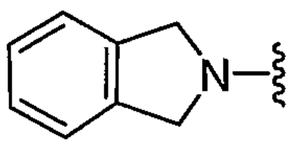
xlii,



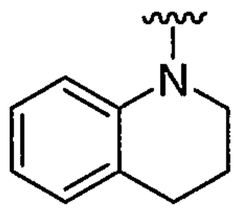
xliii,



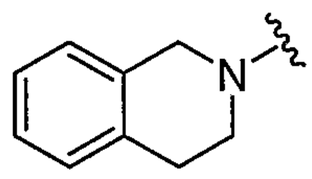
xliv,



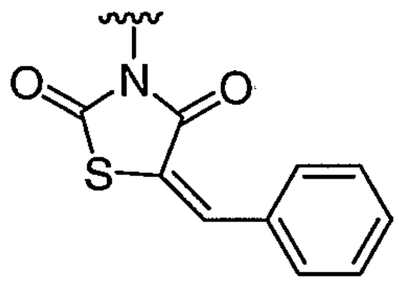
xlv,



xlvi,



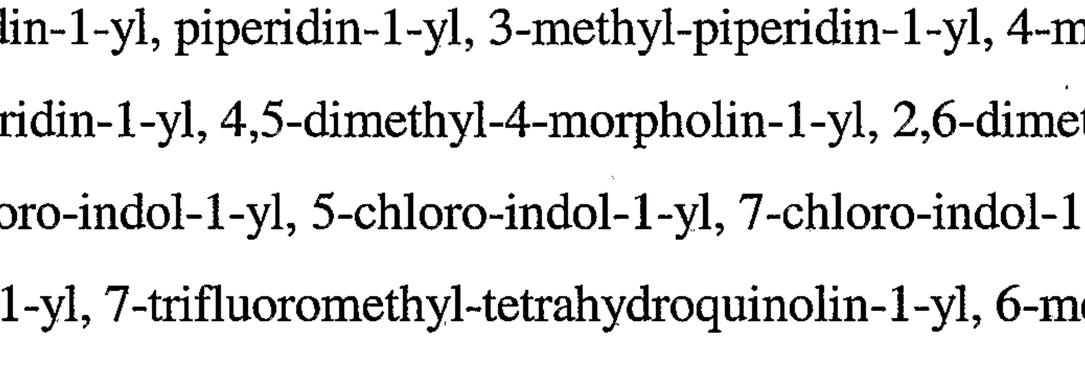
xlvii,



or, **xlviii.**

47. The compound according to claim 1, wherein R^Q is selected from pyrrolidin-1-yl, 3,3-difluoropyrrolidin-1-yl, piperidin-1-yl, 3-methyl-piperidin-1-yl, 4-methyl-piperidin-1-yl, 4,4-difluoropiperidin-1-yl, 4,5-dimethyl-4-morpholin-1-yl, 2,6-dimethyl-morpholin-4-yl, indol-1-yl, 4-fluoro-indol-1-yl, 5-chloro-indol-1-yl, 7-chloro-indol-1-yl, tetrahydroquinolin-1-yl, 7-trifluoromethyl-tetrahydroquinolin-1-yl, 6-methyl-tetrahydroquinolin-1-yl, 6-chloro-tetrahydroquinolin-1-yl, tetrahydro-isoquinolin-2-yl, 7-chloro-tetrahydro-isoquinolin-2-yl, 7-trifluoromethyl-tetrahydro-isoquinolin-2-yl, 7-fluoro-tetrahydro-isoquinolin-2-yl, 6-methyl-tetrahydro-isoquinolin-2-yl, 8-trifluoromethyl-quinolin-4-yl, pyridine-3-yl, or pyridine-4-yl.

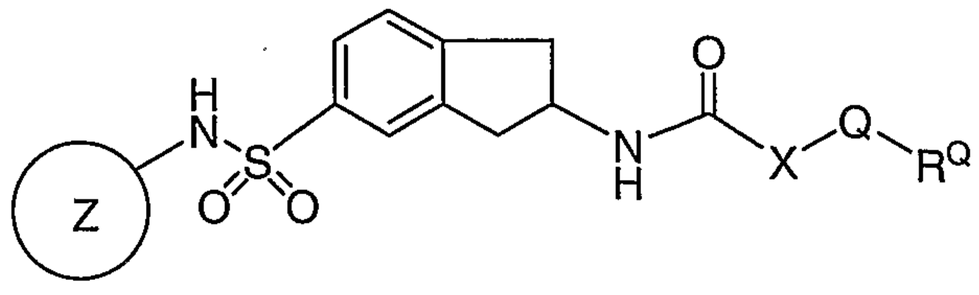
48. The compound according to claim 1, wherein said compound has formula I-A:



I-A;

wherein ring Z, X, Q, and R^Q are defined above.

49. The compound according to claim 1, wherein said compound has formula I-B:



I-B;

wherein ring Z, X, Q, and R^Q are defined above.

50. A compound selected from Table 2.

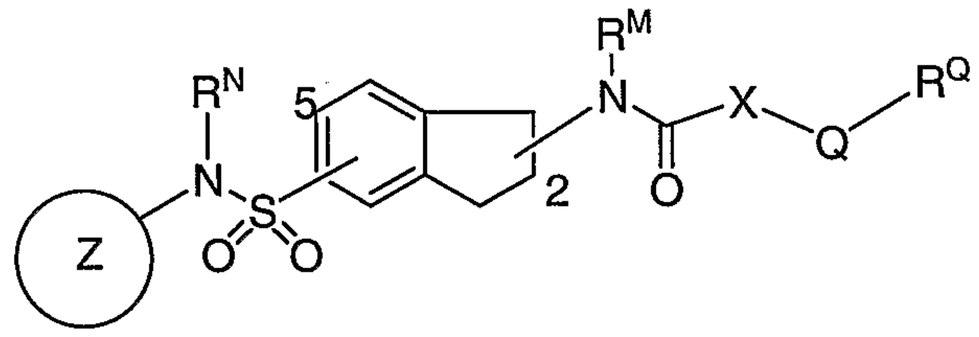
51. A pharmaceutical composition comprising a compound according to any one of claims 1-50, and a pharmaceutically acceptable carrier.

52. A method of inhibiting one or more of NaV1.1, NaV1.2, NaV1.3, NaV1.4, NaV1.5, NaV1.6, NaV1.7, NaV1.8, NaV1.9, or CaV2.2 activity in:

(a) a patient; or

(b) a biological sample;

comprising administering to said patient, or contacting said biological sample with a compound of formula **I**:



(I);

or a pharmaceutically acceptable salt thereof;

wherein:

ring Z is a 5-7 membered unsaturated or aromatic ring having at least one ring heteroatom selected from O, S, N, or NH, wherein and said ring Z is optionally substituted with z occurrence of R^Z;

z is 0-4;

R^Z is selected from R^1, R^2, R^3, R^4, or R^5;

X is a bond, O, NR^2, or $C(R^2)_2$;

Q is a bond or a C1-C6 straight or branched alkylidine chain, wherein up to two non-adjacent methylene units of Q are optionally and independently replaced by –CO-, -CS-, -COCO-, -$CONR^2$-, -$CONR^2NR^2$-, -CO_2-, -OCO-, -NR^2CO_2-, -O-, -

NR^2CONR^2-, -$OCONR^2$-, -NR^2NR^2, -NR^2NR^2CO-, -NR^2CO-, -S-, -SO, -SO_2-, -NR^2-, -SO_2NR^2-, NR^2SO_2-, -$NR^2SO_2NR^2$-, or a spirocycloalkylene moeity;

R^Q is a C_{1-6} aliphatic group, a 3-8-membered saturated, partially unsaturated, or fully unsaturated monocyclic ring having 0-3 heteroatoms independently selected from O, S, N, or NH, or an 8-12 membered saturated, partially unsaturated, or fully unsaturated bicyclic ring system having 0-5 heteroatoms independently selected from O, S, N, or NH;

wherein R^Q is optionally substituted with up to 4 substituents selected from R^1, R^2, R^3, R^4, or R^5;

R^M and R^N are independently R^2;

R^1 is oxo, $=NN(R^6)_2$, $=NN(R^7)_2$, $=NN(R^6R^7)$, R^6 or $(CH_2)_n$-Y;

n is 0, 1 or 2;

Y is halo, CN, NO_2, CF_3, OCF_3, OH, SR^6, $S(O)R^6$, SO_2R^6, NH_2, NHR^6, $N(R^6)_2$, NR^6R^8, COOH, $COOR^6$ or OR^6; or

two R^1 on adjacent ring atoms, taken together, form 1,2-methylenedioxy or 1,2-ethylenedioxy;

R^2 is hydrogen or C1-C6 aliphatic, wherein each R^2 is optionally substituted with up to 2 substituents independently selected from R^1, R^4, or R^5;

R^3 is a C3-C8 cycloaliphatic, C6-C10 aryl, C3-C8 heterocyclic, or C5-C10 heteroaryl ring, optionally substituted with up to 3 substituents, independently selected from R^1, R^2, R^4 or R^5;

R^4 is OR^5, OR^6, $OC(O)R^6$, $OC(O)R^5$, $OC(O)OR^6$, $OC(O)OR^5$, $OC(O)N(R^6)_2$, $OC(O)N(R^5)_2$, $OC(O)N(R^6R^5)$, $OP(O)(OR^6)_2$, $OP(O)(OR^5)_2$, $OP(O)(OR^6)(OR^5)$, SR^6, SR^5, $S(O)R^6$, $S(O)R^5$, SO_2R^6, SO_2R^5, $SO_2N(R^6)_2$, $SO_2N(R^5)_2$, $SO_2NR^5R^6$, SO_3R^6, SO_3R^5, $C(O)R^5$, $C(O)OR^5$, $C(O)R^6$, $C(O)OR^6$, $C(O)N(R^6)_2$, $C(O)N(R^5)_2$, $C(O)N(R^5R^6)$, $C(O)N(OR^6)R^6$, $C(O)N(OR^5)R^6$, $C(O)N(OR^6)R^5$, $C(O)N(OR^5)R^5$, $C(NOR^6)R^6$, $C(NOR^6)R^5$, $C(NOR^5)R^6$, $C(NOR^5)R^5$, $N(R^6)_2$, $N(R^5)_2$, $N(R^5R^6)$, $NR^5C(O)R^5$, $NR^6C(O)R^6$, $NR^6C(O)R^5$, $NR^6C(O)OR^6$, $NR^5C(O)OR^6$, $NR^6C(O)OR^5$, $NR^5C(O)OR^5$, $NR^6C(O)N(R^6)_2$, $NR^6C(O)NR^5R^6$, $NR^6C(O)N(R^5)_2$, $NR^5C(O)N(R^6)_2$, $NR^5C(O)NR^5R^6$, $NR^5C(O)N(R^5)_2$, $NR^6SO_2R^6$, $NR^6SO_2R^5$, $NR^5SO_2R^5$, $NR^6SO_2N(R^6)_2$, $NR^6SO_2NR^5R^6$, $NR^6SO_2N(R^5)_2$, $NR^5SO_2NR^5R^6$, $NR^5SO_2N(R^5)_2$, $N(OR^6)R^6$, $N(OR^6)R^5$, $N(OR^5)R^5$, $N(OR^5)R^6$, $P(O)(OR^6)N(R^6)_2$, $P(O)(OR^6)N(R^5R^6)$, $P(O)(OR^6)N(R^5)_2$, $P(O)(OR^5)N(R^5R^6)$, $P(O)(OR^5)N(R^6)_2$, $P(O)(OR^5)N(R^5)_2$, $P(O)(OR^6)_2$, $P(O)(OR^5)_2$, or $P(O)(OR^6)(OR^5)$;

R^5 is a C3-C8 cycloaliphatic, C6-C10 aryl, C3-C8 heterocyclic, or C5-C10 heteroaryl ring, optionally substituted with up to 3 R^1 substituents;

R^6 is H or C1-C6 aliphatic, wherein R^6 is optionally substituted with a R^7 substituent;

R^7 is a C3-C8 cycloaliphatic, C6-C10 aryl, C3-C8 heterocyclic, or C5-C10 heteroaryl ring, and each R^7 is optionally substituted with up to 2 substituents independently chosen from H, C1-C6 aliphatic, or $(CH_2)_m$-Z' wherein m is 0-2;

Z' is selected from halo, CN, NO_2, $C(halo)_3$, $CH(halo)_2$, $CH_2(halo)$, -$OC(halo)_3$, -$OCH(halo)_2$, -$OCH_2(halo)$,OH, S-(C1-C6) aliphatic, S(O)-(C1-C6) aliphatic, SO_2-(C1-C6)aliphatic, NH_2, NH-(C1-C6)aliphatic, N((C1-C6)aliphatic)$_2$, N((C1-C6)aliphatic)R^8, COOH, C(O)O(-(C1-C6)aliphatic), or O-(C1-C6)aliphatic; and

R^8 is acetyl, C6-C10 aryl sulfonyl, or C1-C6 alkyl sulfonyl.

53. The method according to claim 52, wherein said compound has formula **I**, formula **I-A**, or formula **I-B**.

54. A method of treating or lessening the severity of a disease, disorder, or condition selected from acute, chronic, neuropathic, or inflammatory pain, arthritis, migraine, cluster headaches, trigeminal neuralgia, herpetic neuralgia, general neuralgias, epilepsy or epileptic 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, stroke, bipolar disorders, or cancer pain, comprising the step of administering to said patient an effective amount of a compound according of formula **I**, formula **I-A**, or formula **I-B**.

55. The method according to claim 54, wherein said compound is according to any one of claims 1-50.

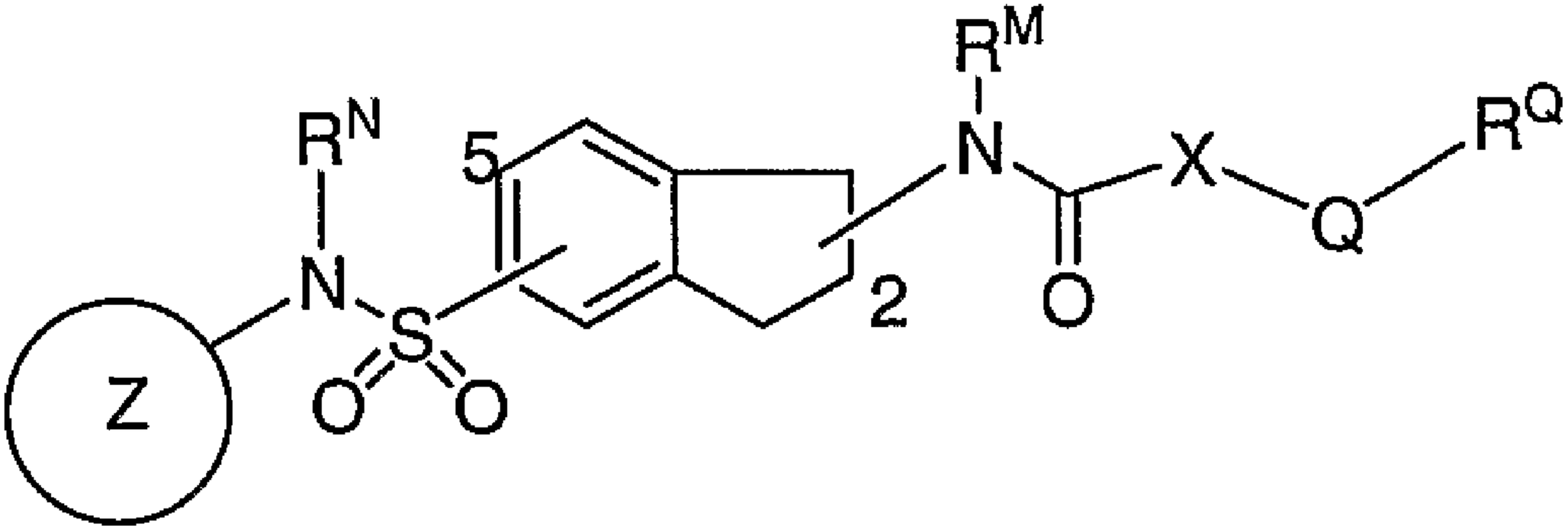
56. The method according to claim 54, wherein the disease, condition, or disorder is implicated in the activation or hyperactivity of voltage-gated sodium channels.

57. The method according to claim 56, wherein the disease, condition, or disorder is radicular pain, sciatica, back pain, head pain, neck pain, or neuropathies.

58. The method according to claim 56, wherein the disease, condition, or disorder is severe or intractable pain, acute pain, post-surgical pain, back pain, or cancer pain.

59. The method according to claim 54, wherein the disease, condition, or disorder is implicated in the activation or hyperactivity of voltage-gated calcium channels.

60. The method according to claim 59, wherein the disease, condition, or disorder is acute, chronic, neuropathic, inflammatory pain, or inflammatory breakthrough pain.



(I)