CONDENSED PYRIMIDINE COMPOUNDS AS INHIBITORS OF VOLTAGE-GATED ION CHANNELS

TECHNICAL FIELD OF THE INVENTION

[0001] The present invention relates to compounds useful as inhibitors of voltage-gated sodium channels and calcium 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

[0002] 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).

[0003] 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).

[0004] 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, Epilepsy
NaV1.4	Skeletal muscle	25nM	Myotonia
NaV1.5	Heart	2μM	Arrythmia, long QT
NaV1.6	CNS widespread, most abuntant	6nM	Pain, movement disorders

Na Isoform	Tissue	TTX IC50	Indications
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

[0005] 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.

[0006] 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.

[0007] 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.

[0008] 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.

[0009] 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 significantly upregulated in animal models of neuropathic pain (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 and Kim, C.H., Youngsuk, O., et al. (2001) "The changes in expression of three subtypes of TTX sensitive sodium channels in sensory neurons after spinal nerve ligation". Mol. Brain Res. **95**:153-61.) The timecourse of the increase in NaV1.3 parallels the appearance of allodynia in animal models subsequent to nerve injury. Up-regulation of Nav1.3 transcription is also observed in a rat model of diabetic neuropathy. (See, Craner, M.J., Klein, J.P. et al. (2002) "Changes of sodium channel expression in experimental painful diabetic neuropathy." Ann Neurol. **52**(6): 786-92. 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 pathophysiological activity accompanying neuropathic pain (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.). Human NaV1.3 channel proteins are expressed in the central and peripheral systems of man. (See, Chen, Y.H., Dale, T.J., et al. (2000) "Cloning, distribution and functional analysis of the type III sodium channel from human brain." Eur. J. Neurosci. **12**: 4281-89). Furthermore, in the periphery, NaV1.3 channel proteins are detectable in injured but not uninjured human nerves indicating that NaV1.3 plays important physiological roles under pathophysiological conditions in humans as well. Given the strong correlation between increased NaV1.3 channel expression and neuronal hyperexcitability, inhibitors of NaV1.3 channels, and in particular selective ones, might therefore provide efficacious therapeutic agents with less-severe side effects than nonselective Na_+ channel inhibitors in the treatment of painful neuropathies. Similarly, NaV1.3 overexpression may also be associated with increased epipleptic neuronal activity as it is significantly upregulated in hippocampal pyramidal neurons of epileptic humans (See, Whitaker, W.R.J., Faull, M., et al.

(2001) "Changes in the mRNAs encoding voltage-gated sodium channel types II and III in human epileptic hippocampus." Neurosci. **106**(2): 275-285.); inhibitors with some selectivity against Nav1.3 could also be particularly attractive anticonvulsants and neuroprotectants.

[0010] 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.

[0011] 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).

[0012] 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)

[0013] 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).

[0014] 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).

[0015] 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 I (Hockerman, G. H., et. al. (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, G. H., et. al. (1997) Annu. Rev. Pharmacol. Toxicol. **37**: 361-96; Striessnig, J. (1999) Cell. Physiol. Biochem. **9**: 242-69). Ten isoforms of the α_1 subunit are known, as indicated in Table I. 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, M.G. and K. P. Campbell (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.

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

[0016] 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.

[0017] $Ca_v2.1$ 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, R. E., et al. (1998) J. Neurosci. **18**: 6319-30; Cizkova, D, 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.

[0018] 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 hand, may last for much longer periods of time and its intensity is more graded. Inflammation may occur for many reasons including tissue damage, autoimmune response, and pathogen invasion. Inflammatory pain is mediated by a variety of agents that are released during inflammation, including substance P, histamines, acid, prostaglandin, bradykinin, CGRP, cytokines, ATP, and other agents (Julius, D. and A. I. Basbaum (2001) Nature **413** (6852): 203-10). The third class of pain is neuropathic and involves nerve damage arising from nerve injury or viral infection and 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.

[0019] 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, COX-2 inhibitors, opioids, tricyclic antidepressants, and anticonvulsants. Neuropathic pain has been particularly difficult to treat as it does not respond well to opioids until high doses are reached. Gabapentin is currently the most widely used therapeutic for the treatment of neuropathic pain, although it works in only 60% of patients and has modest efficacy. The drug is generally safe, although sedation is an issue at higher doses.

[0020] 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, S.S., et al. (1996) J. Pharmacol. Exp. Ther. **279**: 1243-9; Jain, K.K. (2000) Exp. Opin. Invest. Drugs **9**: 2403-10; Vanegas, H. and H. Schaible (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.

[0021] 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

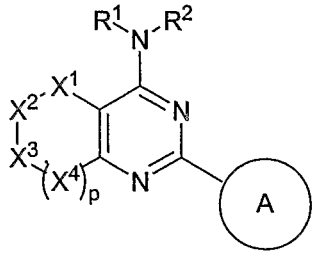
of neurons. The $Ca_V2.2$ antagonist ziconotide is effective in reducing infarct size in a focal ischemia model using laboratory animals, suggesting that $Ca_V2.2$ antagonists could be used for the treatment of stroke. Likewise, reducing excessive calcium influx into neurons may be useful for the treatment 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.

[0022] $Ca_V2.2$ 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.

[0023] 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 antagonists, and Ca channel antagonists preferably those with higher potency and fewer side effects.

SUMMARY OF THE INVENTION

[0024] It has now been found that compounds of this invention, and pharmaceutically acceptable compositions thereof, are useful as inhibitors of voltage-gated sodium channels. These compounds have the general formula **I:**



I

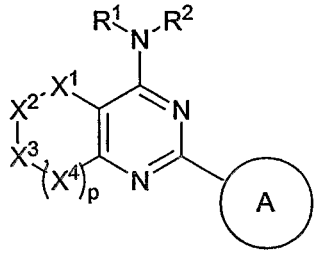
or a pharmaceutically acceptable salt thereof, wherein R^1, R^2, X^1, X^2, X^3, X^4, p, and Ring A are as defined below.

[0025] These compounds, and pharmaceutically acceptable compositions thereof, 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, and incontinence.

DETAILED DESCRIPTION OF THE INVENTION

[0026] *I. General Description of Compounds of the Invention:*

[0027] The present invention relates to compound of formula **I** useful as inhibitor of voltage-gated sodium channels:



I

or a pharmaceutically acceptable salt thereof, wherein:

p is 0, 1 or 2;

X^1, X^2, X^3 and X^4 are each independently selected from NR^3, C=O, CHR^4, S, O, S=O, or SO_2, as valency and stability permit;

R^1 and R^2 are each independently hydrogen, or an optionally substituted group selected from C_{1-6} aliphatic, a 5-6 membered aryl ring having 0-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or a 3-7-membered saturated or partially unsaturated ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur; or R^1 and R^2, taken together with the nitrogen atom to which they are bound, form an optionally substituted 3-8 membered heterocyclyl or heteroaryl ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur, wherein R^1, R^2, or any ring formed by R^1 and R^2 taken together, are

each independently optionally substituted at one or more carbon atoms with 0-4 occurrences of $-R^5$, and at one or more substitutable nitrogen atoms with $-R^6$;

Ring A is a 5-6 membered monocyclic or 8-10 membered bicyclic aryl ring having 0-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or a 3-7-membered saturated or partially unsaturated ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur, optionally substituted at one or more carbon atoms with 0-5 occurrences of $-R^7$, and at one or more substitutable nitrogen atoms with $-R^8$;

each occurrence of R^4, R^5, and R^7 is independently $Q\text{-}R^X$; wherein Q is a bond or is a C_1-C_6 alkylidene chain wherein up to two non-adjacent methylene units of Q are optionally and independently replaced by CO, CO_2, COCO, CONR, OCONR, NRNR, NRNRCO, NRCO, $NRCO_2$, NRCONR, SO, SO_2, $NRSO_2$, SO_2NR, $NRSO_2NR$, O, S, or NR;

each occurrence of R^X is independently selected from R', halogen, NO_2, or CN;

each occurrence of R is independently selected from hydrogen or an optionally substituted C_{1-6} aliphatic group;

each occurrence of R' is independently selected from hydrogen or an optionally substituted group selected from C_{1-8} aliphatic, C_{6-10} aryl, a heteroaryl ring having 5-10 ring atoms, or a heterocyclyl ring having 3-10 ring atoms, or wherein R and R' taken together with the atom(s) to which they are bound, or two occurrences of R' taken together with the atom(s) to which they are bound, form a 5-8 membered cycloalkyl, heterocyclyl, aryl, or heteroaryl ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur; and

each occurrence of R^3, R^6 or R^8 is independently R', -COR', $-CO_2(C_{1-6}$ aliphatic), $-CON(R')_2$, or $-SO_2R'$.

[0028] In certain embodiments, for compounds of the invention as described generally above and herein:

a) R^1 is not hydrogen when R^2 is optionally substituted indazol-3-yl;

b) R^1 is not hydrogen when R^2 is optionally substituted pyrazol-3-yl;

c) R^1 is not hydrogen when R^2 is 1,2,4-triazol-3-yl;

d) when p is 1, then:

i) when R^1 and R^2, taken together with the nitrogen atom, is N-morpholino, and Ring A is unsubstituted phenyl, then X^1, X^2, X^3 and X^4 are not, respectively:

1) CH_2, $CH(CH_2)Ph$, NR^3, and $CHCH_3$;

2) CH_2, CH_2, CH_2, and S;

3) CH_2, S, CH_2, and S;

4) CH_2, CH_2, S, and CH_2;

5) CH_2, CHMe, S, and CH_2; or

6) CHMe, CH_2, $N(CH_2)Ph$, and CH_2;

ii) R^1 is not hydrogen, and R^2 is not CH_2Ph, $(CH_2)_2O(CH_2)_2OH$, or $-CH_2$(1,3-benzodioxol-5-yl) when ring A is imidazol-1-yl;

iii) when R^1 and R^2, taken together with the nitrogen atom, is N-piperidinyl then:

1) when X^1, X^2 and X^3 are CH_2, and X^4 is S, then Ring A is not unsubstituted phenyl; and

2) when X^1, X^2 and X^4 are CH_2; and X^3 is S, then Ring A is not unsubstituted phenyl;

iv) when R^1 and R^2, taken together with the nitrogen atom, is N-piperizinyl, X^1, X^2 and X^3 are CH_2, and X^4 is S, then Ring A is not 3-NO_2Ph, 4-pyridinyl, or unsubstituted phenyl;

v) when one of X^1, X^2, X^3 or X^4 is NR^3 and the others of X^1, X^2, X^3 or X^4 are each CH_2, and R^1 and R^2 are each Me, H, CH_2Ph, or $(CH_2)_2NMe_2$, then Ring A is not pyrid-2-yl substituted at the 6-position;

vi) when X^1, X^2, and X^3 are each CH_2, X^4 is S, R^1 is H, and R^2 is $-CH_2$-C≡CH, then Ring A is not unsubstituted phenyl;

vii) when X^1 is NMe; X^2, X^3 and X^4 are each CH^2, R^1 is H, and R^2 is unsubstituted phenyl, then Ring A is not unsubstituted phenyl; and

viii) when X^1, X^2 and X^4 are each CH_2, X^3 is S, R^1 and R^2 are each Me, then Ring A is not unsubstituted phenyl; and

e) when p is 0, then:

i) when X^1 is CH_2, X^2 is NR^3, X^3 is C=O; or X^1 is C=O, X^2 is CHR^4, and X^3 is NR^3; or X^2 is NR^3, X^2 is C=O, and X^3 is CHR^4; or X^1 is CH_2, X^2 is O, and X^3 is C=O, then when R^1 is hydrogen and R^2 is unsubstituted phenyl or $-CH_2CH_2Cl$, or when R^1 and R^2, taken together form optionally substituted piperazinyl, morpholino, piperidinyl, or pyrrolidinyl, then Ring A is not optionally substituted piperidinyl, piperazinyl, morpholino, or pyrrolidinyl;

ii) when X^1 is CHR^4, X^2 is SO_2, and X^3 is CHR^4, and R^1 and R^2, taken together are piperazinyl, then Ring A is not unsubstituted phenyl;

iii) when X^1 and X^2 are CHR^4, X^3 is O, R^1 is hydrogen, and R^2 is $-C(=O)CH_3$, then Ring A is not substituted furyl;

iv) when X^1 is S, X^2 is CHR^4, X^3 is CHR^4; or X^1 is CHR^4, X^2 is S, and X^3 is CHR^4; or X^1 and X^2 are CHR^4 and X^3 is S, then Ring A is not optionally substituted N-linked morpholino, pyrrolidinyl, piperazinyl, piperidinyl, or is not unsubstituted phenyl or cyclopropyl;

v) when X^1 is CHR^4, X^2 is NR^3, X^3 is CHR^4, and R^1 and R^2 are both methyl, then Ring A is not 6-methyl-2-pyridyl;

vi) when X^1 is NR^3, X^2 is C=O, X^2 is NR^3, and R^1 and R^2 are both methyl, then Ring A is not unsubstituted phenyl; and

vii) when X^1 and X^2 are CHR^4, X^3 is NR^3, R^1 is hydrogen, and R^2 is unsubstituted phenyl, then Ring A is not unsubstituted phenyl.

[0029] In certain other embodiments, for compounds of the invention as described generally above and herein:

a) when each of X^1, X^2, X^3, and X^4 is CHR^4 and p is 0 or 1, then at least one R^4 is other than hydrogen;

b) when each of X^1, X^2, X^3, and X^4 is CHR^4 and Ring A is a substituted or unsubstituted piperizinyl group, then at least one R^4 is other than hydrogen;

c) when each of X^1, X^2, X^3, and X^4 is CHR^4, R^1 is hydrogen, and R^2 is 1H-indazol-3-yl, 7-fluoro-1H-indazol-3-yl, 5-fluoro-1H-indazol-3-yl, 5,7-difluoro-1H-indazol-3-yl or 5-methyl-1H-pyrazolyl, and Ring A is an unsubstituted phenyl group or is a phenyl group substituted in the ortho position with Cl or CF_3, then at least one R^4 is other than hydrogen; and

d) 5(6H)-quinazolinone, 4-anilino-7,8-dihydro-2,7-diphenyl- and 5(6H)-quinazolinone, 4-anilino-7,8-dihydro-7,7-dimethyl-2-phenyl- are excluded.

[0030] *2. Compounds and Definitions:*

[0031] Compounds of this invention include those described generally above, and are further illustrated by the classes, subclasses, and species disclosed herein. As used herein, the following definitions shall apply unless otherwise indicated. 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.

[0032] 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 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.

[0033] 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, or a monocyclic hydrocarbon or bicyclic hydrocarbon that is completely saturated or that contains one or more units of unsaturation, but which is not aromatic (also referred to herein as "carbocycle" "cycloaliphatic" or "cycloalkyl"), that has a single point of attachment to the rest of the molecule. 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. In some embodiments, "cycloaliphatic" (or "carbocycle" or "cycloalkyl") 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. Suitable aliphatic groups include, but are not limited to, linear or branched, substituted or unsubstituted alkyl, alkenyl, alkynyl groups and hybrids thereof such as (cycloalkyl)alkyl, (cycloalkenyl)alkyl or (cycloalkyl)alkenyl.

[0034] The term "heteroaliphatic", as used herein, means aliphatic groups wherein one or two carbon atoms are independently replaced by one or more of oxygen, sulfur, nitrogen, phosphorus, or silicon. Heteroaliphatic groups may be substituted or unsubstituted, branched or unbranched, cyclic or acyclic, and include "heterocycle", "heterocyclyl", "heterocycloaliphatic", or "heterocyclic" groups.

[0035] 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 members is an independently selected heteroatom. In some embodiments, the "heterocycle", "heterocyclyl", "heterocycloaliphatic", 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 system contains 3 to 7 ring members.

[0036] The term "heteroatom" means one or more of 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)).

[0037] The term "unsaturated", as used herein, means that a moiety has one or more units of unsaturation.

[0038] 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.

[0039] The terms "haloalkyl", "haloalkenyl" and "haloalkoxy" means alkyl, alkenyl or alkoxy, as the case may be, substituted with one or more halogen atoms. The term "halogen" means F, Cl, Br, or I.

[0040] 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 members, wherein at least one ring in the system is aromatic and wherein each ring in the system contains 3 to 7 ring members. The term "aryl" may be used interchangeably with the term "aryl ring". The term "aryl" also refers to heteroaryl ring systems as defined hereinbelow.

[0041] 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".

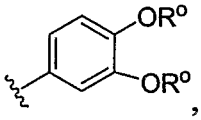
[0042] An aryl (including aralkyl, aralkoxy, aryloxyalkyl and the like) or heteroaryl (including heteroaralkyl and heteroarylalkoxy and the like) group may contain one or more substituents. Suitable substituents on the unsaturated carbon atom of an aryl or heteroaryl group are selected from halogen; -R°; -OR°; -SR°; 1,2-methylene-dioxy; 1,2-ethylenedioxy; phenyl (Ph) optionally substituted with R°; -O(Ph) optionally substituted with R°; $-(CH_2)_{1-2}(Ph)$, optionally substituted with R°; -CH=CH(Ph), optionally substituted with R°; $-NO_2$; -CN; $-N(R°)_2$; -NR°C(O)R°; $-NR°C(O)N(R°)_2$; $-NR°CO_2R°$; -NR°NR°C(O)R°; $-NR°NR°C(O)N(R°)_2$; $-NR°NR°CO_2R°$; -C(O)C(O)R°; $-C(O)CH_2C(O)R°$; $-CO_2R°$; -C(O)R°; $-C(O)N(R°)_2$; $-OC(O)N(R°)_2$; $-S(O)_2R°$; $-SO_2N(R°)_2$; -S(O)R°; $-NR°SO_2N(R°)_2$; $-NR°SO_2R°$; $-C(=S)N(R°)_2$; $-C(=NH)-N(R°)_2$; or $-(CH_2)_{0-2}NHC(O)R°$ wherein each independent occurrence of R° is selected from hydrogen, optionally substituted C_{1-6} aliphatic, an unsubstituted 5-6 membered heteroaryl or heterocyclic ring, phenyl, -O(Ph), or $-CH_2(Ph)$, or, notwithstanding the definition above, two independent occurrences of R°, on the same substituent or different substituents, taken together with the atom(s) to which each R° group is bound, form a 3-8-membered cycloalkyl, heterocyclyl, aryl, or heteroaryl ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur. Optional substituents on the aliphatic group of R° are selected from

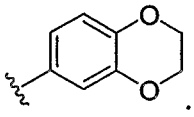
NH_2, $NH(C_{1-4}$aliphatic), $N(C_{1-4}$aliphatic$)_2$, halogen, C_{1-4}aliphatic, OH, $O(C_{1-4}$aliphatic), NO_2, CN, CO_2H, $CO_2(C_{1-4}$aliphatic), O(haloC_{1-4} aliphatic), or haloC_{1-4}aliphatic, wherein each of the foregoing C_{1-4} aliphatic groups of R° is unsubstituted.

[0043] An aliphatic or heteroaliphatic group, or a non-aromatic heterocyclic ring may contain one or more substituents. Suitable substituents on the saturated carbon of an aliphatic or heteroaliphatic group, or of a non-aromatic heterocyclic ring are selected from those listed above for the unsaturated carbon of an aryl or heteroaryl group and additionally include the following: =O, =S, $=NNHR^*$, $=NN(R^*)_2$, $=NNHC(O)R^*$, $=NNHCO_2$(alkyl), $=NNHSO_2$(alkyl), or $=NR^*$, where each R^* is independently selected from hydrogen or an optionally substituted C_{1-6} aliphatic. Optional substituents on the aliphatic group of R^* are selected from NH_2, $NH(C_{1-4}$ aliphatic), $N(C_{1-4}$ aliphatic$)_2$, halogen, C_{1-4} aliphatic, OH, $O(C_{1-4}$ aliphatic), NO_2, CN, CO_2H, $CO_2(C_{1-4}$ aliphatic), O(halo C_{1-4} aliphatic), or halo(C_{1-4} aliphatic), wherein each of the foregoing C_{1-4} aliphatic groups of R^* is unsubstituted.

[0044] Optional substituents on the nitrogen of a non-aromatic heterocyclic ring are selected from $-R^+$, $-N(R^+)_2$, $-C(O)R^+$, $-CO_2R^+$, $-C(O)C(O)R^+$, $-C(O)CH_2C(O)R^+$, $-SO_2R^+$, $-SO_2N(R^+)_2$, $-C(=S)N(R^+)_2$, $-C(=NH)-N(R^+)_2$, or $-NR^+SO_2R^+$; wherein R^+ is hydrogen, an optionally substituted C_{1-6} aliphatic, optionally substituted phenyl, optionally substituted -O(Ph), optionally substituted $-CH_2$(Ph), optionally substituted $-(CH_2)_{1-2}$(Ph); optionally substituted -CH=CH(Ph); or an unsubstituted 5-6 membered heteroaryl or heterocyclic ring having one to four heteroatoms independently selected from oxygen, nitrogen, or sulfur, or, notwithstanding the definition above, two independent occurrences of R^+, on the same substituent or different substituents, taken together with the atom(s) to which each R^+ group is bound, form a 3-8-membered cycloalkyl, heterocyclyl, aryl, or heteroaryl ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur. Optional substituents on the aliphatic group or the phenyl ring of R^+ are selected from NH_2, $NH(C_{1-4}$ aliphatic), $N(C_{1-4}$ aliphatic$)_2$, halogen, C_{1-4} aliphatic, OH, $O(C_{1-4}$ aliphatic), NO_2, CN, CO_2H, $CO_2(C_{1-4}$ aliphatic), O(halo C_{1-4} aliphatic), or halo(C_{1-4} aliphatic), wherein each of the foregoing C_{1-4} aliphatic groups of R^+ is unsubstituted.

[0045] 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.

[0046] As detailed above, in some embodiments, two independent occurrences of R^o (or R^+, or any other variable similarly defined herein), are taken together together with the atom(s) to which each variable is bound to form a 3-8-membered cycloalkyl, heterocyclyl, aryl, or heteroaryl ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur. Exemplary rings that are formed when two independent occurrences of R^o (or R^+, or any other variable similarly defined herein) are taken together with the atom(s) to which each variable is bound include, but are not limited to the following: a) two independent occurrences of R^o (or R^+, or any other variable similarly defined herein) that are bound to the same atom and are taken together with that atom to form a ring, for example, $N(R^o)_2$, where both occurrences of R^o are taken together with the nitrogen atom to form a piperidin-1-yl, piperazin-1-yl, or morpholin-4-yl group; and b) two independent occurrences of R^o (or R^+, or any other variable similarly defined herein) that are bound to different atoms and are taken together with both of those atoms to form a ring, for example where a phenyl group is substituted with two occurrences of OR^o 

, these two occurrences of R^o are taken together with the oxygen atoms to which they are bound to form a fused 6-membered oxygen containing ring: 

. It will be appreciated that a variety of other rings can be formed when two independent occurrences of R^o (or R^+, or any other variable similarly defined herein) are taken together with the atom(s) to which each variable is bound and that the examples detailed above are not intended to be limiting.

[0047] 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.

[0048] *3. Description of Exemplary Compounds:*

[0049] In certain embodiments, the present invention provides a compound wherein p is 0 or 1 In certain other embodiments, p is 0. Or, p is 1. Or, in certain embodiments, p is 2.

[0050] In other embodiments, the present invention provides a compound wherein Ring A is a 5-6 membered aryl ring having 0-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or a 3-7-membered saturated or partially unsaturated ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur, optionally substituted at one or more carbon atoms with 0-5 occurrences of $-R^7$, and at one or more substitutable nitrogen atoms with $-R^8$, wherein R^7 and R^8 are as defined above.

[0051] In one embodiment of formula I, X^1, X^2, and X^4 are CH_2, and X^3 is CH-Me or N-(C_{1-4} alkyl), N-benzyl, p is 0, 1 or 2, R^1 is methyl and R^2 is furan-2-ylmethyl, dimethylaminoethyl, or methyl, or R^1 and R^2 taken together form piperidinyl, piperazinyl, 4-methylpiperidinyl, 4-C_{1-4} alkoxypiperidinyl, morpholinyl, 4-carboxy-C_{1-4}alkylpiperazinyl, or 4-C_{1-4} alkylsulfonylpiperazinyl, and ring A is 2-hydroxyphenyl, 2-hydroxy-6-fluorophenyl, phenyl-2-disodium phosphate, or pyrrolyl.

[0052] In one embodiment of formula I, X^1, X^2, and X^4 are CH_2, and X^3 is CH-Me or N-Me, p is 1, R^1 is methyl and R^2 is furan-2-ylmethyl or methyl, or R^1 and R^2 taken together form piperidinyl, 4-methylpiperidinyl, morpholinyl, or 4-C_{1-4} alkylsulfonylpiperazinyl, and ring A is 2-hydroxyphenyl or 2-hydroxy-6-fluorophenyl.

[0053] In one embodiment of formula I, X^1, X^2, and X^4 are CH_2, and X^3 is CH-Me, p is 1, R^1 is methyl and R^2 is furan-2-ylmethyl or methyl, or R^1 and R^2 taken together form piperidinyl, 4-methylpiperidinyl, or 4-C_{1-4} alkylsulfonylpiperazinyl, and ring A is 2-hydroxyphenyl or 2-hydroxy-6-fluorophenyl.

[0054] In one embodiment of formula I, X^1, X^2, and X^4 are CH_2, and X^3 is CH-Me, p is 1, R^1 and R^2 taken together form 4-methylpiperidinyl or 4-C_{1-4} alkylsulfonylpiperazinyl, and ring A is 2-hyhdroxy or 2-hydroxy-6-fluorophenyl.

[0055] In one embodiment of formula I, X^1, and X^2 are CH_2, X^4 is CHOH or CH_2, and X^3 is CH_2, CH-Me, or C(O)-Me, p is 1, R^1 is methyl and R^2 methyl or methylaminoethyl, or R^1 and R^2 taken together form 1-piperidinyl, 1-piperazinyl, or 4-methylpiperazinyl, and ring A is 2-hydroxyphenyl, 2-fluorophenyl, or 1-pyrrolyl.

[0056] In one embodiment of formula I, X^1, X^2, and X^4 are CH_2, and X^3 is CH_2 or CH-Me, p is 1, R^1 is methyl and R^2 methyl or methylaminoethyl, or R^1 and R^2 taken together form 1-piperazinyl or 4-methylpiperazinyl, and ring A is 2-hydroxyphenyl or 1-pyrrolyl.

[0057] In one embodiment of formula I, X^1 and X^4 are CH_2, X^2 is CH_2, CHMe, or C(O)OMe, and X^3 is N-benzyl, N-(3-methoxybenzyl), N-(4-carboxymethylbenzyl), CH_2, or CH-Me, p is 1, R^1 is methyl or benzyl and R^2 is methyl or dimethylaminoethyl, or R^1 and R^2 taken together form a 1-piperazinyl, 1-piperidinyl, 4-carboxyethylpiperazinyl, 4-C_{1-4} alkylsulfonyl piperazinyl, 4-methylpiperidinyl, 4-methoxypiperidinyl, 4-methylpiperazinyl, 3-diethylaminocarbonylpiperidinyl, or morpholinyl, and ring A is 2-hydroxyphenyl, 2-methoxyphenyl, or 1-pyrrolyl.

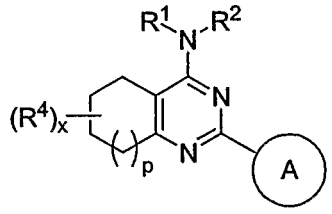
[0058] In one embodiment of formula I, X^1, X^2, and X^4 are CH_2, and X^3 is N-benzyl, N-(3-methoxybenzyl), N-(4-carboxymethylbenzyl), CH_2, or CH-Me, p is 1, R^1 is methyl or benzyl and R^2 is methyl or dimethylaminoethyl, or R^1 and R^2 taken together form a 1-piperazinyl, 1-piperidinyl, 4-carboxyethylpiperazinyl, 4-C_{1-4} alkylsulfonyl piperazinyl, 4-methylpiperidinyl, 4-methoxypiperidinyl, 3-diethylaminocarbonylpiperidinyl, or morpholinyl, and ring A is 2-hydroxyphenyl, 2-methoxyphenyl, or 1-pyrrolyl.

[0059] In one embodiment of formula I, X^1, X^2, and X^4 are CH_2, and X^3 is N-benzyl, N-(3-methoxybenzyl), N-(4-carboxymethylbenzyl), or CH-Me, p is 1, R^1 is methyl or benzyl and R^2 is methyl or dimethylaminoethyl, or R^1 and R^2 taken together form a 4-C_{1-4} alkylsulfonyl piperazinyl, 4-methylpiperidinyl, or 3-diethylaminocarbonylpiperidinyl, and ring A is 2-hydroxyphenyl or 2-methoxyphenyl.

[0060] In one embodiment of formula I, X^1, X^2, and X^4 are CH_2, and X^3 is N-(3-methoxybenzyl) or CH-Me, p is 1, R^1 and R^2 are both methyl, or R^1 and R^2 taken together form a 4-methylsulfonylpiperazinyl or 4-ethylsulfonylpiperazinyl, and ring A is 2-hydroxyphenyl or 2-methoxyphenyl.

[0061] In one embodiment of formula I, X^1, X^2, and X^4 are CH_2, and X^3 is CH_2 or CH-Me, p is 1, R^1 and R^2 each are methyl or R^1 and R^2 taken together form 1-piperazinyl, and ring A is 2-hydroxyphenyl or 1-pyrrolyl.

[0062] In certain embodiments, the present invention provides a compound of formula **I'**:



I'

or a pharmaceutically acceptable salt thereof, wherein:

R^1 and R^2 are each independently hydrogen, or an optionally substituted group selected from C_{1-6} aliphatic, a 5-6 membered aryl ring having 0-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or a 3-7-membered saturated or partially unsaturated ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur; or R^1 and R^2, taken together with the nitrogen atom to which they are bound, form an optionally substituted 3-8 membered heterocyclyl or heteroaryl ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur, wherein R^1, R^2, or any ring formed by R^1 and R^2 taken together, are each independently optionally substituted at one or more carbon atoms with 0-4 occurrences of $-R^5$, and at one or more substitutable nitrogen atoms with $-R^6$;

Ring A is a 5-6 membered monocyclic or 8-10 membered bicyclic aryl ring having 0-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or a 3-7-membered saturated or partially unsaturated ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur, optionally substituted at one or more carbon atoms with 0-5 occurrences of $-R^7$, and at one or more substitutable nitrogen atoms with $-R^8$;

x is 0-6;

p is 0, 1, or 2; and

each occurrence of R^4, R^5, and R^7 is independently $Q\text{-}R^X$; wherein Q is a bond or is a C_1-C_6 alkylidene chain wherein up to two non-adjacent methylene units of Q are optionally and independently replaced by CO, CO_2, COCO, CONR, OCONR, NRNR, NRNRCO, NRCO, $NRCO_2$, NRCONR, SO, SO_2, $NRSO_2$, SO_2NR, $NRSO_2NR$, O, S, or NR;

each occurrence of R is independently selected from hydrogen or an optionally substituted C_{1-6} aliphatic group;

each occurrence of R' is independently selected from hydrogen or an optionally substituted group selected from C_{1-8} aliphatic, C_{6-10} aryl, a heteroaryl ring having 5-10 ring atoms, or a heterocyclyl ring having 3-10 ring atoms, or wherein R and R' taken together with the atom(s) to which they are bound, or two occurrences of R' taken together with the atom(s) to which they are bound, form a 5-8 membered cycloalkyl, heterocyclyl, aryl, or heteroaryl ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur; and

each occurrence of R^6 or R^8 is independently R', -COR', -CO_2(C_{1-6} aliphatic), -CON(R')$_2$, or -SO_2R'.

[0063] In certain other embodiments, for compounds of formula **I'** describe generally above and herein:

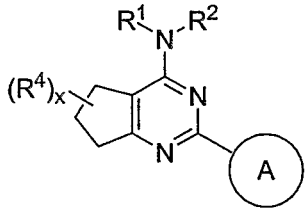
a) when p is 0 or 1, then at least one R^4 is other than hydrogen;

b) when Ring A is a substituted or unsubstituted piperizinyl group, then at least one R^4 is other than hydrogen;

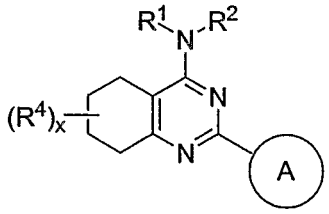
c) when R^1 is hydrogen and R^2 is 1H-indazol-3-yl, 7-fluoro-1H-indazol-3-yl, 5-fluoro-1H-indazol-3-yl, 5,7-difluoro-1H-indazol-3-yl or 5-methyl-1H-pyrazolyl, and Ring A is an unsubstituted phenyl group or is a phenyl group substituted in the ortho position with Cl or CF_3, then at least one R^4 is other than hydrogen; and

d) 5(6H)-quinazolinone, 4-anilino-7,8-dihydro-2,7-diphenyl- and 5(6H)-quinazolinone, 4-anilino-7,8-dihydro-7,7-dimethyl-2-phenyl- are excluded.

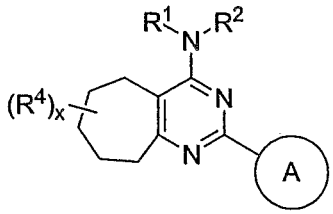
[0064] As described generally above for compounds of formula **I'**, p is 0, 1, or 2, and thus compounds have the structure shown in formula **I-A, I-B,** or **I-C**:



I-A



I-B



I-C

[0065] In certain preferred embodiments of formula **I'**, p is 1 and compounds have the structure as shown in **I-B**.

[0066] In one embodiment of formula I-B:

(i) ring A is pyrrolyl, pyridyl, fluorophenyl, hydroxyphenyl, acyloxyphenyl, hydroxy-fluorophenyl, methoxyphenyl, phenyl-phosphate disodium salt, methylpiperidyl, ethyl-carbamic acid phenyl ester;

(ii) x is 0-2, and R^4 is C_{1-4} alkyl optionally substituted with hydroxy,C_{1-4} alkoxy, or halo, hydroxy, C_{1-4} alkylcarbonyloxy or carbo(C_{1-4}alkoxy);

(iii) R^1 is hydrogen, C_{1-4} alkyl, or benzyl, and R^2 is C_{1-4} alkyl, di(C_{1-4} alkyl)amino-C_{1-4} alkyl, 2-(2'-tetrahydrofuranyl)methyl, 2-hydroxy-1-methyl-ethyl, or imidazol-5-yl-ethyl, or

(iii) R^1 and R^2 taken together form a ring selected from N-pyrrolidinyl, N-piperidinyl, N-piperazinyl, morpholinyl, thiomorpholinyl, (C_{1-4} alkyl)sulfonylpiperazinyl, wherein said ring is optionally substituted with up to 3 substituents selected from halo, oxo, hydroxy, trifluoromethyl, -O- C_{1-4} alkyl, C_{1-4} alkyl optionally substituted with hydroxy, amino, aminocarbonyl, di(C_{1-4}alkyl)aminocarbonyl, or carboxy.

[0067] In one embodiment of formula I-B:

(i) ring A is 1-pyrrolyl, 2-pyridyl, 2-fluorophenyl, 2-hydroxyphenyl, 2-acyloxyphenyl, 2-hydroxy-6-fluorophenyl, 2-methoxyphenyl, phenyl-2-phosphate disodium salt, or 4-methylpiperidyl, 2- ethyl-carbamic acid phenyl ester

(ii) x is 0, or x is 1 and R^4 is 6-methyl, 7-methyl, 8-hydroxy, or 2-t-butylcarbonyloxy, or x is 2, and R^4 is 6-carboxymethyl and 7-carboxymethyl;

(iii) R^1 is hydrogen, methyl, ethyl, or benzyl, and R^2 is methyl, ethyl, dimethylaminoethyl, 2-(2'-tetrahydrofuranyl)methyl, 2-hydroxy-1-methyl-ethyl, methylaminoethyl, imidazol-5-yl-ethyl, or

(iii) R^1 and R^2 taken together form 4-methoxypiperidinyl, N-pyrrolidinyl, 3-trifluoromethyl-1-pyrrolidinyl, 4-butylsulfonyl-piperazinyl, 1-piperidinyl, 1-piperazinyl, 4-methylpiperidinyl, 4-hydroxypiperidinyl, 4-morpholinyl, 4-methylsulfonylpiperazinyl, 4-ethylsulfonylpiperazinyl, 4-isopropylsulfonylpiperazinyl, N-piperidinyl, 3-diethylaminocarbonyl-1-piperidinyl, 4-oxo-piperidinyl, 3-aminocarbonyl-piperidinyl, 4-methylpiperazinyl, or 4-carboxyethyl-piperazinyl.

[0068] In one embodiment of formula I-B, ring A is 2-pyridyl, 2-fluorophenyl, 2-hydroxyphenyl, 2-acyloxyphenyl, 2-hydroxy-6-fluorophenyl, 2-methoxyphenyl, or 4-methylpiperidyl, x is 0, or x is 1 and R^4 is 6-methyl, 7-methyl, or 8-hydroxy, R^1 is methyl, ethyl, or benzyl, and R^2 is methyl, ethyl, dimethylaminoethyl, or 2-(2'-tetrahydrofuranyl)methyl, or R^1

and R^2 taken together form 4-methoxypiperidinyl, N-pyrrolidinyl, 4-butylsulfonyl-piperazinyl, piperidinyl, 4-methylpiperidinyl, 4-hydroxypiperidinyl, 4-morpholinyl, 4-methylsulfonylpiperazinyl, 4-ethylsulfonylpiperazinyl, N-piperidinyl, 3-diethylaminocarbonyl-1-piperidinyl, or 4-carboxyethyl-piperazinyl

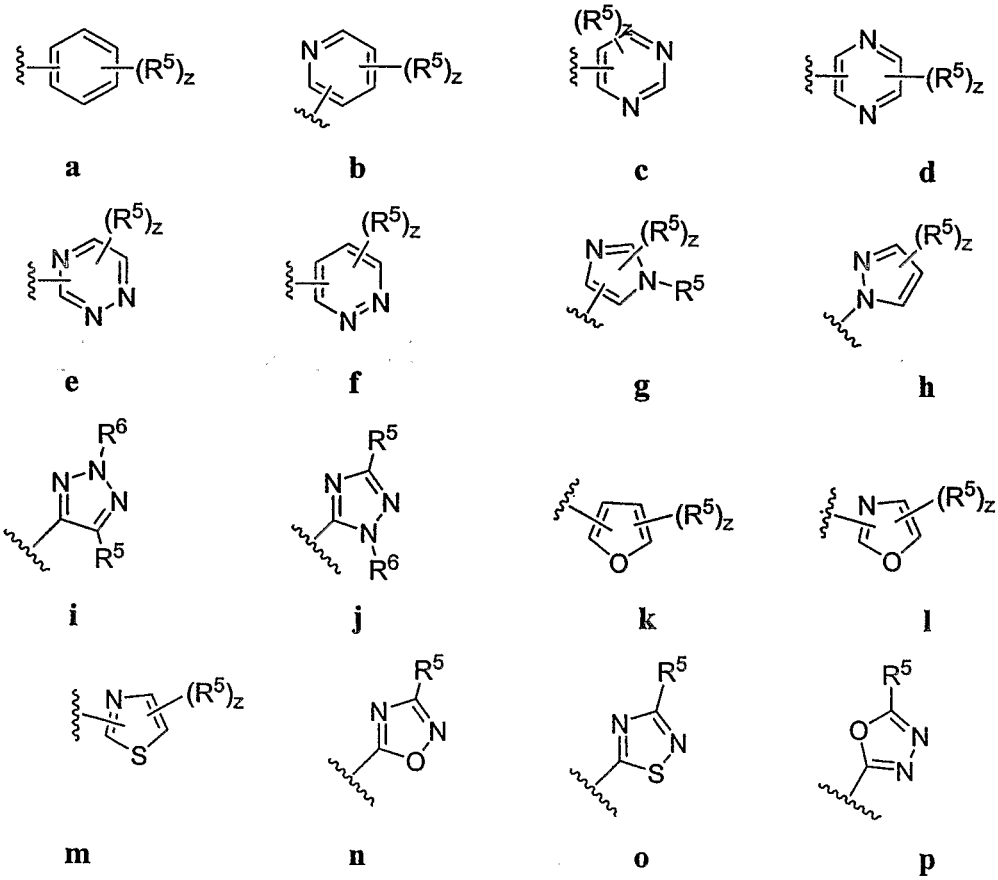
[0069] In one embodiment of formula I-B, ring A is 2-pyridyl, 2-hydroxyphenyl, 2-acyloxyphenyl, 2-hydroxy-6-fluorophenyl, or 4-methylpiperidyl, x is 0, or x is 1 and R^4 is 7-methyl, R^1 is methyl and R^2 is methyl or 2-(2'-tetrahydrofuranyl)methyl, or R^1 and R^2 taken together form 4-butylsulfonyl-piperazinyl, piperidinyl, 4-methylpiperidinyl, 4-morpholinyl, 4-methylsulfonylpiperazinyl, 4-ethylsulfonylpiperazinyl, 4-piperidinyl, or 4-carboxyethyl-piperazinyl.

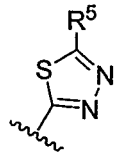
[0070] In one embodiment of formula I-B, ring A is 2-hydroxyphenyl, R^1 and R^2, taken together, form a 1-piperidinyl ring, x is 1, and R^4 is 7-methyl.

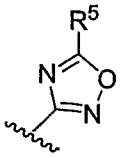
[0071] In certain preferred embodiments of any of formulae **I'**, **I-A**, **I-B**, and **I-C**, neither R^1 nor R^2 is hydrogen, and R^1 and R^2 are each independently selected from a 5- or 6-membered aryl ring having 0-5 heteroatoms independently selected from N, O, or S, a 3-7-membered saturated or partially unsaturated ring having 0-3 heteroatoms independently selected from N, O, or S, or an optionally substituted C_{1-4} aliphatic group, wherein one or more methylene units in the C_{1-4} aliphatic group are optionally and independently replaced with NR, O, (CO)O, O(CO), NR(CO), (CO)NR, SO_2(NR), or (NR)SO_2. In more preferred embodiments of any of formulae **I'**, **I-A**, **I-B**, and **I-C**, both R^1 and R^2 are each independently an optionally substituted C_{1-4} aliphatic group, wherein one or more methylene units in the C_{1-4} aliphatic group are optionally and independently replaced with NR, O, (CO)O, O(CO), NR(CO), (CO)NR, SO_2(NR), or (NR)SO_2. In yet other preferred embodiments of any of formulae **I'**, **I-A**, **I-B**, and **I-C**, when R^1 and R^2 are each independently an optionally substituted C_{1-4} aliphatic group, wherein one or more methylene units in the C_{1-4} aliphatic group are optionally and independently replaced with NR, O, (CO)O, O(CO), NR(CO), (CO)NR, SO_2(NR), or (NR)SO_2, preferred R^1 and R^2 groups are each independently optionally substituted methyl, ethyl, cyclopropyl, n-propyl, propenyl, cyclobutyl, (CO)OCH_2CH_3, $(CH_2)_2OCH_3$, CH_2(CO)OCH_2CH_3, CH_2(CO)OCH_3, $CH(CH_3)CH_2CH_3$, or t-butyl, or n-butyl. Most preferred R^1 and R^2 groups of any of formulae **I'**, **I-A**, **I-B**, and **I-C** include those shown below in Table 2.

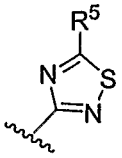
[0072] In other preferred embodiments of any of formulae **I'**, **I-A**, **I-B**, and **I-C**, one of R^1 or R^2 is hydrogen and the other of R^1 or R^2 is a 5-6 membered aryl ring having 0-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or a 3-7-membered saturated or partially unsaturated ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur. In other embodiments, one of R^1 or R^2 is hydrogen, and the other of R^1 or R^2 is an optionally substituted C_{1-4} aliphatic group, wherein one or more methylene units in the C_{1-4} aliphatic group are optionally and independently replaced with NR, O, (CO)O, O(CO), NR(CO), (CO)NR, SO_2(NR), or (NR)SO_2.

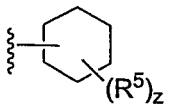
[0073] For those embodiments described above and herein where R^1 or R^2 is a 5- or 6-membered aryl ring having 0-5 heteroatoms independently selected from N, O, or S, or a 3-7 membered saturated or partially unsaturated ring having 0-3 heteroatoms independently selected from N, O, or S, preferred R^1 and R^2 groups are selected from:

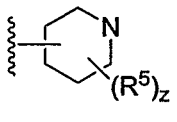


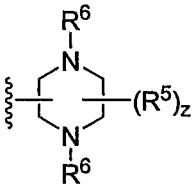

q

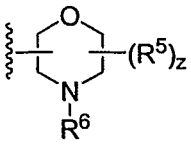

r

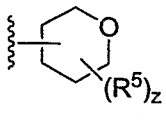

s

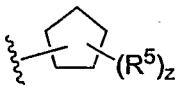

t

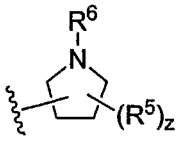

u

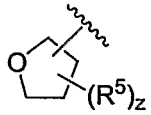

v

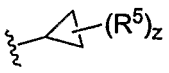

w


x


y

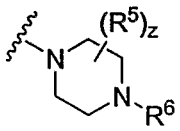

z

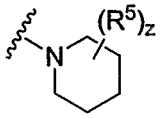

aa

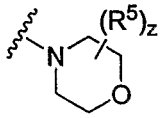

bb

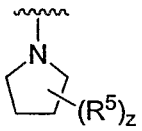
wherein each R^5 and R^6 are as previously defined and each z is independently 0-4. Most preferred rings include those shown below in Table 2.

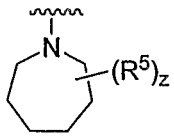
[0074] In still other embodiments, for compounds of any of formulae **I'**, **I-A**, **I-B**, and **I-C**, R^1 and R^2, taken together with the nitrogen atom to which they are bound, form an optionally substituted 3-8 membered heterocyclyl ring having 1-3 heteroatoms independently selected from nitrogen or oxygen. In certain preferred embodiments of any of formulae **I'**, **I-A**, **I-B**, and **I-C**, R^1 and R^2 are taken together with the nitrogen atom to which they are bound and form a 3-8 membered heterocyclyl group selected from:

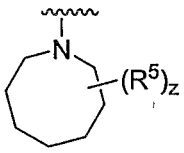

cc


dd


ee


ff


gg


hh

wherein each R^5 and R^6 are as previously defined and each z is independently 0-4.

[0075] In other preferred embodiments, for compounds of any of formulae **I'**, **I-A**, **I-B**, and **I-C**, R^1 and R^2 taken together are optionally substituted pyrrolidin-1-yl (**ff**), piperidinl-yl (**dd**), piperazin-1-yl (**cc**), or morpholin-4-yl (**ee**).

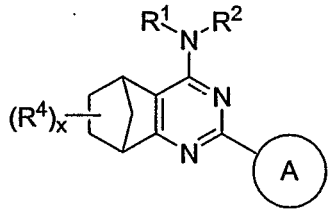
[0076] In preferred embodiments of any of formulae **I'**, **I-A**, **I-B**, and **I-C**, z is 0-2. In other preferred embodiments of any of formulae **I'**, **I-A**, **I-B**, and **I-C**, z is 0 and the ring is unsubstituted.

[0077] Preferred R^5 groups of any of formulae **I'**, **I-A**, **I-B**, and **I-C**, when present, are independently halogen, CN, NO_2, or an optionally substituted group selected from C_{1-6} alkyl, aryl, aryl(C_{1-6})alkyl, -N(R')$_2$, -CH_2N(R')$_2$, OR', -CH_2OR', SR', -CH_2SR', COOR', -NRCOR', -(CH_2)$_2$N(R')$_2$, -(CH_2)$_2$OR', -(CH_2)$_2$SR', -COR', -CON(R')$_2$, or -S(O)$_2$N(R')$_2$. In more preferred embodiments of any of formulae **I'**, **I-A**, **I-B**, and **I-C**, R^5 groups are each independently Cl, Br, F, CF_3, Me, Et, CN, NO_2, -COOH, NH_2, –N(CH_3)$_2$, -N(Et)$_2$, -N(iPr)$_2$, -O(CH_2)$_2$OCH_3, -$CONH_2$, -$COOCH_3$, -OH, -CH_2OH, -NHCOCH_3, -SO_2NH_2, SO_2N(CH_3)$_2$, piperidinyl, piperizinyl, morpholino, or an optionally substituted group selected from C_{1-4} alkoxy, phenyl, phenyloxy, benzyl, or benzyloxy. Most preferred R^5 groups include those shown below in Table 2.

[0078] In preferred embodiments of any of formulae **I'**, **I-A**, **I-B**, and **I-C**, R^6 groups are independently hydrogen, or an optionally substituted group selected from C_{1-6} alkyl, aryl, aryl(C_{1-6})alkyl, -N(R')$_2$, -CH_2N(R')$_2$, -CH_2OR', -CH_2SR', -(CH_2)$_2$N(R')$_2$, -(CH_2)$_2$OR', -(CH_2)$_2$SR', -COR', -CON(R')$_2$, or -S(O)$_2$N(R')$_2$. In more preferred embodiments of any of formulae **I'**, **I-A**, **I-B**, and **I-C**, R^6 groups are each independently H, Me, CF_3, ethyl, propyl, butyl, pentyl, CO(C_1-C_4alkyl), -$CONH_2$, -COO(C_1-C_4alkyl), -CH_2OH, -SO_2NH_2, SO_2N(CH_3)$_2$, or optionally substituted phenyl. Most preferred R^6 groups of any of formulae **I'**, **I-A**, **I-B**, and **I-C** include those shown below in Table 2.

[0079] In preferred embodiments of any of formulae **I'**, **I-A**, **I-B**, and **I-C**, x is 0, 1, or 2 and each R^4 is independently hydrogen, halogen, CN, NO_2, or an optionally substituted group selected from C_{1-6} alkyl, aryl, aryl(C_{1-6})alkyl, -N(R')$_2$, -CH_2N(R')$_2$, OR', -CH_2OR', SR', -CH_2SR', COOR', -NRCOR', -(CH_2)$_2$N(R')$_2$, -(CH_2)$_2$OR', -(CH_2)$_2$SR', -COR', -CON(R')$_2$, or -S(O)$_2$N(R')$_2$. In more preferred embodiments of any of formulae **I'**, **I-A**, **I-B**, and **I-C**, each R^4 is independently H, Cl, Br, F, CF_3, Me, Et, CN, NO_2, -COOH, NH_2, –N(CH_3)$_2$, -N(Et)$_2$, -N(iPr)$_2$, -O(CH_2)$_2$OCH_3, -$CONH_2$, -$COOCH_3$, -OH, -CH_2OH, -NHCOCH_3, -SO_2NH_2, SO_2N(CH_3)$_2$,

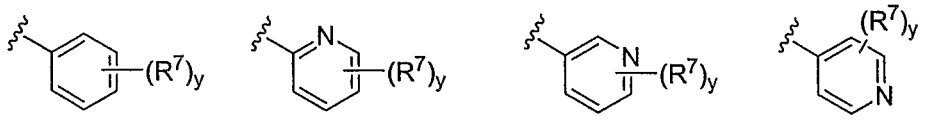
piperidinyl, piperizinyl, morpholino, or an optionally substituted group selected from C_{1-4} alkoxy, phenyl, phenyloxy, benzyl, or benzyloxy. In still other preferred embodiments of any of formulae **I'**, **I-A**, **I-B**, and **I-C**, two occurrences of R^4, taken together form an optionally substituted 3-7-membered saturated or partially unsaturated ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur. In some preferred embodiments of any of formulae **I'**, **I-A**, **I-B**, and **I-C**, two occurrences of R^4, taken together form a cycloalkyl group and compounds have the structure as shown in formula **I-B-i**:



I-B-i

[0080] Other preferred R^4 groups of any of formulae **I'**, **I-A**, **I-B**, and **I-C** include those shown below in Table 2.

[0081] In certain embodiments, for compounds of any of formulae **I'**, **I-A**, **I-B**, and **I-C**, Ring A is a phenyl, pyridinyl, pyrimidinyl, pyridazinyl, pyrazinyl, pyrrolyl, piperidinyl, indolyl, indazolyl, benzotriazolyl, pyrazolyl, benzopyrazolyl, imidazolyl, benzimidazolyl, thiazolyl, benzthizolyl, oxazolyl, benzoxazolyl, isoxazolyl, benzisoxazolyl, isothiazolyl, benzisothiazolyl, triazolyl, benzotriazolyl, thiadiazolyl, thienyl, benzothienyl, furanoyl, benzofuranoyl, or triazinyl ring, each optionally substituted at one or more carbon atoms with 0-5 occurrences of $-R^7$, and at one or more substitutable nitrogen atoms with $-R^8$. It will be appreciated that Ring A can be attached to the pyrimidinyl ring through any available carbon or nitrogen atom (e.g., a thiazole ring can be attached in the 2-, 4-, or 5-position). In certain preferred embodiments of any of formulae **I'**, **I-A**, **I-B**, and **I-C**, Ring A is optionally substituted phenyl, 2-pyridyl, 3-pyridyl, or 4-pyridyl:



a **b** **c** **d**

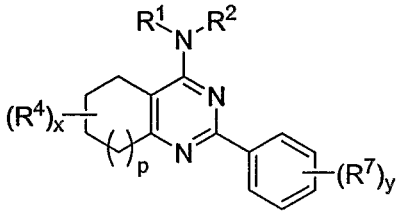
wherein each y is independently 0-5 and R^7 is as defined generally above and herein.

[0082] In preferred embodiments of any of formulae **I'**, **I-A**, **I-B**, and **I-C**, y is 0-2. In other preferred embodiments of any of formulae **I'**, **I-A**, **I-B**, and **I-C**, y is 0 and Ring A is

unsubstituted. In preferred embodiments of any of formulae **I'**, **I-A**, **I-B**, and **I-C**, R^7 groups are independently hydrogen, halogen, CN, NO_2, or an optionally substituted group selected from C_{1-6} alkyl, aryl, aryl(C_{1-6})alkyl, -N(R')$_2$, -CH_2N(R')$_2$, OR', -CH_2OR', SR', -CH_2SR', COOR', -NRCOR', -$(CH_2)_2$N(R')$_2$, -$(CH_2)_2$OR', -$(CH_2)_2$SR', -COR', -CON(R')$_2$, or -S(O)$_2$N(R')$_2$. In more preferred embodiments of any of formulae **I'**, **I-A**, **I-B**, and **I-C**, R^7 groups are each independently H, Cl, Br, F, CF_3, Me, Et, CN, NO_2, -COOH, NH_2, –N(CH_3)$_2$, -N(Et)$_2$, -N(iPr)$_2$, -O$(CH_2)_2OCH_3$, -$CONH_2$, -$COOCH_3$, -OH, -CH_2OH, -$NHCOCH_3$, -SO_2NH_2, SO_2N(CH_3)$_2$, piperidinyl, piperizinyl, morpholino, or an optionally substituted group selected from C_{1-4} alkoxy, phenyl, phenyloxy, benzyl, or benzyloxy. Most preferred R^7 groups of any of formulae **I'**, **I-A**, **I-B**, and **I-C**, include those shown below in Table 2.

[0083] In preferred embodiments of any of formulae **I'**, **I-A**, **I-B**, and **I-C**, R^8 groups are independently hydrogen, or an optionally substituted group selected from C_{1-6} alkyl, aryl, aryl(C_{1-6})alkyl, -N(R')$_2$, -CH_2N(R')$_2$, -CH_2OR', -CH_2SR', -$(CH_2)_2$N(R')$_2$, -$(CH_2)_2$OR', -$(CH_2)_2$SR', -COR', -CON(R')$_2$, or -S(O)$_2$N(R')$_2$. In more preferred embodiments of any of formulae **I'**, **I-A**, **I-B**, and **I-C**, R^8 groups are each independently H, Me, CF_3, ethyl, propyl, butyl, pentyl, CO(C_1-C_4 alkyl), -$CONH_2$, -COO(C_1-C_4 alkyl), -CH_2OH, -SO_2NH_2, SO_2N(CH_3)$_2$, or optionally substituted phenyl. Most preferred R^8 groups of any of formulae **I'**, **I-A**, **I-B**, and **I-C** include those shown below in Table 2.

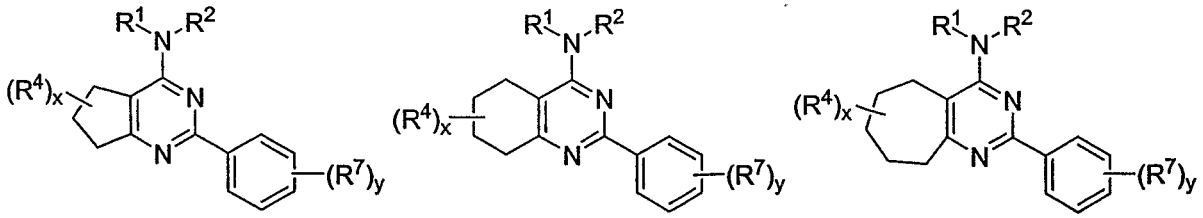
[0084] In another embodiment, Ring A is optionally substituted phenyl and compounds of formula **II** are provided:



II

wherein R^1, R^2, R^4, R^7, p, and y are as defined generally and in subsets above and herein.

[0085] In certain other preferred embodiments, for compounds of formula **I-A**, **I-B**, or **I-C**, Ring A is phenyl and compounds have the structure shown in formula **II-A**, **II-B**, or **II-C**.

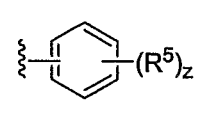


II-A II-B II-C

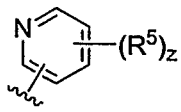
[0086] In certain preferred embodiments for compounds of any of formulae **II, II-A, II-B**, or **II-C**, neither R^1 nor R^2 is hydrogen, and R^1 and R^2 are each independently selected from a 5- or 6-membered aryl ring having 0-5 heteroatoms independently selected from N, O, or S; a 3-7 membered saturated or partially unsaturated ring having 0-3 heteroatoms independently selected from N, O, or S, or an optionally substituted C_{1-4} aliphatic group, wherein one or more methylene units in the C_{1-4} aliphatic group are optionally and independently replaced with NR, O, (CO)O, O(CO), NR(CO), (CO)NR, SO_2(NR), or (NR)SO_2. In more preferred embodiments of any of formulae **II, II-A, II-B**, or **II-C**, both R^1 and R^2 are an optionally substituted C_{1-4} aliphatic group, wherein one or more methylene units in the C_{1-4} aliphatic group are optionally and independently replaced with NR, O, (CO)O, O(CO), NR(CO), (CO)NR, SO_2(NR), or (NR)SO_2. In yet other preferred embodiments of any of formulae **II, II-A, II-B**, or **II-C**, when R^1 and R^2 are an optionally substituted C_{1-4} aliphatic group, wherein one or more methylene units in the C_{1-4} aliphatic group are optionally and independently replaced with NR, O, (CO)O, O(CO), NR(CO), (CO)NR, SO_2(NR), or (NR)SO_2, preferred R^1 and R^2 groups are optionally substituted methyl, ethyl, cyclopropyl, n-propyl, propenyl, cyclobutyl, (CO)OCH_2CH_3, $(CH_2)_2OCH_3$, CH_2(CO)OCH_2CH_3, CH_2(CO)OCH_3, $CH(CH_3)CH_2CH_3$, or t-butyl, or n-butyl. Most preferred R^1 and R^2 groups of any of formulae **II, II-A, II-B**, or **II-C** include those shown below in Table 2.

[0087] In other preferred embodiments of any of formulae **II, II-A, II-B**, or **II-C**, one of R^1 or R^2 is hydrogen and the other of R^1 or R^2 is a 5-6 membered aryl ring having 0-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or a 3-7-membered saturated or partially unsaturated ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur. In other embodiments of any of formulae **II, II-A, II-B**, or **II-C**, one of R^1 or R^2 is hydrogen, and the other of R^1 or R^2 is an optionally substituted C_{1-4} aliphatic group, wherein one or more methylene units in the C_{1-4} aliphatic group are optionally and independently replaced with NR, O, (CO)O, O(CO), NR(CO), (CO)NR, SO_2(NR), or (NR)SO_2.

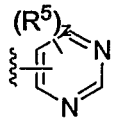
[0088] For those embodiments described above and herein where R^1 or R^2 is a 5- or 6-membered aryl ring having 0-5 heteroatoms independently selected from N, O, or S, or a 3-7 membered saturated or partially unsaturated ring having 0-3 heteroatoms independently selected from N, O, or S, preferred R^1 and R^2 groups are selected from:



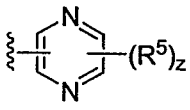
a



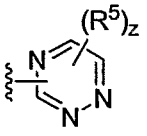
b



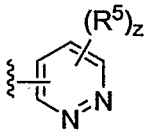
c



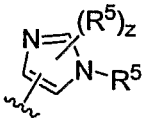
d



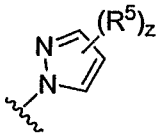
e



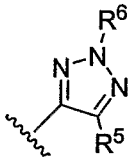
f



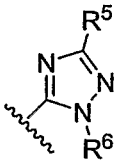
g



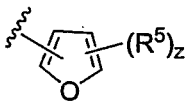
h



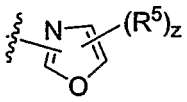
i



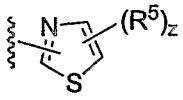
j



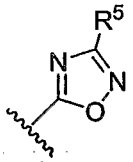
k



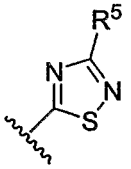
l



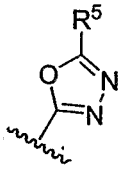
m



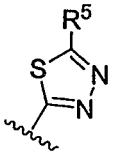
n



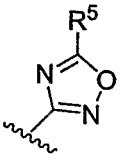
o



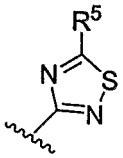
p



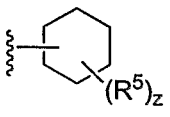
q



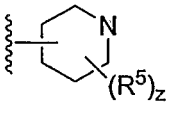
r



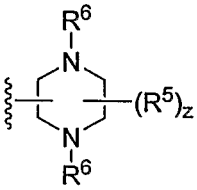
s



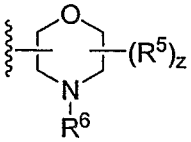
t



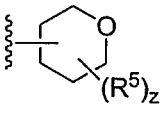
u



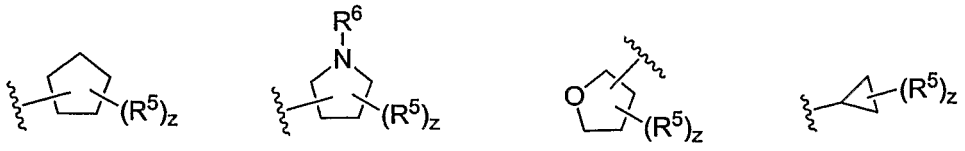
v



w



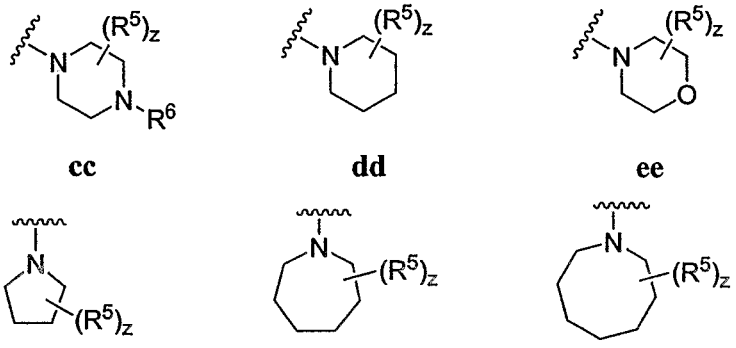
x



y **z** **aa** **bb**

wherein each R^5 and R^6 are as previously defined and each z is independently 0-4. Most preferred rings include those shown below in Table 2.

[0089] In still other embodiments, for compounds of any of formulae **II, II-A, II-B**, or **II-C**, R^1 and R^2, taken together with the nitrogen atom to which they are bound, form an optionally substituted 3-8 membered heterocyclyl ring having 1-3 heteroatoms independently selected from nitrogen or oxygen. In certain preferred embodiments of any of formulae **II, II-A, II-B**, or **II-C**, R^1 and R^2 are taken together with the nitrogen atom to which they are bound and form a 3-8 membered heterocyclyl group selected from:



cc **dd** **ee**

ff **gg** **hh**

wherein each of R^5 and R^6 are as previously defined and each z is independently 0-4.

[0090] In other preferred embodiments, for compounds of any of formulae **II, II-A, II-B**, or **II-C**, R^1 and R^2 taken together are optionally substituted pyrrolidin-1-yl (**ff**), piperidin1-yl (**dd**), piperazin-1-yl (**cc**), or morpholin-4-yl (**ee**).

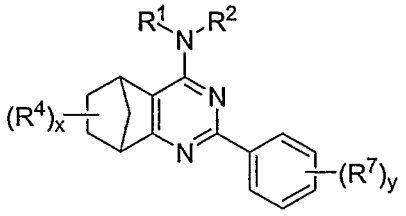
[0091] In preferred embodiments of any of formulae **II, II-A, II-B**, or **II-C**, z is 0-2. In other preferred embodiments of any of formulae **II, II-A, II-B**, or **II-C**, z is 0 and the ring is unsubstituted.

[0092] Preferred R^5 groups of any of formulae **II, II-A, II-B**, or **II-C**, when present, are independently halogen, CN, NO_2, or an optionally substituted group selected from C_{1-6} alkyl, aryl, aryl(C_{1-6})alkyl, -N(R')$_2$, -CH_2N(R')$_2$, OR', -CH_2OR', SR', -CH_2SR', COOR', -NRCOR', -$(CH_2)_2$N(R')$_2$, -$(CH_2)_2$OR', -$(CH_2)_2$SR', -COR', -CON(R')$_2$, or -$S(O)_2$N(R')$_2$. In more preferred embodiments of any of formulae **II, II-A, II-B**, or **II-C**, R^5 groups are each

independently Cl, Br, F, CF_3, Me, Et, CN, NO_2, -COOH, NH_2, $-N(CH_3)_2$, $-N(Et)_2$, $-N(iPr)_2$, $-O(CH_2)_2OCH_3$, $-CONH_2$, $-COOCH_3$, -OH, $-CH_2OH$, $-NHCOCH_3$, $-SO_2NH_2$, $SO_2N(CH_3)_2$, piperidinyl, piperizinyl, morpholino, or an optionally substituted group selected from C_{1-4} alkoxy, phenyl, phenyloxy, benzyl, or benzyloxy. Most preferred R^5 groups of any of formulae **II, II-A, II-B**, or **II-C** include those shown below in Table 2.

[0093] In preferred embodiments of any of formulae **II, II-A, II-B**, or **II-C**, R^6 groups are independently hydrogen, or an optionally substituted group selected from C_{1-6} alkyl, aryl, aryl(C_{1-6}) alkyl, $-N(R')_2$, $-CH_2N(R')_2$, $-CH_2OR'$, $-CH_2SR'$, $-(CH_2)_2N(R')_2$, $-(CH_2)_2OR'$, $-(CH_2)_2SR'$, -COR', $-CON(R')_2$, or $-S(O)_2N(R')_2$. In more preferred embodiments of any of formulae **II, II-A, II-B**, or **II-C**, R^6 groups are each independently H, Me, CF_3, ethyl, propyl, butyl, pentyl, $CO(C_1\text{-}C_4$ alkyl), $-CONH_2$, $-COO(C_1\text{-}C_4$ alkyl), $-CH_2OH$, $-SO_2NH_2$, $SO_2N(CH_3)_2$, or optionally substituted phenyl. Most preferred R^6 groups of any of formulae **II, II-A, II-B**, or **II-C** include those shown below in Table 2.

[0094] In preferred embodiments of any of formulae **II, II-A, II-B**, or **II-C**, x is 0, 1, or 2 and each R^4 is independently hydrogen, halogen, CN, NO_2, or an optionally substituted group selected from C_{1-6} alkyl, aryl, aryl(C_{1-6})alkyl, $-N(R')_2$, $-CH_2N(R')_2$, OR', $-CH_2OR'$, SR', $-CH_2SR'$, COOR', -NRCOR', $-(CH_2)_2N(R')_2$, $-(CH_2)_2OR'$, $-(CH_2)_2SR'$, -COR', $-CON(R')_2$, or $-S(O)_2N(R')_2$. In more preferred embodiments of any of formulae **II, II-A, II-B**, or **II-C**, each R^3 is independently H, Cl, Br, F, CF_3, Me, Et, CN, NO_2, -COOH, NH_2, $-N(CH_3)_2$, $-N(Et)_2$, $-N(iPr)_2$, $-O(CH_2)_2OCH_3$, $-CONH_2$, $-COOCH_3$, -OH, $-CH_2OH$, $-NHCOCH_3$, $-SO_2NH_2$, $SO_2N(CH_3)_2$, piperidinyl, piperizinyl, morpholino, or an optionally substituted group selected from C_{1-4} alkoxy, phenyl, phenyloxy, benzyl, or benzyloxy. In still other preferred embodiments of any of formulae **II, II-A, II-B**, or **II-C**, two occurrences of R^4, taken together form an optionally substituted 3-7-membered saturated or partially unsaturated ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur. In some preferred embodiments of any of formulae **II, II-A, II-B**, or **II-C**, two occurrences of R^4, taken together form a cycloalkyl group and compounds have the structure as shown in formula **II-B-i**:

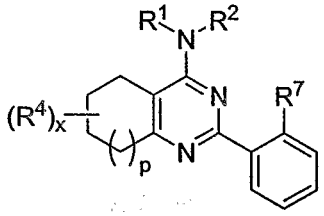


II-B-i

[0095] Other preferred R^4 groups of any of formulae **II**, **II-A**, **II-B**, or **II-C** include those shown below in Table 2.

[0096] In preferred embodiments, y is 0-2. In other preferred embodiments, y is 0 and Ring A is unsubstituted. In preferred embodiments, R^7 groups are independently hydrogen, halogen, CN, NO_2, or an optionally substituted group selected from C_{1-6} alkyl, aryl, aryl(C_{1-6})alkyl, -N(R')$_2$, -CH_2N(R')$_2$, OR', -CH_2OR', SR', -CH_2SR', COOR', -NRCOR', -(CH_2)$_2$N(R')$_2$, -(CH_2)$_2$OR', -(CH_2)$_2$SR', -COR', -CON(R')$_2$, or -S(O)$_2$N(R')$_2$. In more preferred embodiments, R^7 groups are each independently H, Cl, Br, F, CF_3, Me, Et, CN, NO_2, -COOH, NH_2, –N(CH_3)$_2$, -N(Et)$_2$, -N(iPr)$_2$, -O(CH_2)$_2$OCH_3, -$CONH_2$, -$COOCH_3$, -OH, -CH_2OH, -NHCOCH_3, -SO_2NH_2, SO_2N(CH_3)$_2$, piperidinyl, piperizinyl, morpholino, or an optionally substituted group selected from C_{1-4} alkoxy, phenyl, phenyloxy, benzyl, or benzyloxy. Most preferred R^7 groups include those shown below in Table 2.

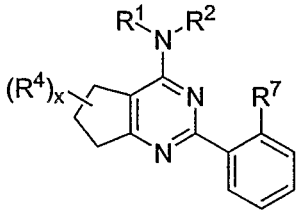
[0097] In yet other preferred embodiments y is 1 and compounds have the general formula **III**:



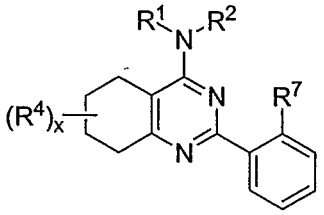
III

wherein R^1, R^2, R^4, x, and p are described generally above and herein, and R^7 is halogen, CN, NO_2, or an optionally substituted group selected from C_{1-4} alkyl, aryl, aralkyl, -N(R')$_2$, -CH_2N(R')$_2$, -OR', -CH_2OR', -SR', -CH_2SR', -COOR', -NRCOR', -CON(R')$_2$, or -S(O)$_2$N(R')$_2$.

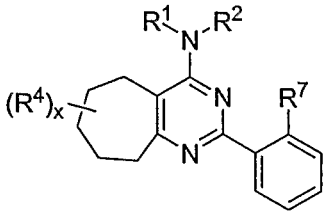
[0098] In other preferred embodiments p is 0, 1, or 2, and compounds have the structure of formula **III-A**, **III-B**, or **III-C**:



III-A



III-B



III-C

wherein R^1, R^2, R^4, and x are described generally above and herein, and each R^7 is independently halogen, CN, NO_2, or an optionally substituted group selected from C_{1-4} alkyl, aryl, aralkyl, $-N(R')_2$, $-CH_2N(R')_2$, -OR', $-CH_2OR'$, -SR', $-CH_2SR'$, -COOR', -NRCOR', $-CON(R')_2$, or $-S(O)_2N(R')_2$.

[0099] In one embodiment of formula III-A, x is 0, R^7 is hydroxy, R^1 and R^2 are both C_{1-4} alkyl, or R^1 and R^2, taken together, form a pyrrolidyl, piperidinyl, or morpholinyl ring. In another embodiment of formula IIIA, x is 0, R^7 is hydroxy, R^1 and R^2 are both methyl, or R^1 and R^2, taken together, form a pyrrolidyl or piperidinyl ring. Or, in another embodiment, x is 0, R^7 is hydroxy, R^1 and R^2 are both methyl, or R^1 and R^2, taken together, form a pyrrolidyl ring.

[00100] In one embodiment of formula III-B,

[00101] In still other preferred embodiments compounds of the invention are defined according to formula **III, III-A, III-B,** or **III-C** and one or more of, or all of, R^1, R^2, R^4 or x are further defined according to one or more of, or all of, the following groups:

a. R^1 and R^2 are each independently selected from a 5- or 6-membered aryl ring having 0-5 heteroatoms independently selected from N, O, or S, a 3-7-membered saturated or partially unsaturated ring having 0-3 heteroatoms independently selected from N, O, or S, or an optionally substituted C_{1-4} aliphatic group, wherein one or more methylene units in the C_{1-4} aliphatic group are optionally and independently replaced with NR, O, (CO)O, O(CO), NR(CO), (CO)NR, $SO_2(NR)$, or $(NR)SO_2$; and

b. x is 0, 1, or 2, and R^4 is hydrogen, halogen, CN, NO_2, or an optionally substituted group selected from C_{1-6} alkyl, aryl, aryl(C_{1-6})alkyl, $-N(R')_2$, $-CH_2N(R')_2$, OR', $-CH_2OR'$, SR', $-CH_2SR'$, COOR', -NRCOR', $-(CH_2)_2N(R')_2$, $-(CH_2)_2OR'$, $-(CH_2)_2SR'$, -COR', $-CON(R')_2$, or $-S(O)_2N(R')_2$.

[00102] In still other preferred embodiments compounds of the invention are defined according to formula **III, III-A, III-B,** or **III-C** and one or more of, or all of, R^1, R^2, R^4, x, or R^7 are further defined according to one or more of, or all of, the following groups:

a. R^1 and R^2 are each independently optionally substituted methyl, ethyl, cyclopropyl, n-propyl, propenyl, cyclobutyl, $(CO)OCH_2CH_3$, $(CH_2)_2OCH_3$, $CH_2(CO)OCH_2CH_3$, $CH_2(CO)OCH_3$, $CH(CH_3)CH_2CH_3$, or t-butyl, or n-butyl; and

b. x is 0, 1, or 2, and each R^4 is independently H, Cl, Br, F, CF_3, Me, Et, CN, NO_2, -COOH, NH_2, $-N(CH_3)_2$, $-N(Et)_2$, $-N(iPr)_2$, $-O(CH_2)_2OCH_3$, $-CONH_2$, $-COOCH_3$, -OH, $-CH_2OH$, $-NHCOCH_3$, $-SO_2NH_2$, $SO_2N(CH_3)_2$, piperidinyl, piperizinyl, morpholino, or an optionally substituted group selected from C_{1-4} alkoxy, phenyl, phenyloxy, benzyl, or benzyloxy.

[00103] In still other preferred embodiments compounds of the invention are defined according to formula **III, III-A, III-B**, or **III-C** and one or more of, or all of, R^1, R^2, R^4, x, or R^7 are further defined according to one or more of, or all of, the following groups:

a. R^1 and R^2 are each independently optionally substituted methyl, ethyl, cyclopropyl, n-propyl, propenyl, cyclobutyl, $(CO)OCH_2CH_3$, $(CH_2)_2OCH_3$, $CH_2(CO)OCH_2CH_3$, $CH_2(CO)OCH_3$, $CH(CH_3)CH_2CH_3$, or t-butyl, or n-butyl;

b. x is 0, 1, or 2, and each R^4 is independently H, Cl, Br, F, CF_3, Me, Et, CN, NO_2, -COOH, NH_2, $-N(CH_3)_2$, $-N(Et)_2$, $-N(iPr)_2$, $-O(CH_2)_2OCH_3$, $-CONH_2$, $-COOCH_3$, -OH, $-CH_2OH$, $-NHCOCH_3$, $-SO_2NH_2$, $SO_2N(CH_3)_2$, piperidinyl, piperizinyl, morpholino, or an optionally substituted group selected from C_{1-4} alkoxy, phenyl, phenyloxy, benzyl, or benzyloxy; and

c. R^7 is Cl, Br, F, CF_3, Me, Et, CN, NO_2, -COOH, NH_2, $-N(CH_3)_2$, $-N(Et)_2$, $-N(iPr)_2$, $-O(CH_2)_2OCH_3$, $-CONH_2$, $-COOCH_3$, -OH, $-CH_2OH$, $-NHCOCH_3$, $-SO_2NH_2$, $SO_2N(CH_3)_2$, piperidinyl, piperizinyl, morpholino, or an optionally substituted group selected from C_{1-4} alkoxy, phenyl, phenyloxy, benzyl, or benzyloxy.

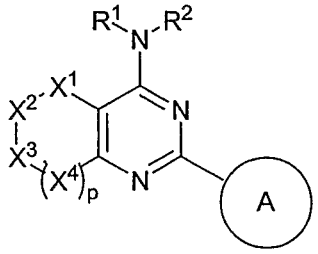
[00104] In one embodiment, formula III-C has one or more of the following features:

(i) R^7 is hydroxy;

(ii) R^1 and R^2 are both C_{1-4} alkyl, preferably, methyl, or R^1 and R^2, taken together, form a pyrrolinyl ring or morpholinyl ring; and

(iii) x is 0.

[00105] In certain embodiments, the present invention provides a compound of formula **IV**:



IV

or a pharmaceutically acceptable salt thereof, wherein:

p is 0, 1 or 2;

X^1, X^2, X^3 and X^4 are each independently selected from NR^3, C=O, CHR^4, S, O, S=O, or SO_2, as valency and stability permit, provided that that X^1, X^2, X^3 and X^4 are not each simultaneously CHR^4;

R^1 and R^2 are each independently hydrogen, or an optionally substituted group selected from C_{1-6} aliphatic, a 5-6 membered aryl ring having 0-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or a 3-7-membered saturated or partially unsaturated ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur; or R^1 and R^2, taken together with the nitrogen atom to which they are bound, form an optionally substituted 3-8 membered heterocyclyl or heteroaryl ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur, wherein R^1, R^2, or any ring formed by R^1 and R^2 taken together, are each independently optionally substituted at one or more carbon atoms with 0-4 occurrences of $-R^5$, and at one or more substitutable nitrogen atoms with $-R^6$;

Ring A is a 5-6 membered monocyclic or 8-10 membered bicyclic aryl ring having 0-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or a 3-7-membered saturated or partially unsaturated ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur, optionally substituted at one or more carbon atoms with 0-5 occurrences of $-R^7$, and at one or more substitutable nitrogen atoms with $-R^8$;

each occurrence of R^4, R^5, and R^7 is independently $Q\text{-}R^X$; wherein Q is a bond or is a C_{1-6} alkylidene chain wherein up to two non-adjacent methylene units of Q are optionally and independently replaced by CO, CO_2, COCO, CONR, OCONR, NRNR, NRNRCO, NRCO, $NRCO_2$, NRCONR, SO, SO_2, $NRSO_2$, SO_2NR, $NRSO_2NR$, O, S, or NR;

each occurrence of R^X is independently selected from R', halogen, NO_2, or CN;

each occurrence of R is independently selected from hydrogen or an optionally substituted C_{1-6} aliphatic group;

each occurrence of R' is independently selected from hydrogen or an optionally substituted group selected from C_{1-8} aliphatic, C_{6-10} aryl, a heteroaryl ring having 5-10 ring atoms, or a heterocyclyl ring having 3-10 ring atoms, or wherein R and R' taken together with the atom(s) to which they are bound, or two occurrences of R' taken together with the atom(s) to

which they are bound, form a 5-8 membered cycloalkyl, heterocyclyl, aryl, or heteroaryl ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur; and

each occurrence of R^3, R^6 or R^8 is independently R', -COR', $-CO_2(C_{1-6}$ aliphatic), $-CON(R')_2$, or $-SO_2R'$.

[00106] In certain embodiments, for compounds of formula **IV**:

a) R^1 is not hydrogen when R^2 is optionally substituted indazol-3-yl;

b) R^1 is not hydrogen when R^2 is optionally substituted pyrazol-3-yl;

c) R^1 is not hydrogen when R^2 is 1,2,4-triazol-3-yl;

d) when p is 1, then:

i) when R^1 and R^2, taken together with the nitrogen atom, is N-morpholino, and Ring A is unsubstituted phenyl, then X^1, X^2, X^3 and X^4 are not, respectively:

1) CH_2, $CH(CH_2)Ph$, NR^3, and $CHCH_3$;

2) CH_2, CH_2, CH_2, and S;

3) CH_2, S, CH_2, and S;

4) CH_2, CH_2, S, and CH_2;

5) CH_2, CHMe, S, and CH_2; or

6) CHMe, CH_2, $N(CH_2)Ph$, and CH_2;

ii) R^1 is not hydrogen, and R^2 is not CH_2Ph, $(CH_2)_2O(CH_2)_2OH$, or $-CH_2$(1,3-benzodioxol-5-yl) when Ring A is imidazol-1-yl;

iii) when R^1 and R^2, taken together with the nitrogen atom, is N-piperidinyl then:

1) when X^1, X^2 and X^3 are CH_2, and X^4 is S, then Ring A is not unsubstituted phenyl;and

2) when X^1, X^2 and X^4 are CH_2; and X^3 is S, then Ring A is not unsubstituted phenyl;

iv) when R^1 and R^2, taken together with the nitrogen atom, is N-piperizinyl, X^1, X^2 and X^3 are CH_2; and X^4 is S, then Ring A is not 3-NO_2Ph, 4-pyridinyl, or unsubstituted phenyl;

v) when one of X^1, X^2, X^3 or X^4 is NR^3 and the others of X^1, X^2, X^3 or X^4 are each CH_2, and R^1 and R^2 are each Me, H, CH_2Ph, or $(CH_2)_2NMe_2$, then Ring A is not pyrid-2-yl substituted at the 6-position;

vi) when X^1, X^2, and X^3 are each CH_2, X^4 is S, R^1 is H, and R^2 is $-CH_2-C\equiv CH$, then Ring A is not unsubstituted phenyl;

vii) when X^1 is NMe; X^2, X^3 and X^4 are each CH^2, R^1 is H, and R^2 is unsubstituted phenyl, then Ring A is not unsubstituted phenyl; and

viii) when X^1, X^2 and X^4 are each CH_2; X^3 is S, R^1 and R^2 are each Me, then Ring A is not unsubstituted phenyl; and

e) when p is 0, then:

i) when X^1 is CH_2, X^2 is NR^3, X^3 is C=O; or X^1 is C=O, X^2 is CHR^4, and X^3 is NR^3; or X^2 is NR^3, X^2 is C=O, and X^3 is CHR^4; or X^1 is CH_2, X^2 is O, and X^3 is C=O, then when R^1 is hydrogen and R^2 is unsubstituted phenyl or $-CH_2CH_2Cl$, or when R^1 and R^2, taken together form optionally substituted piperazinyl, morpholino, piperidinyl, or pyrrolidinyl, then Ring A is not optionally substituted piperidinyl, piperazinyl, morpholino, or pyrrolidinyl;

ii) when X^1 is CHR^4, X^2 is SO_2, and X^3 is CHR^4, and R^1 and R^2, taken together are piperazinyl, then Ring A is not unsubstituted phenyl;

iii) when X^1 and X^2 are CHR^4, X^3 is O, R^1 is hydrogen, and R^2 is $-C(=O)CH_3$, then Ring A is not substituted furyl;

iv) when X^1 is S, X^2 is CHR^4, X^3 is CHR^4; or X^1 is CHR^4, X^2 is S, and X^3 is CHR^4; or X^1 and X^2 are CHR^4 and X^3 is S, then Ring A is not optionally substituted N-linked morpholino, pyrrolidinyl, piperazinyl, piperidinyl, or is not unsubstituted phenyl or cyclopropyl;

v) when X^1 is CHR^4, X^2 is NR^3, X^3 is CHR^4, and R^1 and R^2 are both methyl, then Ring A is not 6-methyl-2-pyridyl;

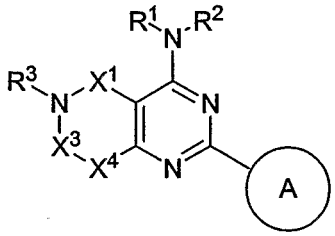
vi) when X^1 is NR^3, X^2 is C=O, X^2 is NR^3, and R^1 and R^2 are both methyl, then Ring A is not unsubstituted phenyl; and

vii) when X^1 and X^2 are CHR^4, X^3 is NR^3, R^1 is hydrogen, and R^2 is unsubstituted phenyl, then Ring A is not unsubstituted phenyl.

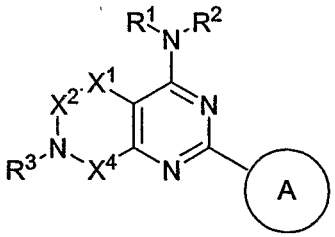
[00107] As described generally above, for compounds of formula **IV**, p is 0, 1, or 2, and X^1, X^2, X^3 and X^4 are each independently selected from NR^3, CHR^4, S, O, S=O, or SO_2, as valency and stability permit, provided that when p is 1, X^1, X^2, X^3 and X^4 are not each simultaneously CHR^4, or when p is 0, X^1, X^2, and X^3 are not each simultaneously CHR^4.

[00108] In certain embodiments, p is 0 or 1.

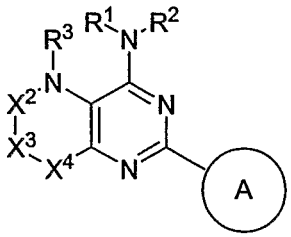
[00109] In certain preferred embodiments of formula **IV**,one or two of X^1, X^2, X^3, or X^4 is NR^3, S, O, S=O, or SO_2, and the remaining one, two, or three are each CHR^4. In more preferred embodiments of formula **IV**, one of X^1, X^2, X^3, or X^4 is NR^3, S, or O, and the remaining two (when p is 0) or three (when p is 1) are each CHR^4, and compounds have one of the following structures:



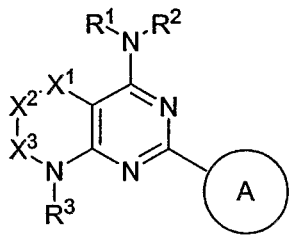
IV-A



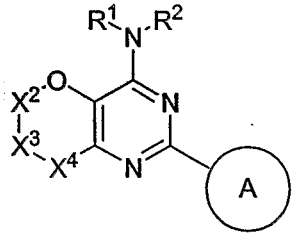
IV-B



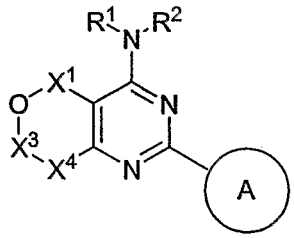
IV-C



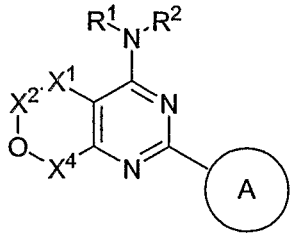
IV-D



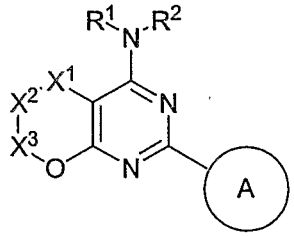
IV-E



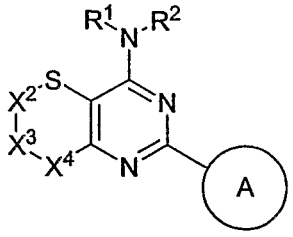
IV-F



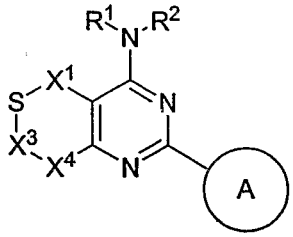
IV-G



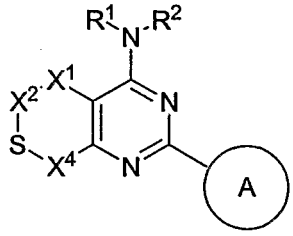
IV-H



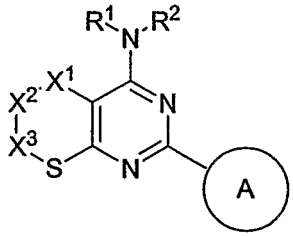
IV-I



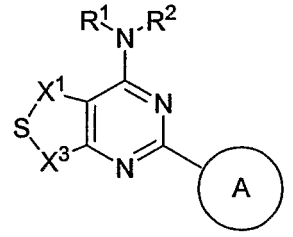
IV-J



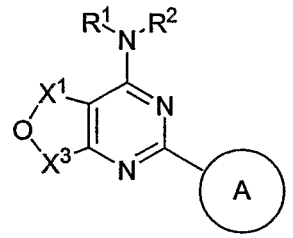
IV-K



IV-L



IV-M



IV-N

wherein each R^1, R^2, Ring A, X^1, X^2, X^3 and X^4 is as defined above and herein.

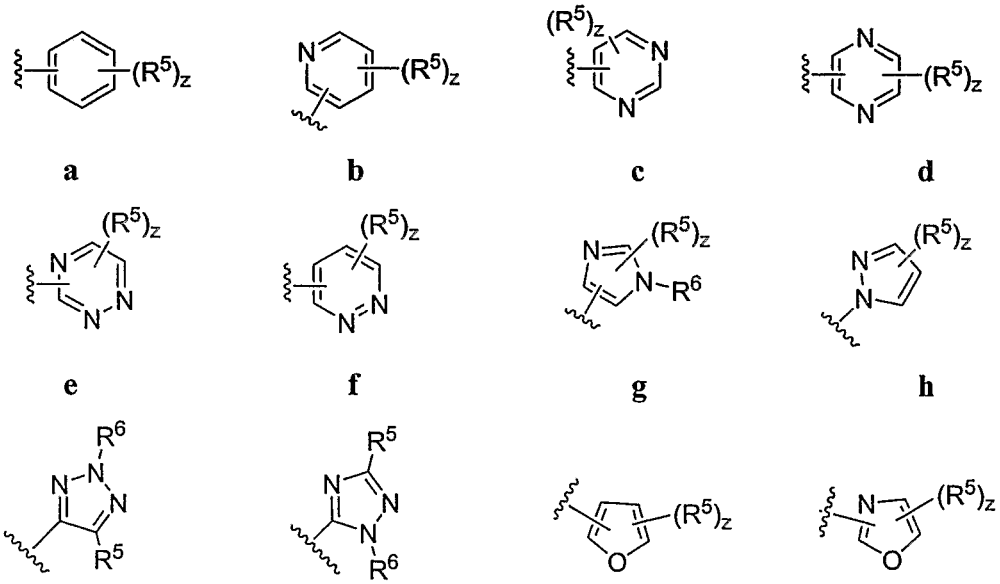
[00110] In one embodiment of formula IV-I, formula IV-J, formula IV-K, formula IV-L, or formula IV-M, the sulfur ring atom is replaced with sulfoxy. Or, the sulfur ring atom is replaced with sulfonyl.

[00111] In certain preferred embodiments of formula **IV**, neither R^1 nor R^2 is hydrogen, and R^1 and R^2 are each independently selected from a 5- or 6-membered aryl ring having 0-5 heteroatoms independently selected from N, O, or S, a 3-7-membered saturated or partially unsaturated ring having 0-3 heteroatoms independently selected from N, O, or S, or an optionally substituted C_{1-4} aliphatic group, wherein one or more methylene units in the C_{1-4} aliphatic group are optionally and independently replaced with NR, O, (CO)O, O(CO), NR(CO), (CO)NR, SO_2(NR), or (NR)SO_2. In more preferred embodiments of formula **IV**, both R^1 and R^2 are an optionally substituted C_{1-4} aliphatic group, wherein one or more methylene units in the C_{1-4} aliphatic group are optionally and independently replaced with NR, O, (CO)O, O(CO), NR(CO),

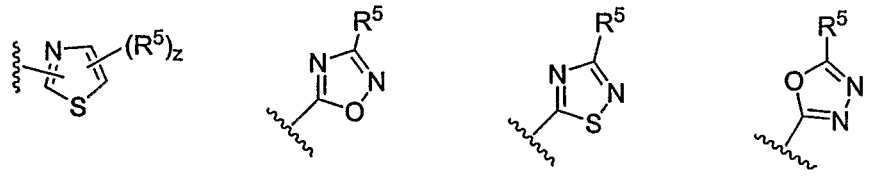
(CO)NR, SO_2(NR), or (NR)SO_2. In yet other preferred embodiments of formula **IV**, when R^1 and R^2 are an optionally substituted C_{1-4} aliphatic group, wherein one or more methylene units in the C_{1-4} aliphatic group are optionally and independently replaced with NR, O, (CO)O, O(CO), NR(CO), (CO)NR, SO_2(NR), or (NR)SO_2, preferred R^1 and R^2 groups are optionally substituted methyl, ethyl, cyclopropyl, n-propyl, propenyl, cyclobutyl, $(CO)OCH_2CH_3$, $(CH_2)_2OCH_3$, $CH_2(CO)OCH_2CH_3$, $CH_2(CO)OCH_3$, $CH(CH_3)CH_2CH_3$, or t-butyl, or n-butyl. Most preferred R^1 and R^2 groups of formula **IV** include those shown below in Table 2.

[00112] In other preferred embodiments of formula **IV**, one of R^1 or R^2 is hydrogen and the other of R^1 or R^2 is a 5-6 membered aryl ring having 0-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or a 3-7-membered saturated or partially unsaturated ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur. In other embodiments of formula **IV**, one of R^1 or R^2 is hydrogen, and the other of R^1 or R^2 is an optionally substituted C_{1-4} aliphatic group, wherein one or more methylene units in the C_{1-4} aliphatic group are optionally and independently replaced with NR, O, (CO)O, O(CO), NR(CO), (CO)NR, SO_2(NR), or (NR)SO_2.

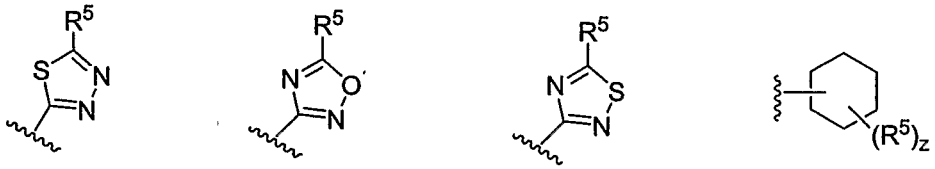
[00113] For those embodiments described above and herein for compounds of formula **IV** where R^1 or R^2 is a 5- or 6-membered aryl ring having 0-5 heteroatoms independently selected from N, O, or S, or a 3-7-membered saturated or partially unsaturated ring having 0-3 heteroatoms independently selected from N, O, or S, preferred R^1 and R^2 groups are selected from:



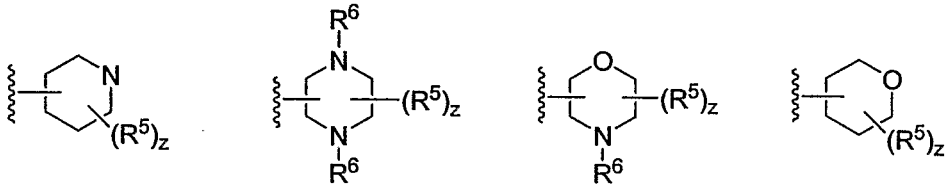
i j k l



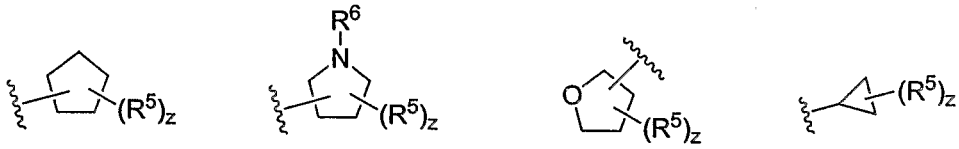
m n o p



q r s t



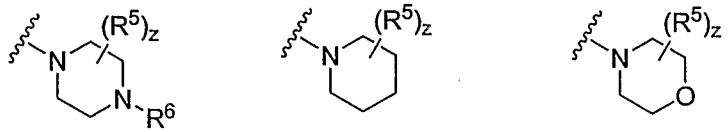
u v w x



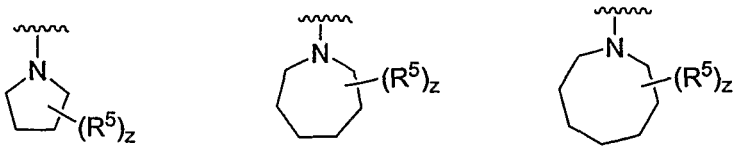
y z aa bb

wherein each R^5 and R^6 is as previously defined and each z is independently 0-4. Most preferred rings include those shown below in Table 2.

[00114] In still other embodiments for compounds of formula **IV**, R^1 and R^2, taken together with the nitrogen atom to which they are bound, form an optionally substituted 3-8 membered heterocyclyl ring having 1-3 heteroatoms independently selected from nitrogen or oxygen. In certain preferred embodiments, R^1 and R^2 are taken together with the nitrogen atom to which they are bound and form a 3-8 membered heterocyclyl group selected from:



cc dd ee



ff **gg** **hh**

wherein each R^5 and R^6 is as previously defined and each z is independently 0-4.

[00115] In other preferred embodiments of formula **IV**, R^1 and R^2 taken together are optionally substituted pyrrolidin-1-yl (**ff**), piperidin1-yl (**dd**), piperazin-1-yl (**cc**), or morpholin-4-yl (**ee**).

[00116] In preferred embodiments of formula **IV**, z is 0-2. In other preferred embodiments of formula **IV**, z is 0 and the ring is unsubstituted.

[00117] Preferred R^5 groups of formula **IV**, when present, are independently halogen, CN, NO_2, or an optionally substituted group selected from C_{1-6} alkyl, aryl, aryl(C_{1-6})alkyl, -$N(R')_2$, -$CH_2N(R')_2$, OR', -CH_2OR', SR', -CH_2SR', COOR', -NRCOR', -$(CH_2)_2N(R')_2$, -$(CH_2)_2OR'$, -$(CH_2)_2SR'$, -COR', -$CON(R')_2$, SO_2R', or -$SO_2N(R')_2$. In more preferred embodiments of formula **IV**, R^5 groups are each independently Cl, Br, F, CF_3, Me, Et, CN, NO_2, -COOH, NH_2, -$N(CH_3)_2$, -$N(Et)_2$, -$N(iPr)_2$, -$O(CH_2)_2OCH_3$, -$CO(C_1$-C_4 alkyl), -$CONH_2$, -$COOCH_3$, -OH, -CH_2OH, -$NHCOCH_3$, -$SO_2(C_1$-C_4 alkyl), -SO_2NH_2, -$SO_2N(CH_3)_2$, piperidinyl, piperizinyl, morpholino, or an optionally substituted group selected from C_{1-4} alkoxy, phenyl, phenyloxy, benzyl, or benzyloxy. Most preferred R^5 groups of formula **IV** include those shown below in Table 2.

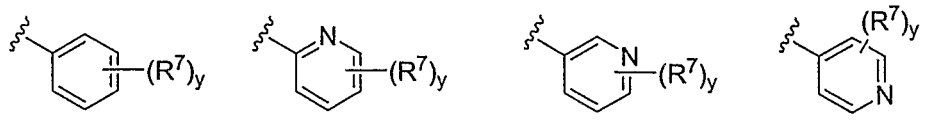
[00118] In preferred embodiments of formula **IV**, R^6 groups are independently hydrogen, or an optionally substituted group selected from C_{1-6} alkyl, aryl, aryl(C_{1-6})alkyl, -$N(R')_2$, -$CH_2N(R')_2$, -CH_2OR', -CH_2SR', -$(CH_2)_2N(R')_2$, -$(CH_2)_2OR'$, -$(CH_2)_2SR'$, -COR', -$CON(R')_2$, SO_2R', or -$S(O)_2N(R')_2$. In more preferred embodiments of formula **IV**, R^6 groups are each independently H, Me, CF_3, ethyl, propyl, butyl, pentyl, $CO(C_1$-C_4 alkyl), -$CONH_2$, -$COO(C_1$-C_4 alkyl), -CH_2OH, -$SO_2(C_1$-C_4alkyl), -SO_2NH_2, $SO_2N(CH_3)_2$, or optionally substituted phenyl or benzyl. Most preferred R^6 groups of formula **IV** include those shown below in Table 2.

[00119] In preferred embodiments of formula **IV**, R^4 groups are independently hydrogen, halogen, CN, NO_2, or an optionally substituted group selected from C_{1-6} alkyl, aryl, aryl(C_{1-6})alkyl, -$N(R')_2$, -$CH_2N(R')_2$, OR', -CH_2OR', SR', -CH_2SR', COOR', -NRCOR', -$(CH_2)_2N(R')_2$, -$(CH_2)_2OR'$, -$(CH_2)_2SR'$, -COR', -$CON(R')_2$, SO_2R', or -$SO_2N(R')_2$. In more preferred

embodiments of formula **IV**, R^4 groups are each independently H, Cl, Br, F, CF_3, Me, Et, CN, NO_2, -COOH, NH_2, $-N(CH_3)_2$, $-N(Et)_2$, $-N(iPr)_2$, $-O(CH_2)_2OCH_3$, $-CO(C_1\text{-}C_4alkyl)$, $-CONH_2$, $-COOCH_3$, -OH, $-CH_2OH$, $-NHCOCH_3$, $-SO_2(C_1\text{-}C_4alkyl)$, $-SO_2NH_2$, $-SO_2N(CH_3)_2$, piperidinyl, piperizinyl, morpholino, or an optionally substituted group selected from $C_{1\text{-}4}$ alkoxy, phenyl, phenyloxy, benzyl, or benzyloxy. Most preferred R^4 groups of formula **IV** include those shown below in Table 2.

[00120] In preferred embodiments of formula **IV**, R^3 groups are independently hydrogen, or an optionally substituted group selected from $C_{1\text{-}6}$ alkyl, aryl, aryl($C_{1\text{-}6}$)alkyl, $-N(R')_2$, $-CH_2N(R')_2$, $-CH_2OR'$, $-CH_2SR'$, $-(CH_2)_2N(R')_2$, $-(CH_2)_2OR'$, $-(CH_2)_2SR'$, -COR', $-CON(R')_2$, SO_2R', or $-S(O)_2N(R')_2$. In more preferred embodiments of formula **IV**, R^3 groups are each independently H, Me, CF_3, ethyl, propyl, butyl, pentyl, $CO(C_1\text{-}C_4alkyl)$, $-CONH_2$, $-COO(C_1\text{-}C_4alkyl)$, $-CH_2OH$, $-SO_2(C_1\text{-}C_4alkyl)$, $-SO_2NH_2$, $SO_2N(CH_3)_2$, or optionally substituted phenyl or benzyl. Most preferred R^3 groups of formula **IV** include those shown below in Table 2.

[00121] As described generally above of formula **IV**, Ring A is a 5-6 membered aryl ring having 0-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or a 3-7-membered saturated or partially unsaturated ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur, optionally substituted at one or more carbon atoms with 0-5 occurrences of $-R^7$, and at one or more substitutable nitrogen atoms with $-R^8$. In certain embodiments, for compounds of formula **IV** or compounds of formulae **IV-A** through **IV-N**, Ring A is a phenyl, pyridinyl, pyrimidinyl, pyridazinyl, pyrazinyl, pyrrolyl, piperidinyl, indolyl, indazolyl, benzotriazolyl, pyrazolyl, benzopyrazolyl, imidazolyl, benzimidazolyl, thiazolyl, benzthizolyl, oxazolyl, benzoxazolyl, isoxazolyl, benzisoxazolyl, isothiazolyl, benzisothiazolyl, triazolyl, benzotriazolyl, thiadiazolyl, thienyl, benzothienyl, furanoyl, benzofuranoyl, or triazinyl ring, each optionally substituted at one or more carbon atoms with 0-5 occurrences of $-R^7$, and at one or more substitutable nitrogen atoms with $-R^8$. It will be appreciated that Ring A can be attached to the pyrimidinyl ring through any available carbon or nitrogen atom (e.g., a thiazole ring can be attached in the 2-, 4-, or 5-position). In certain preferred embodiments of formula **IV**, Ring A is optionally substituted phenyl, 2-pyridyl, 3-pyridyl, or 4-pyridyl:



a **b** **c** **d**

wherein each y is independently 0-5 and each R^7 is as defined generally above.

[00122] In preferred embodiments of formula **IV**, y is 0-2. In other preferred embodiments of formula **IV**, y is 0 and Ring A is unsubstituted.

[00123] In preferred embodiments of formula **IV**, R^7 groups are independently hydrogen, halogen, CN, NO_2, or an optionally substituted group selected from C_{1-6} alkyl, aryl, aryl(C_{1-6})alkyl, -N(R')$_2$, -CH_2N(R')$_2$, OR', -CH_2OR', SR', -CH_2SR', COOR', -NRCOR', -(CH_2)$_2$N(R')$_2$, -(CH_2)$_2$OR', -(CH_2)$_2$SR', -COR', -CON(R')$_2$, SO_2R', or -SO_2N(R')$_2$. In more preferred embodiments of formula **IV**, R^7 groups are each independently H, Cl, Br, F, CF_3, Me, Et, CN, NO_2, -COOH, NH_2, –N(CH_3)$_2$, -N(Et)$_2$, -N(iPr)$_2$, -O(CH_2)$_2$OCH_3, -CO(C_1-C_4alkyl), -$CONH_2$, -$COOCH_3$, -OH, -CH_2OH, -NHCOCH_3, -SO_2(C_1-C_4alkyl), -SO_2NH_2, -SO_2N(CH_3)$_2$, piperidinyl, piperizinyl, morpholino, or an optionally substituted group selected from C_{1-4} alkoxy, phenyl, phenyloxy, benzyl, or benzyloxy. Most preferred R^7 groups of formula **IV** include those shown below in Table 2.

[00124] In preferred embodiments of formula **IV**, R^8 groups are independently hydrogen, or an optionally substituted group selected from C_{1-6} alkyl, aryl, aryl(C_{1-6})alkyl, -N(R')$_2$, -CH_2N(R')$_2$, -CH_2OR', -CH_2SR', -(CH_2)$_2$N(R')$_2$, -(CH_2)$_2$OR', -(CH_2)$_2$SR', -COR', -CON(R')$_2$, SO_2R', or -S(O)$_2$N(R')$_2$. In more preferred embodiments of formula **IV**, R^8 groups are each independently H, Me, CF_3, ethyl, propyl, butyl, pentyl, CO(C_1-C_4alkyl), -$CONH_2$, -COO(C_1-C_4alkyl), -CH_2OH, -SO_2(C_1-C_4alkyl), -SO_2NH_2, SO_2N(CH_3)$_2$, or optionally substituted phenyl or benzyl. Most preferred R^8 groups of formula **IV** include those shown below in Table 2.

[00125] In one embodiment of formula IV-A, R^1 hydrogen or methyl, and R^2 is methyl, 5-methyl-pyrazol-3-yl, 5-fluoro-benzopyrazol-3-yl, or benzopyrazol-3-yl, X^1, X^3, and X^4 each is CH_2, R^3 is hydrogen, acyl, 1-oxo-2-methoxy-ethyl, 1-oxo-propyl, methylsulfonyl, ethylsulfonyl, benzyl, and ring A is phenyl optionally substituted with halo, trifluoromethyl, hydroxy, C_{1-4} alkyl, or C_{1-4} alkoxy, preferably, methoxy, or ring A is 2,3-Dihydro-benzo[1,4]dioxin-3-yl.

[00126] In one embodiment of formula IV-A, R^1 hydrogen or methyl, and R^2 is methyl, 5-methyl-pyrazol-3-yl, 5-fluoro-benzopyrazol-3-yl, or benzopyrazol-3-yl, X^1, X^3, and X^4 each is CH_2, R^3 is hydrogen or benzyl, and ring A is phenyl optionally substituted with halo, trifluoromethyl, hydroxy, C_{1-4} alkyl, or C_{1-4} alkoxy, preferably, methoxy, or ring A is 2,3-Dihydro-benzo[1,4]dioxin-3-yl.

[00127] In one embodiment of formula IV-A, R^1 hydrogen or methyl, and R^2 is methyl, 5-methyl-pyrazol-3-yl, 5-fluoro-benzopyrazol-3-yl, or benzopyrazol-3-yl, X^1, X^3, and X^4 each is CH_2, R^3 is hydrogen or benzyl, and ring A is phenyl optionally substituted with halo, hydroxy or C_{1-4} alkoxy, preferably, methoxy.

[00128] In one embodiment of formula IV-B, R^1 is hydrogen or methyl, R^2 is methyl or 5-fluorobenzimidazol-3-yl, 5-methylimidazol-3-yl, X^1, X^3, and X^4 each is CH_2, R^3 is hydrogen, C_{1-4} alkyl, benzyl optionally substituted with carboxy-C_{1-4} alkyl, C_{1-4} alkylsulfonyl, acyl, methylcarboxyethyl, C_{1-4} alkylcarbonyl, methoxymethylcarbonyl, or benzoyl, and ring A is phenyl substituted with 2-hydroxy, 2-trifluoromethyl, 4-methyl, 4-carboxylic acid, 4-trifluoromethyloxy, or 2-C_{1-4} alkoxy, preferably, methoxy.

[00129] In one embodiment of formula IV-B, R^1 is hydrogen or methyl, R^2 is methyl or 5-fluorobenzimidazol-3-yl, X^1, X^3, and X^4 each is CH_2, R^3 is C_{1-4} alkyl, benzyl optionally substituted with carboxy-C_{1-4} alkyl, C_{1-4} alkylsulfonyl, acyl, methylcarboxyethyl, C_{1-4} alkylcarbonyl, or benzoyl, and ring A is phenyl substituted with 2-hydroxy, 2-trifluoromethyl, or 2-C_{1-4} alkoxy, preferably, methoxy.

[00130] In one embodiment of formula IV-B, R^1 and R^2, each is methyl, X^1, X^3, and X^4 each is CH_2, R^3 is C_{1-4} alkyl, benzyl optionally substituted with carboxy-C_{1-4} alkyl, C_{1-4} alkylsulfonyl, or benzoyl, and ring A is phenyl substituted with 2-hydroxy or 2-C_{1-4} alkoxy, preferably, methoxy.

[00131] In one embodiment of formula IV-B, R^1 and R^2, each is methyl, X^1, X^3, and X^4 each is CH_2, R^3 is C_{1-4} alkyl, or benzyl optionally substituted with carboxy-C_{1-4} alkyl, and ring A is phenyl substituted with 2-hydroxy or 2-C_{1-4} alkoxy, preferably, methoxy.

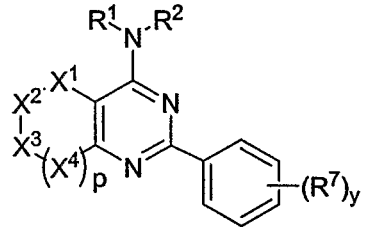
[00132] In one embodiment of formula IV-B, R^1 and R^2, each is methyl, X^1, X^3, and X^4 each is CH_2, R^3 is C_{1-4} alkyl, benzyl optionally substituted with carboxy-C_{1-4} alkyl, C_{1-4} alkoxy, and ring A is 2-hydroxy phenyl or 2-C_{1-4} alkoxyphenyl.

[00133] In one embodiment of formula IV-B, R^1 and R^2, each is methyl, X^1, X^3, and X^4 each is CH_2, R^3 is benzyl optionally substituted with carboxy-C_{1-4} alkyl, C_{1-4} alkoxy, and ring A is 2-hydroxy phenyl.

[00134] In one embodiment of formula IV-M, R^1 is hydrogen or methyl, and R^2 is methyl, benzimidazol-3-yl, 5-methyl-imidazol-3-yl, ring A is 2-hydroxyphenyl, 2-fluorophenyl, 2-trifluoromethylphenyl or phenyl.

[00135] In one embodiment of formula IV-M, R^1 is hydrogen or methyl, and R^2 is methyl, benzimidazol-3-yl, 5-methyl-imidazol-3-yl, ring A is 2-trifluoromethylphenyl or phenyl.

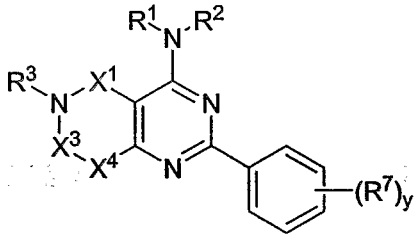
[00136] In another embodiment, Ring A is optionally substituted phenyl, and compounds of formula V are provided:



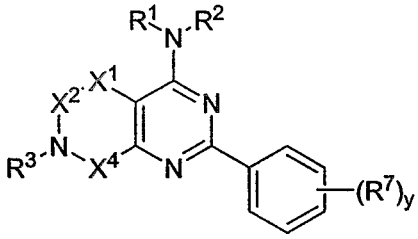
V

wherein each of R^1, R^2, X^1, X^2, X^3, X^4, R^7, and y are as defined generally and in subsets above and herein.

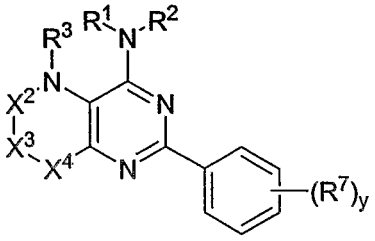
[00137] In certain preferred embodiments of formula V, one or two of X^1, X^2, X^3, or X^4 is independently NR^3, S, C=O, O, S=O, or SO_2, and the remaining two or three are each CHR^4. In more preferred embodiments of formula V, one of X^1, X^2, X^3, or X^4 is NR^3, S, or O, and the remaining three are each CHR^4, and compounds have one of the following structures:



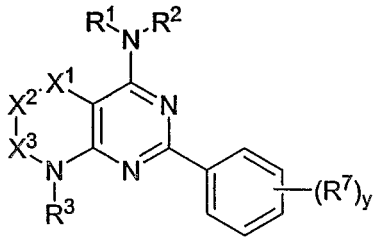
V-A



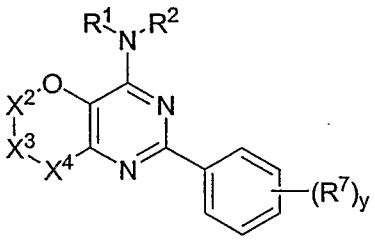
V-B

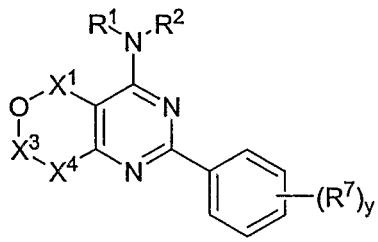


V-C

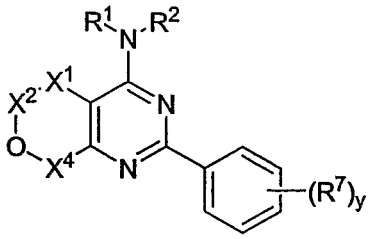


V-D

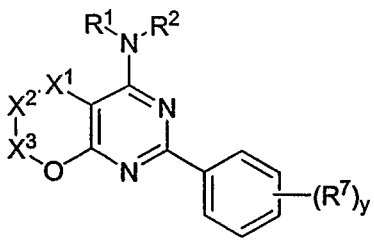




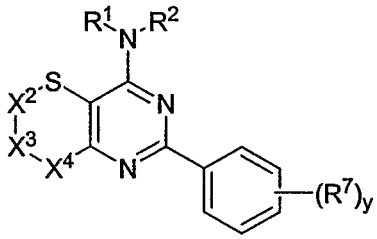
V-E



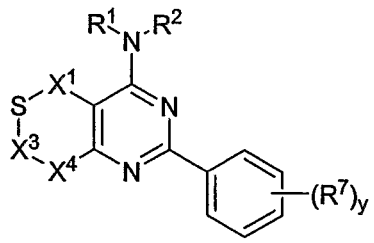
V-F



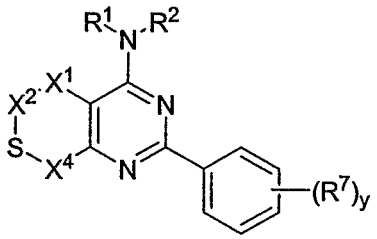
V-G



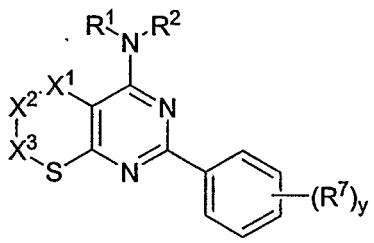
V-H



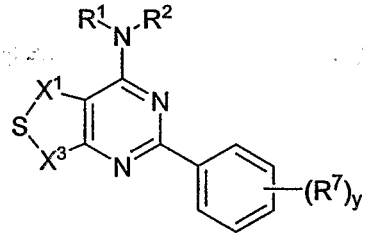
V-I



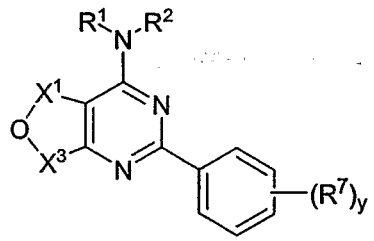
V-J



V-K



V-L



V-M

V-N

[00138] As described generally above for compounds of general formula V-A through V-N, R^1 and R^2 are each independently hydrogen, or an optionally substituted group selected from C_{1-6} aliphatic, a 5-6 membered aryl ring having 0-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or a 3-7-membered saturated or partially unsaturated ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or R^1 and R^2, taken together with the nitrogen atom to which they are bound, form an optionally substituted 3-8 membered heterocyclyl or heteroaryl ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur, wherein R^1, R^2, or any ring formed by R^1 and R^2 taken together, are

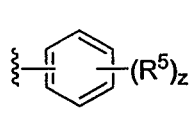
each independently optionally substituted at one or more carbon atoms with 0-4 occurrences of $-R^5$, and at one or more substitutable nitrogen atoms with $-R^6$.

[00139] In certain preferred embodiments, for compounds of any of **V-A** through **V-N**, neither R^1 nor R^2 is hydrogen, and R^1 and R^2 are each independently selected from a 5- or 6-membered aryl ring having 0-5 heteroatoms independently selected from N, O, or S, a 3-7-membered saturated or partially unsaturated ring having 0-3 heteroatoms independently selected from N, O, or S, or an optionally substituted C_{1-4} aliphatic group, wherein one or more methylene units in the C_{1-4} aliphatic group are optionally and independently replaced with NR, O, (CO)O, O(CO), NR(CO), (CO)NR, SO_2(NR), or (NR)SO_2. In more preferred embodiments of any of formulae **V-A** through **V-N**, both R^1 and R^2 are an optionally substituted C_{1-4} aliphatic group, wherein one or more methylene units in the C_{1-4} aliphatic group are optionally and independently replaced with NR, O, (CO)O, O(CO), NR(CO), (CO)NR, SO_2(NR), or (NR)SO_2. In yet other preferred embodiments of any of formulae **V-A** through **V-N**, when R^1 and R^2 are an optionally substituted C_{1-4} aliphatic group, wherein one or more methylene units in the C_{1-4} aliphatic group are optionally and independently replaced with NR, O, (CO)O, O(CO), NR(CO), (CO)NR, SO_2(NR), or (NR)SO_2, preferred R^1 and R^2 groups are optionally substituted methyl, ethyl, cyclopropyl, n-propyl, propenyl, cyclobutyl, (CO)OCH_2CH_3, $(CH_2)_2OCH_3$, CH_2(CO)OCH_2CH_3, CH_2(CO)OCH_3, $CH(CH_3)CH_2CH_3$, or t-butyl, or n-butyl. Most preferred R^1 and R^2 groups of any of formulae **V-A** through **V-N** include those shown below in Table 2.

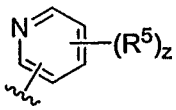
[00140] In other preferred embodiments of any of formulae **V-A** through **V-N**, one of R^1 or R^2 is hydrogen and the other of R^1 or R^2 is a 5-6 membered aryl ring having 0-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or a 3-7-membered saturated or partially unsaturated ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur. In other embodiments of any of formulae **V-A** through **V-N**, one of R^1 or R^2 is hydrogen, and the other of R^1 or R^2 is an optionally substituted C_{1-4} aliphatic group, wherein one or more methylene units in the C_{1-4} aliphatic group are optionally and independently replaced with NR, O, (CO)O, O(CO), NR(CO), (CO)NR, SO_2(NR), or (NR)SO_2.

[00141] For those embodiments described above and herein, for any of formulae **V-A** through **V-N**, where R^1 or R^2 is a 5- or 6-membered aryl ring having 0-5 heteroatoms independently selected from N, O, or S, or a 3-7-membered saturated or partially unsaturated ring having 0-3

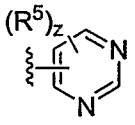
heteroatoms independently selected from N, O, or S, preferred R^1 and R^2 groups are selected from:



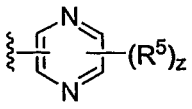
a



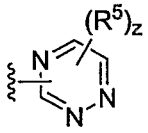
b



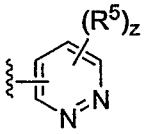
c



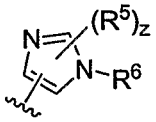
d



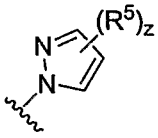
e



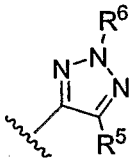
f



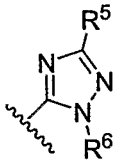
g



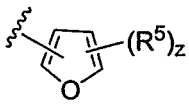
h



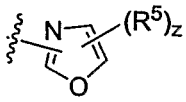
i



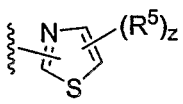
j



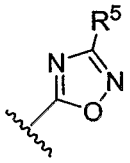
k



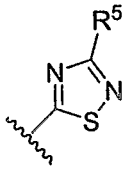
l



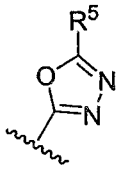
m



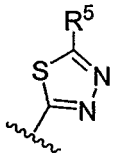
n



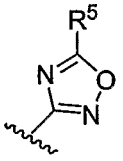
o



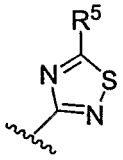
p



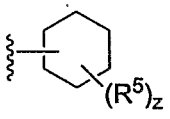
q



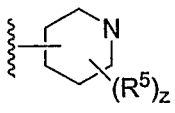
r



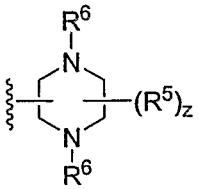
s



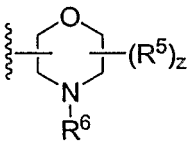
t



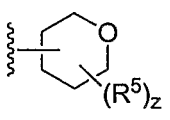
u



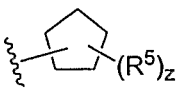
v

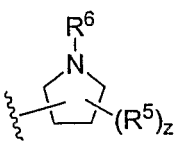


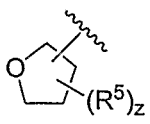
w

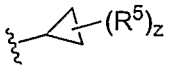


x





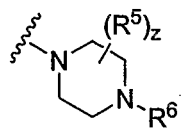




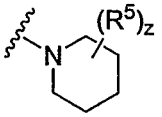
y **z** **aa** **bb**

wherein each R^5 and R^6 is as previously defined and each z is independently 0-4. Most preferred rings include those shown below in Table 2.

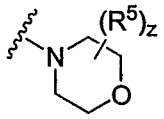
[00142] In still other embodiments of any of formulae **V-A** through **V-N**, R^1 and R^2, taken together with the nitrogen atom to which they are bound, form an optionally substituted 3-8 membered heterocyclyl ring having 1-3 heteroatoms independently selected from nitrogen or oxygen. In certain preferred embodiments of any of formulae **V-A** through **V-N**, R^1 and R^2 are taken together with the nitrogen atom to which they are bound and form a 3-8 membered heterocyclyl group selected from:



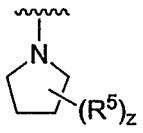
cc



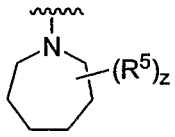
dd



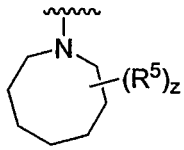
ee



ff



gg



hh

wherein each R^5 and R^6 is as previously defined and each z is independently 0-4.

[00143] In other preferred embodiments of any of formulae **V-A** through **V-N**, R^1 and R^2 taken together are optionally substituted pyrrolidin-1-yl (**ff**), piperidinl-yl (**dd**), piperazin-1-yl (**cc**), or morpholin-4-yl (**ee**).

[00144] As described generally above for any of formulae **V-A** through **V-N**, when R^1 or R^2 is a 5-6 membered aryl ring having 0-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or a 3-7 membered saturated or partially unsaturated ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or when R^1 and R^2, taken together with the nitrogen atom to which they are bound, form an optionally substituted 3-8 membered heterocyclyl or heteroaryl ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur, the ring can be substituted with up to four independent occurrences of R^5.

[00145] In preferred embodiments of any of formulae **V-A** through **V-N**, z is 0-2. In other preferred embodiments of any of formulae **V-A** through **V-N**, z is 0 and the ring is unsubstituted.

[00146] Preferred R^5 groups of any of formulae **V-A** through **V-N**, when present, are independently halogen, CN, NO_2, or an optionally substituted group selected from C_{1-6} alkyl,

aryl, aryl(C_{1-6})alkyl, -N(R')$_2$, -CH_2N(R')$_2$, OR', -CH_2OR', SR', -CH_2SR', COOR', -NRCOR', -$(CH_2)_2$N(R')$_2$, -$(CH_2)_2$OR', -$(CH_2)_2$SR', -COR', -CON(R')$_2$, SO_2R', or -SO_2N(R')$_2$. In more preferred embodiments of any of formulae **V-A** through **V-N**, R^5 groups are each independently Cl, Br, F, CF_3, Me, Et, CN, NO_2, -COOH, NH_2, –N(CH_3)$_2$, -N(Et)$_2$, -N(iPr)$_2$, -O$(CH_2)_2OCH_3$, -CO(C_1-C_4alkyl), -$CONH_2$, -$COOCH_3$, -OH, -CH_2OH, -$NHCOCH_3$, -SO_2(C_1-C_4alkyl), -SO_2NH_2, -SO_2N(CH_3)$_2$, piperidinyl, piperizinyl, morpholino, or an optionally substituted group selected from C_{1-4} alkoxy, phenyl, phenyloxy, benzyl, or benzyloxy. Most preferred R^5 groups of any of formulae **V-A** through **V-N** include those shown below in Table 2.

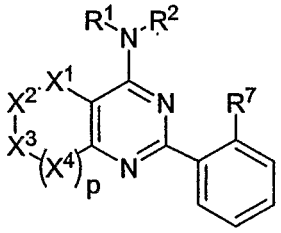
[00147] In preferred embodiments of any of formulae **V-A** through **V-N** R^6 groups are independently hydrogen, or an optionally substituted group selected from C_{1-6} alkyl, aryl, aryl(C_{1-6})alkyl, -N(R')$_2$, -CH_2N(R')$_2$, -CH_2OR', -CH_2SR', -$(CH_2)_2$N(R')$_2$, -$(CH_2)_2$OR', -$(CH_2)_2$SR', -COR', -CON(R')$_2$, SO_2R', or -$S(O)_2$N(R')$_2$. In more preferred embodiments of any of formulae **V-A** through **V-N**, R^6 groups are each independently H, Me, CF_3, ethyl, propyl, butyl, pentyl, CO(C_1-C_4alkyl), -$CONH_2$, -COO(C_1-C_4alkyl), -CH_2OH, -SO_2(C_1-C_4alkyl), -SO_2NH_2, SO_2N(CH_3)$_2$, or optionally substituted phenyl or benzyl. Most preferred R^6 groups of any of formulae **V-A** through **V-N** include those shown below in Table 2.

[00148] As described generally above for compounds of formula **V-A** through **V-N**, one or more of X^1, X^2, X^3, or X^4 is CHR^4 or NR^3. In preferred embodiments of any of formulae **V-A** through **V-N**, R^4 groups are independently hydrogen, halogen, CN, NO_2, or an optionally substituted group selected from C_{1-6} alkyl, aryl, aryl(C_{1-6})alkyl, -N(R')$_2$, -CH_2N(R')$_2$, OR', -CH_2OR', SR', -CH_2SR', COOR', -NRCOR', -$(CH_2)_2$N(R')$_2$, -$(CH_2)_2$OR', -$(CH_2)_2$SR', -COR', -CON(R')$_2$, SO_2R', or -SO_2N(R')$_2$. In more preferred embodiments of any of formulae **V-A** through **V-N**, R^4 groups are each independently H, Cl, Br, F, CF_3, Me, Et, CN, NO_2, -COOH, NH_2, –N(CH_3)$_2$, -N(Et)$_2$, -N(iPr)$_2$, -O$(CH_2)_2OCH_3$, -CO(C_1-C_4alkyl), -$CONH_2$, -$COOCH_3$, -OH, -CH_2OH, -$NHCOCH_3$, -SO_2(C_1-C_4alkyl), -SO_2NH_2, -SO_2N(CH_3)$_2$, piperidinyl, piperizinyl, morpholino, or an optionally substituted group selected from C_{1-4} alkoxy, phenyl, phenyloxy, benzyl, or benzyloxy. Most preferred R^4 groups of any of formulae **V-A** through **V-N** include those shown below in Table 2.

[00149] In preferred embodiments of any of formulae **V-A** through **V-N**, R^3 groups are hydrogen, or an optionally substituted group selected from C_{1-6} alkyl, aryl, aryl(C_{1-6})alkyl, -N(R')$_2$, -CH_2N(R')$_2$, -CH_2OR', -CH_2SR', -$(CH_2)_2$N(R')$_2$, -$(CH_2)_2$OR', -$(CH_2)_2$SR', -COR',

-CON(R')$_2$, SO_2R', or -S(O)$_2$N(R')$_2$. In more preferred embodiments, R^3 groups are each independently H, Me, CF_3, ethyl, propyl, butyl, pentyl, CO(C_1-C_4alkyl), -$CONH_2$, -COO(C_1-C_4alkyl), -CH_2OH, -SO_2(C_1-C_4alkyl), -SO_2NH_2, $SO_2N(CH_3)_2$, or optionally substituted phenyl or benzyl. Most preferred R^3 groups of any of formulae **V-A** through **V-N** include those shown below in Table 2.

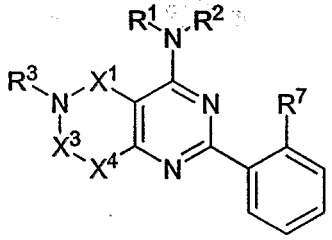
[00150] In yet other preferred embodiments of formula **V** y is 1 and compounds have the general formula **VI**:



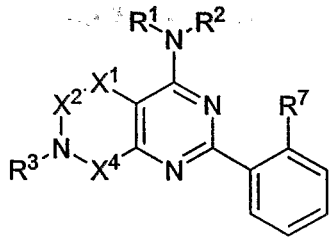
VI

wherein each of R^1, R^2, X^1, X^2, X^3, X^4, and p is as described generally above and herein, and R^7 is halogen, CN, NO_2, or an optionally substituted group selected from C_{1-4} alkyl, aryl, aralkyl, -N(R')$_2$, -CH_2N(R')$_2$, -OR', -CH_2OR', -SR', -CH_2SR', -COOR', -NRCOR', -CON(R')$_2$, or -S(O)$_2$N(R')$_2$.

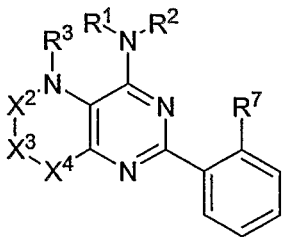
[00151] In other preferred embodiments of formula VI, p is 0, 1, or 2, and compounds have the structure of formulae **VI-A** through **VI-N**:



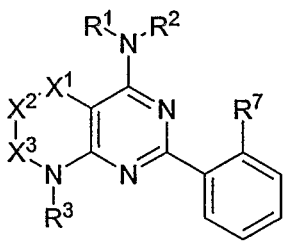
VI-A



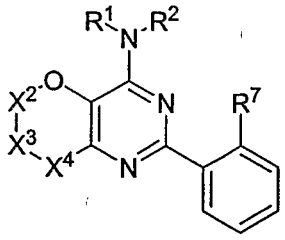
VI-B



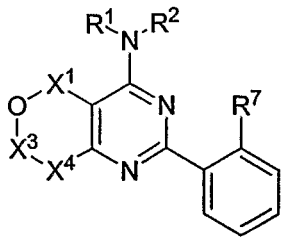
VI-C



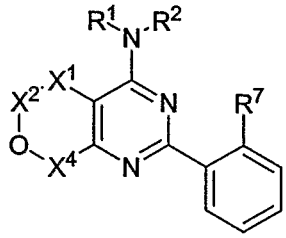
VI-D



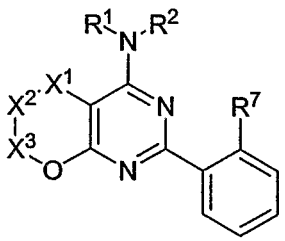
VI-E



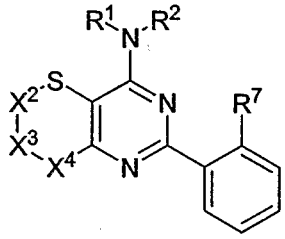
VI-F



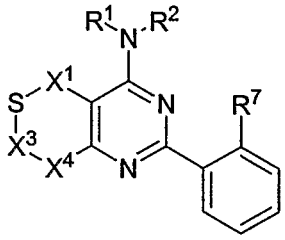
VI-G



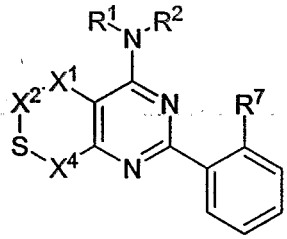
VI-H



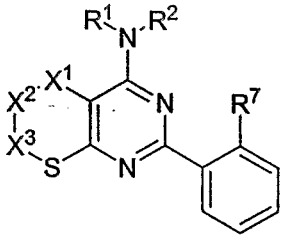
VI-I



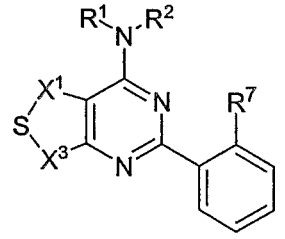
VI-J



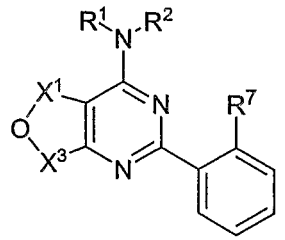
VI-K



VI-L



VI-M



VI-N

wherein each R^1, R^2, X^1, X^2, X^3, and X^4 is as described generally above and herein, and R^7 is halogen, CN, NO_2, or an optionally substituted group selected from C_{1-4} alkyl, aryl, aralkyl,

$-N(R')_2$, $-CH_2N(R')_2$, -OR', $-CH_2OR'$, -SR', $-CH_2SR'$, -COOR', -NRCOR', $-CON(R')_2$, or $-S(O)_2N(R')_2$.

[00152] In still other preferred embodiments compounds of the invention are defined according to any of formulae **VI, VI-A, VI-B, VI-C, VI-D, VI-E, VI-F, VI-G, VI-H, VI-I, VI-J, VI-K, VI-L, VI-M,** or **VI-N,** and one or more of, or all of, R^1, R^2, R^3 or R^4 are further defined according to one or more of, or all of, the following groups:

a. R^1 and R^2 are each independently selected from a 5- or 6-membered aryl ring having 0-5 heteroatoms independently selected from N, O, or S; a 3-7-membered saturated or partially unsaturated ring having 0-3 heteroatoms independently selected from N, O, or S; or or an optionally substituted C_{1-4} aliphatic group, wherein one or more methylene units in the C_{1-4} aliphatic group are optionally and independently replaced with NR, O, (CO)O, O(CO), NR(CO), (CO)NR, $SO_2(NR)$, or $(NR)SO_2$;

b. each occurrence of R^3 is independently hydrogen, or an optionally substituted group selected from C_{1-6} alkyl, aryl, aryl(C_{1-6})alkyl, $-N(R')_2$, $-CH_2N(R')_2$, $-CH_2OR'$, $-CH_2SR'$, $-(CH_2)_2N(R')_2$, $-(CH_2)_2OR'$, $-(CH_2)_2SR'$, -COR', $-CON(R')_2$, SO_2R', or $-S(O)_2N(R')_2$; and

c. each occurrence of R^4 is independently hydrogen, halogen, CN, NO_2, or an optionally substituted group selected from C_{1-6} alkyl, aryl, aryl(C_{1-6})alkyl, $-N(R')_2$, $-CH_2N(R')_2$, OR', $-CH_2OR'$, SR', $-CH_2SR'$, COOR', -NRCOR', $-(CH_2)_2N(R')_2$, $-(CH_2)_2OR'$, $-(CH_2)_2SR'$, -COR', $-CON(R')_2$, SO_2R', or $-SO_2N(R')_2$.

[00153] In still other preferred embodiments compounds of the invention are defined according to any of formulae **VI, VI-A, VI-B, VI-C, VI-D, VI-E, VI-F, VI-G, VI-H, VI-I, VI-J, VI-K, VI-L, VI-M,** or **VI-N,** and one or more of, or all of, R^1, R^2, R^3 or R^4 are further defined according to one or more of, or all of, the following groups:

a. R^1 and R^2 are each independently optionally substituted methyl, ethyl, cyclopropyl, n-propyl, propenyl, cyclobutyl, $(CO)OCH_2CH_3$, $(CH_2)_2OCH_3$, $CH_2(CO)OCH_2CH_3$, $CH_2(CO)OCH_3$, $CH(CH_3)CH_2CH_3$, or t-butyl, or n-butyl;

b. each occurrence of R^3 is independently H, Me, CF_3, ethyl, propyl, butyl, pentyl, $CO(C_1\text{-}C_4alkyl)$, $-CONH_2$, $-COO(C_1\text{-}C_4alkyl)$, $-CH_2OH$, $-SO_2(C_1\text{-}C_4alkyl)$, $-SO_2NH_2$, $SO_2N(CH_3)_2$, or optionally substituted phenyl or benzyl; and

c. each occurrence of R^4 is independently H, Cl, Br, F, CF_3, Me, Et, CN, NO_2, -COOH, NH_2, $-N(CH_3)_2$, $-N(Et)_2$, $-N(iPr)_2$, $-O(CH_2)_2OCH_3$, $-CO(C_1\text{-}C_4alkyl)$, $-CONH_2$, $-COOCH_3$, -OH, $-CH_2OH$, $-NHCOCH_3$, $-SO_2(C_1\text{-}C_4alkyl)$, $-SO_2NH_2$, $-SO_2N(CH_3)_2$, piperidinyl, piperizinyl, morpholino, or an optionally substituted group selected from $C_{1\text{-}4}$ alkoxy, phenyl, phenyloxy, benzyl, or benzyloxy.

[00154] In still other preferred embodiments compounds of the invention are defined according to any of formulae **VI, VI-A, VI-B, VI-C, VI-D, VI-E, VI-F, VI-G, VI-H, VI-I, VI-J, VI-K, VI-L, VI-M,** or **VI-N**, and one or more of, or all of, R^1, R^2, R^3, R^4 or R^7 are further defined according to one or more of, or all of, the following groups:

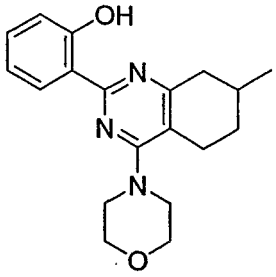
a. R^1 and R^2 are each independently optionally substituted methyl, ethyl, cyclopropyl, n-propyl, propenyl, cyclobutyl, $(CO)OCH_2CH_3$, $(CH_2)_2OCH_3$, $CH_2(CO)OCH_2CH_3$, $CH_2(CO)OCH_3$, $CH(CH_3)CH_2CH_3$, or t-butyl, or n-butyl;

b. each occurrence of R^3 is independently H, Me, CF_3, ethyl, propyl, butyl, pentyl, $CO(C_1\text{-}C_4alkyl)$, $-CONH_2$, $-COO(C_1\text{-}C_4alkyl)$, $-CH_2OH$, $-SO_2(C_1\text{-}C_4alkyl)$, $-SO_2NH_2$, $SO_2N(CH_3)_2$, or optionally substituted phenyl or benzyl;

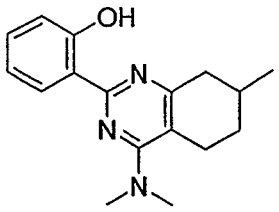
c. each occurrence of R^4 is independently H, Cl, Br, F, CF_3, Me, Et, CN, NO_2, -COOH, NH_2, $-N(CH_3)_2$, $-N(Et)_2$, $-N(iPr)_2$, $-O(CH_2)_2OCH_3$, $-CO(C_1\text{-}C_4alkyl)$, $-CONH_2$, $-COOCH_3$, -OH, $-CH_2OH$, $-NHCOCH_3$, $-SO_2(C_1\text{-}C_4alkyl)$, $-SO_2NH_2$, $-SO_2N(CH_3)_2$, piperidinyl, piperizinyl, morpholino, or an optionally substituted group selected from $C_{1\text{-}4}$ alkoxy, phenyl, phenyloxy, benzyl, or benzyloxy; and

d. R^7 is Cl, Br, F, CF_3, Me, Et, CN, NO_2, -COOH, NH_2, $-N(CH_3)_2$, $-N(Et)_2$, $-N(iPr)_2$, $-O(CH_2)_2OCH_3$, $-CO(C_1\text{-}C_4alkyl)$, $-CONH_2$, $-COOCH_3$, -OH, $-CH_2OH$, $-NHCOCH_3$, $-SO_2(C_1\text{-}C_4alkyl)$, $-SO_2NH_2$, $-SO_2N(CH_3)_2$, piperidinyl, piperizinyl, morpholino, or an optionally substituted group selected from $C_{1\text{-}4}$ alkoxy, phenyl, phenyloxy, benzyl, or benzyloxy.

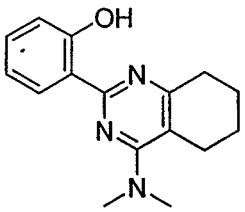
[00155] Representative examples of compounds as described above and herein are set forth below and in Table 2.



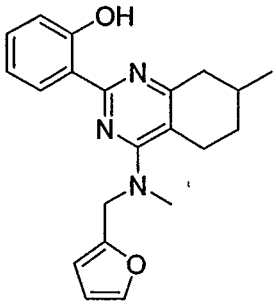
I-1



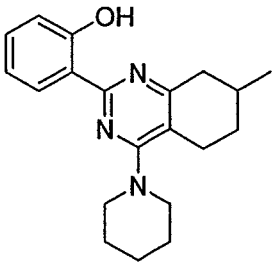
I-2



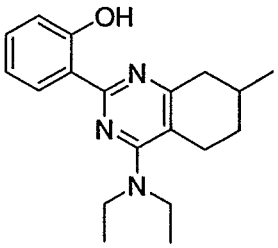
I-3



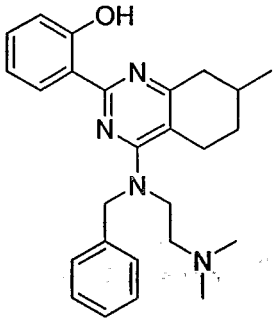
I-4



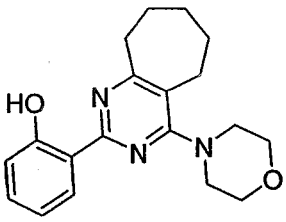
I-5



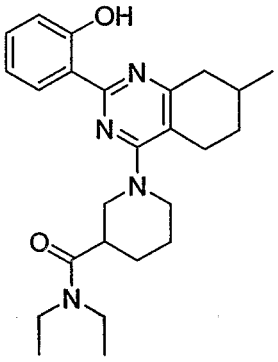
I-6



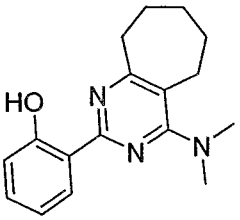
I-7



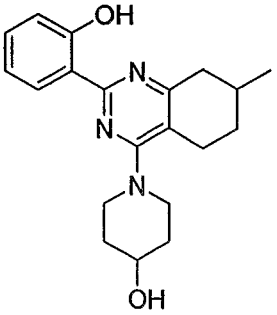
I-8



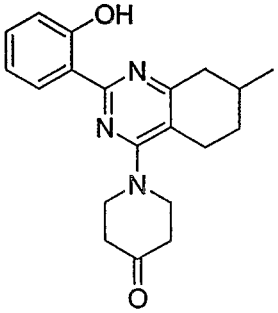
I-9



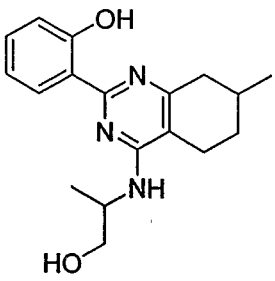
I-10



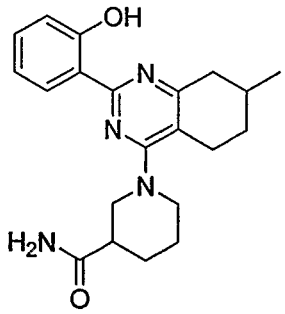
I-11



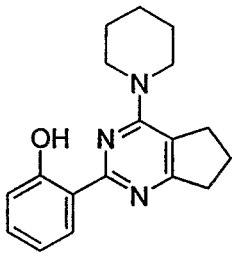
I-12



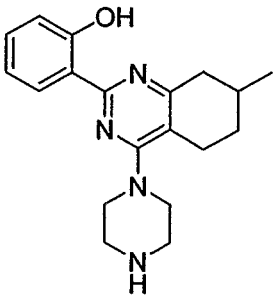
I-13



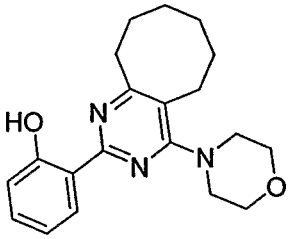
I-14



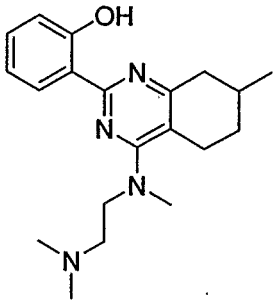
I-15



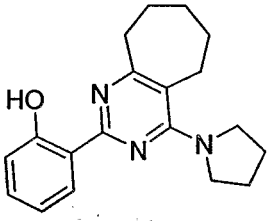
I-16



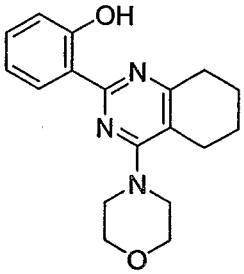
I-17



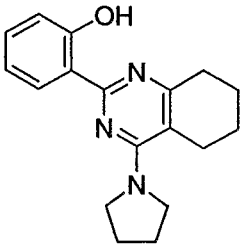
I-18



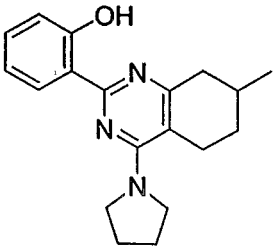
I-19



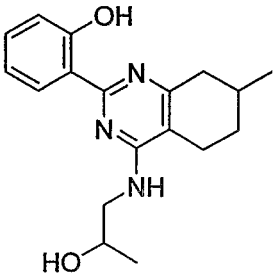
I-20



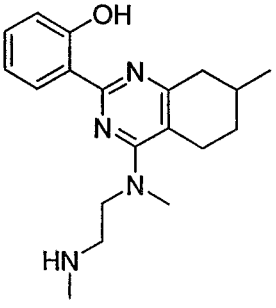
I-21



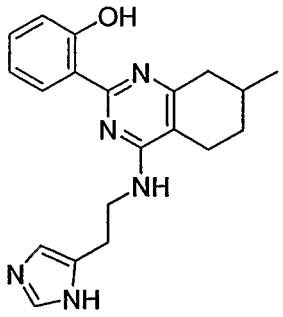
I-22



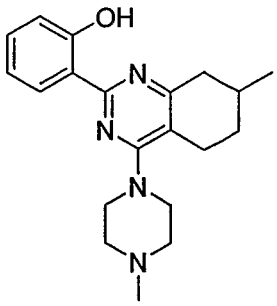
I-23



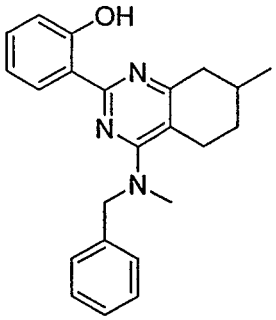
I-24



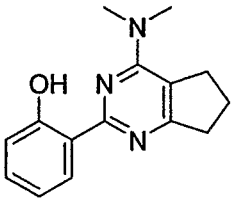
I-25



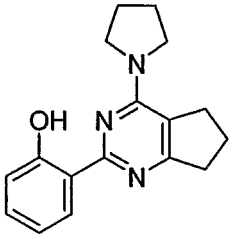
I-26



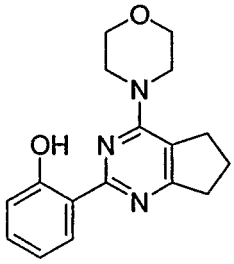
I-27



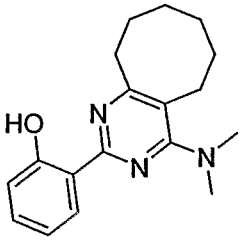
I-28



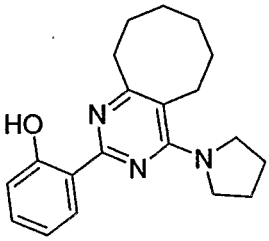
I-29



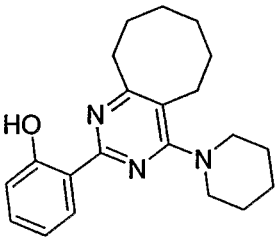
I-30



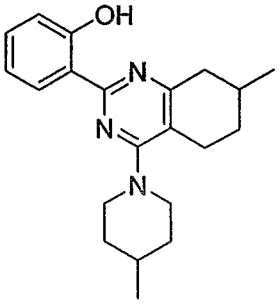
I-31



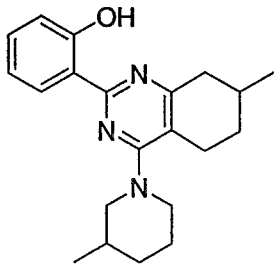
I-32



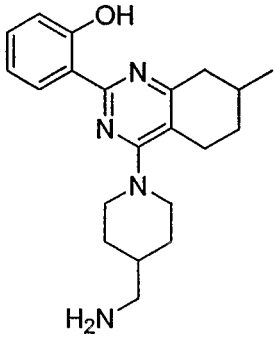
I-33



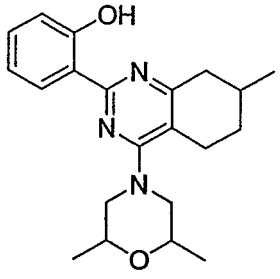
I-34



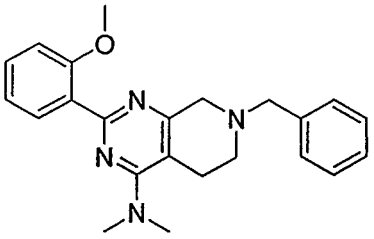
I-35



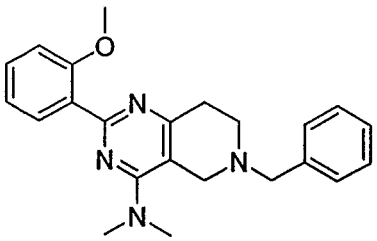
I-36



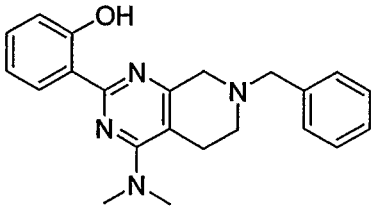
I-37



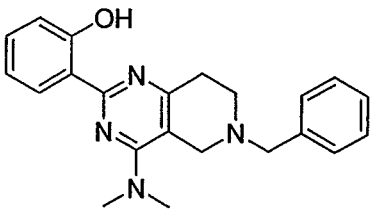
I-38



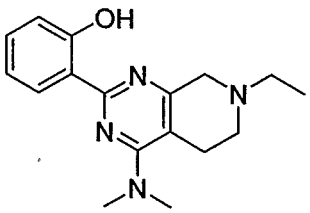
I-39



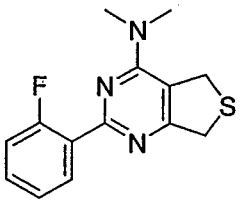
I-40



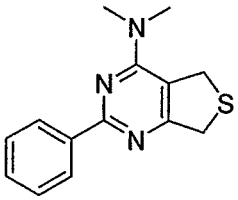
I-41



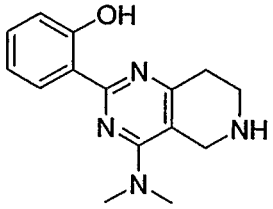
I-42



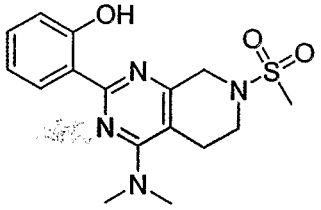
I-43



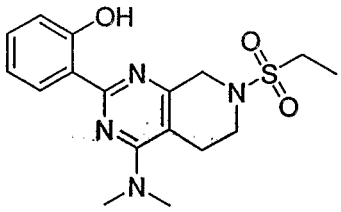
I-44



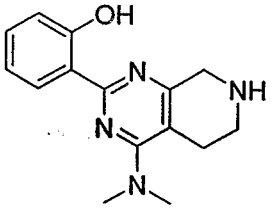
I-45



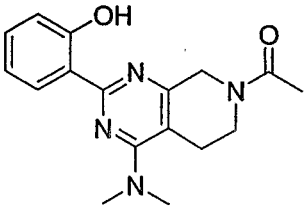
I-46



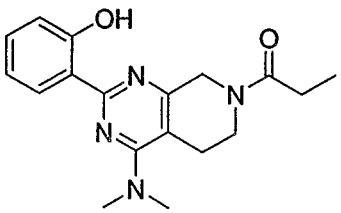
I-47



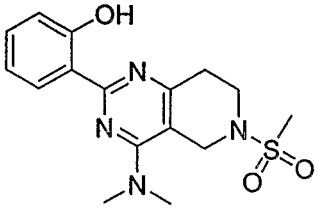
I-48



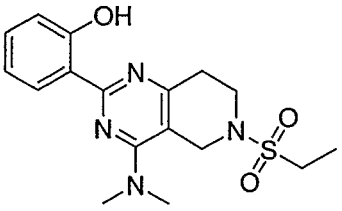
I-49



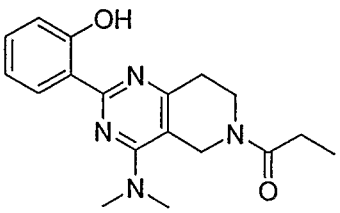
I-50



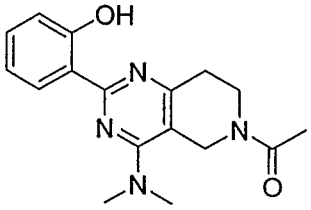
I-51



[00156] I-52

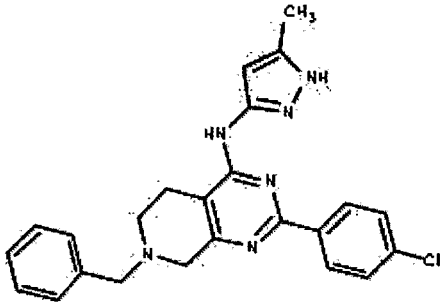
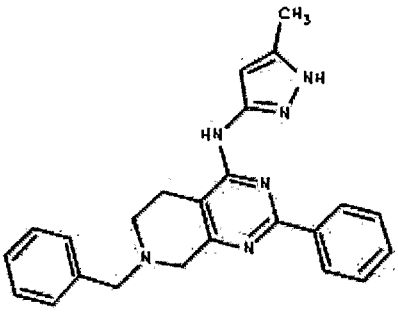
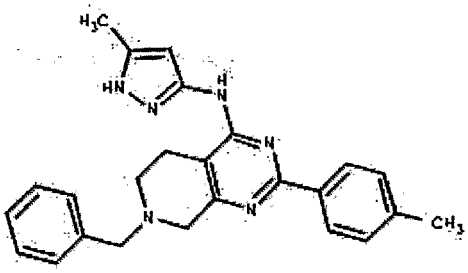
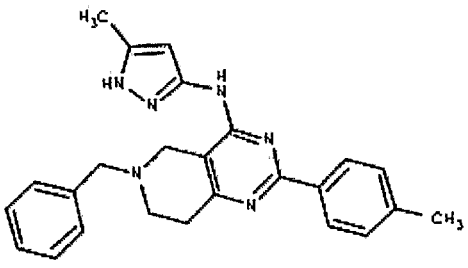


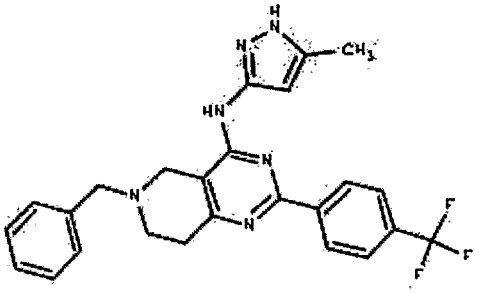
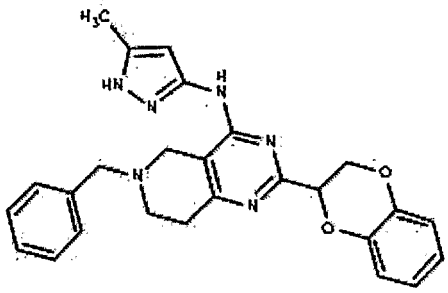
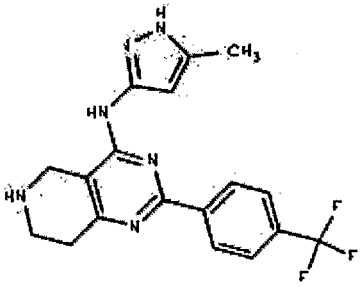
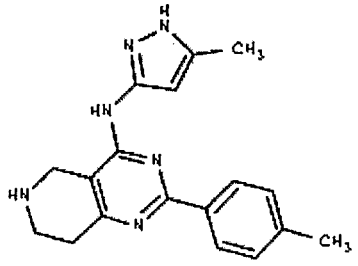
I-53

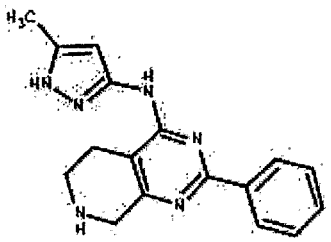
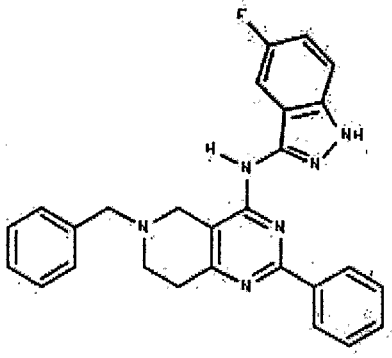
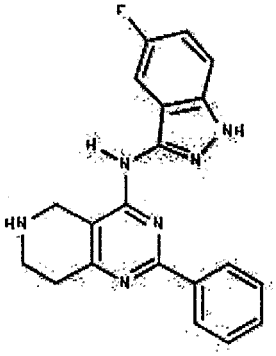
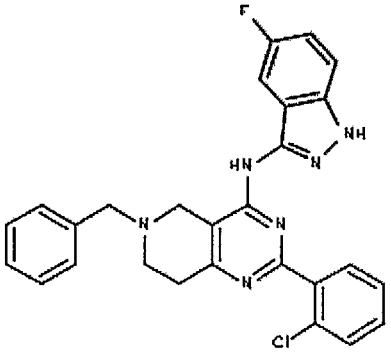


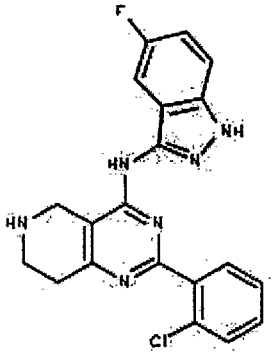
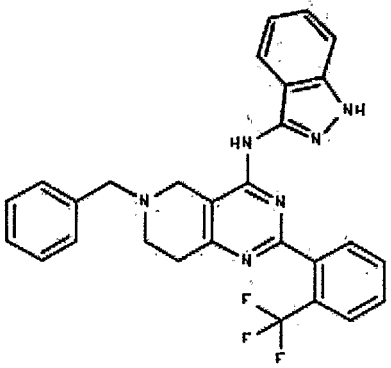
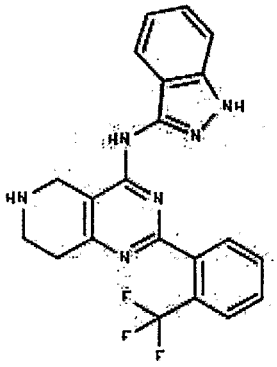
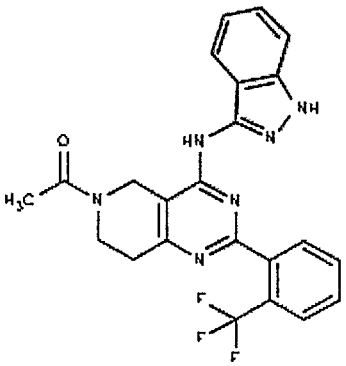
or I-54.

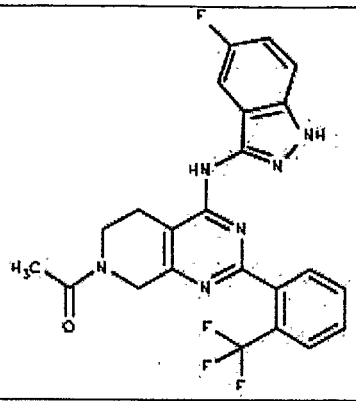
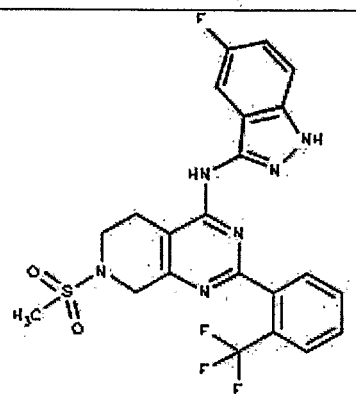
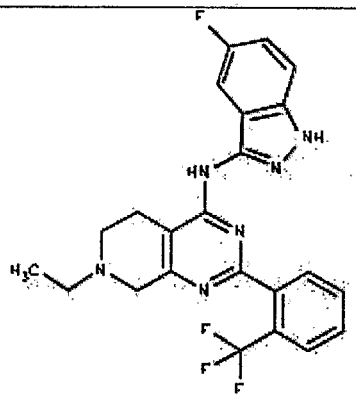
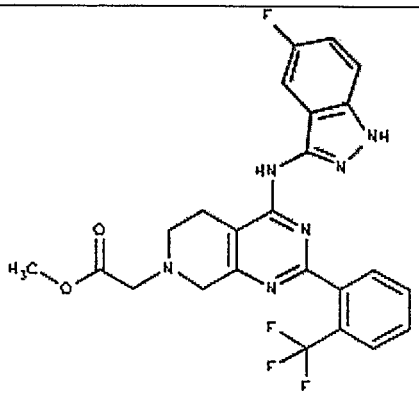
[00157] Table 2. Examples of Compounds of Formula I:

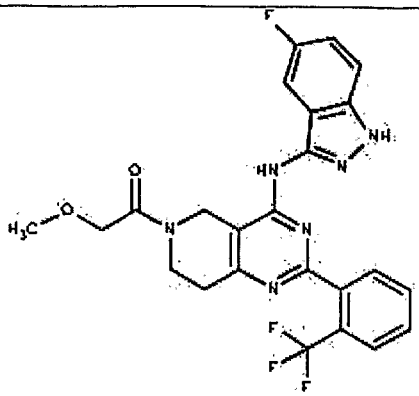
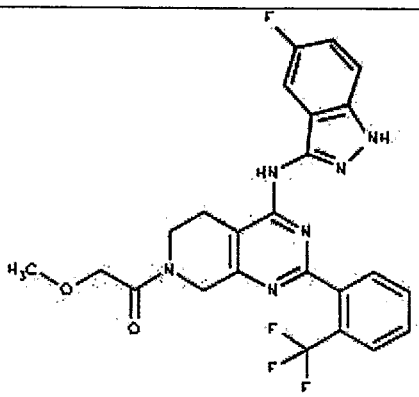
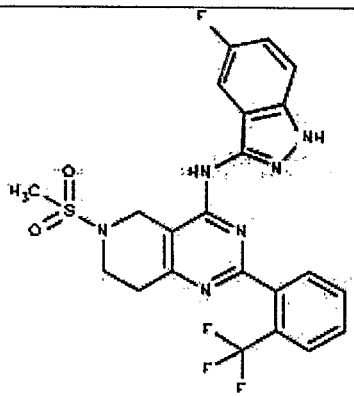
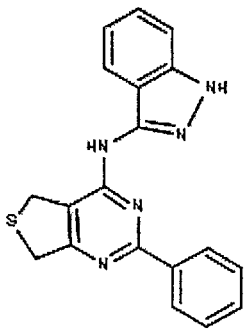
Cmpd	Structure
1	
2	
3	
4	

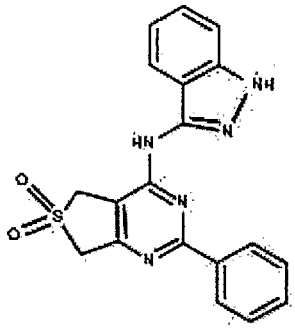
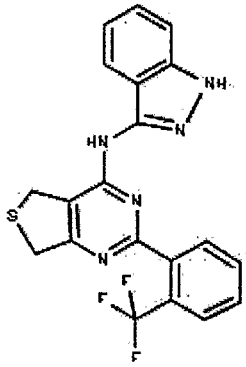
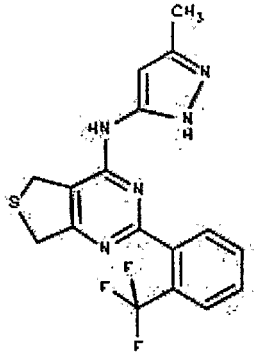
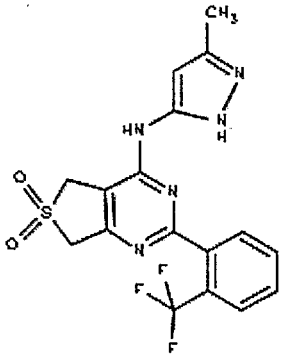
Cmpd	Structure
5	
6	
7	
8	

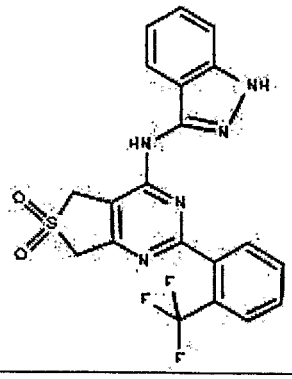
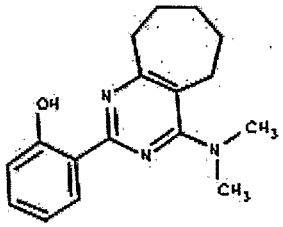
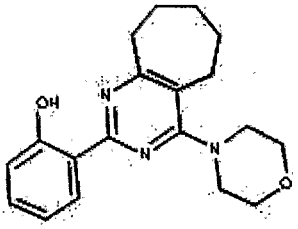
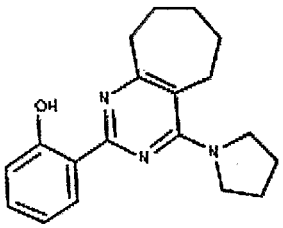
Cmpd	Structure
9	
10	
11	
12	

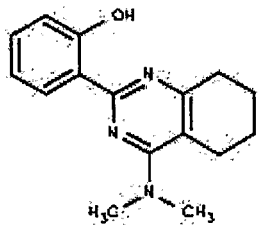
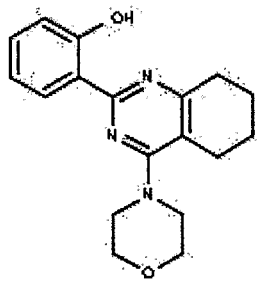
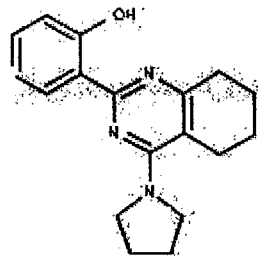
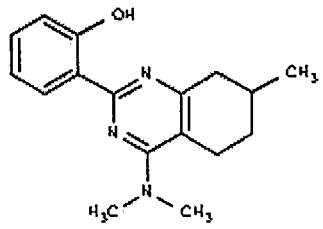
Cmpd	Structure
13	
14	
15	
16	

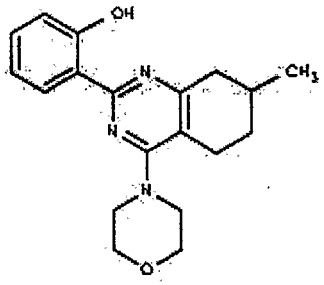
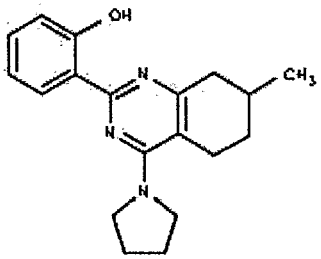
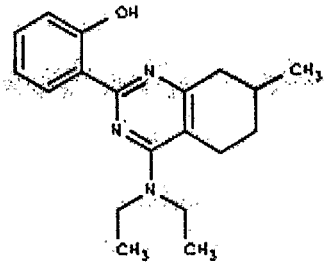
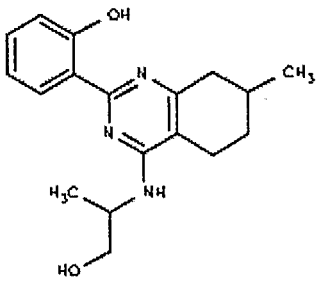
Cmpd	Structure
17	
18	
19	
20	

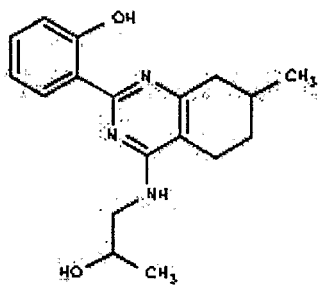
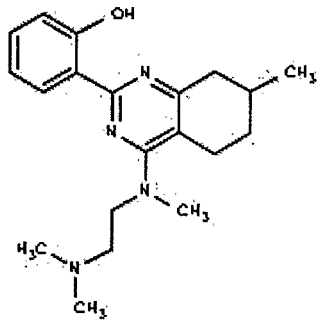
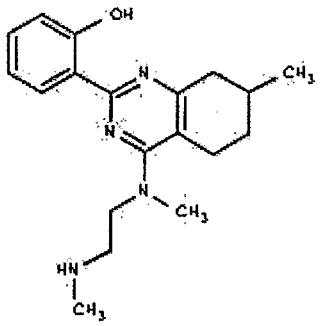
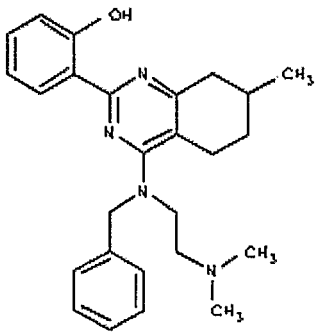
Cmpd	Structure
21	
22	
23	
24	

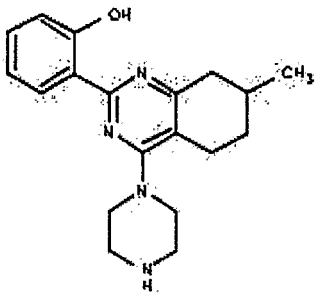
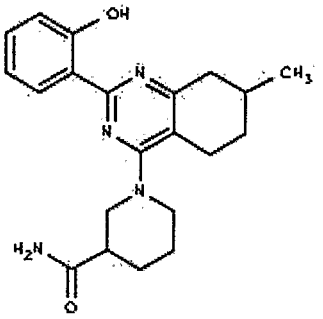
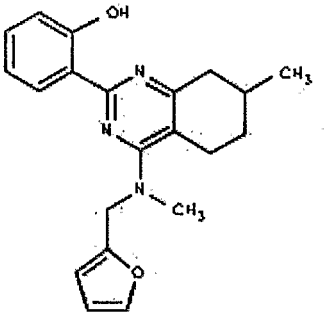
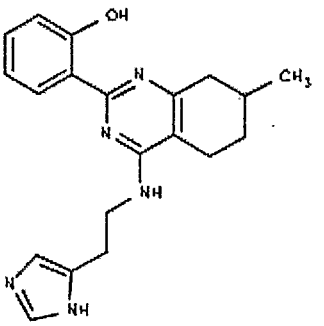
Cmpd	Structure
25	
26	
27	
28	

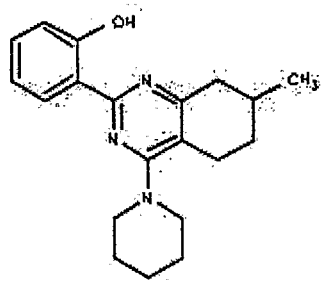
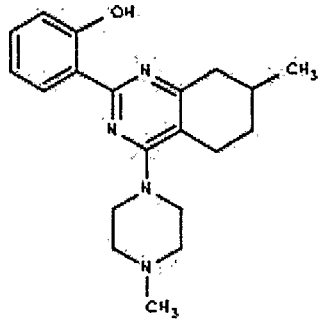
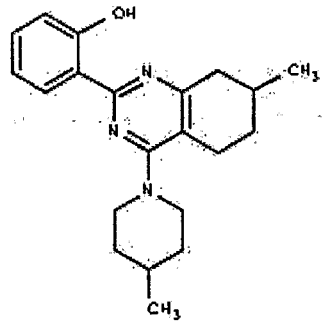
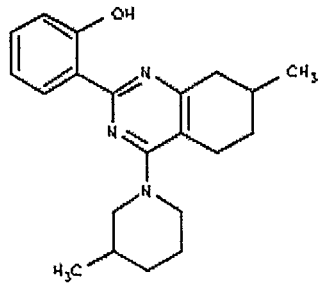
Cmpd	Structure
29	
30	
31	
32	

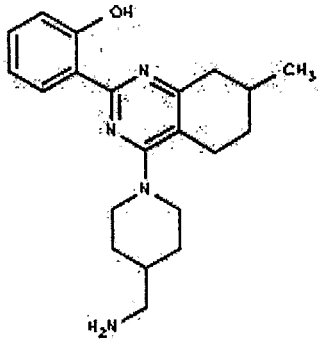
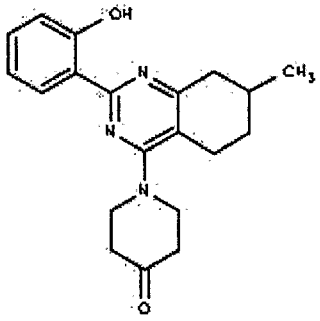
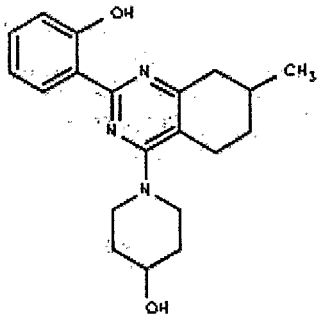
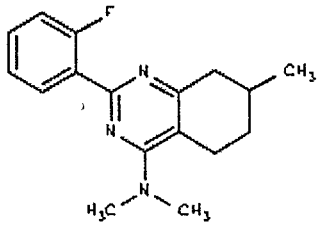
Cmpd	Structure
33	
34	
35	
36	

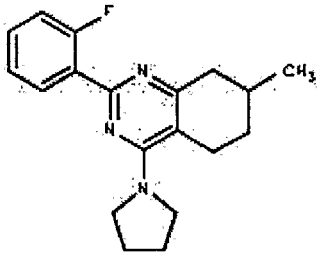
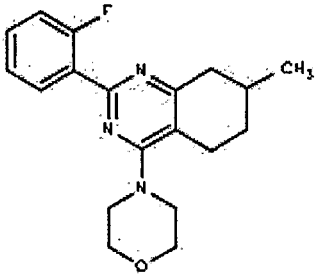
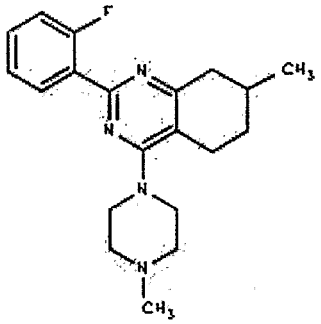
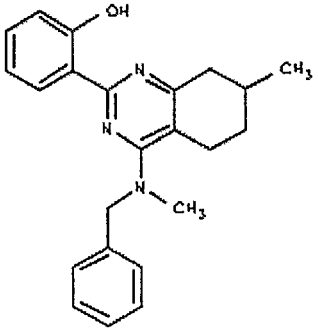
Cmpd	Structure
37	
38	
39	
40	

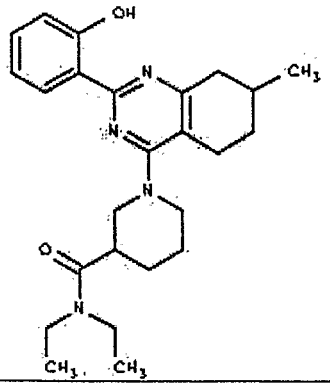
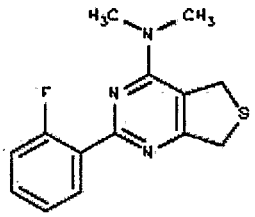
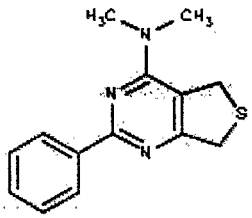
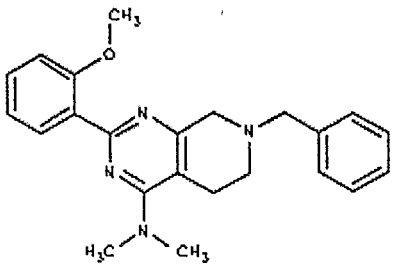
Cmpd	Structure
41	
42	
43	
44	

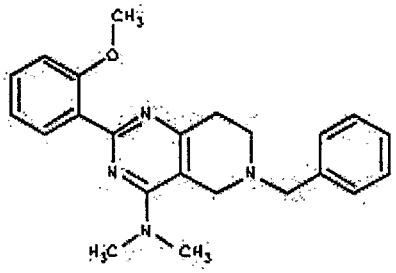
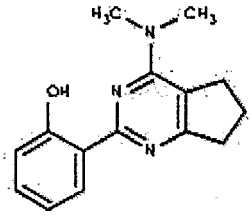
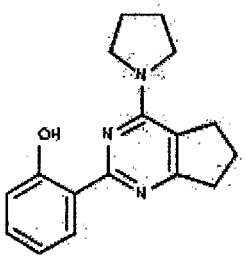
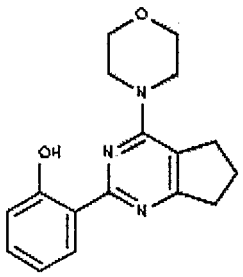
Cmpd	Structure
45	
46	
47	
48	

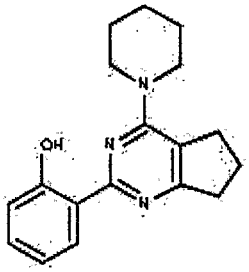
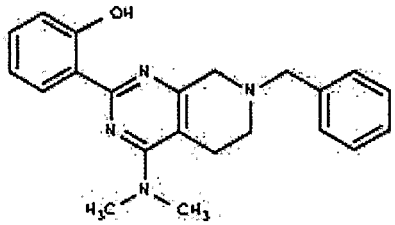
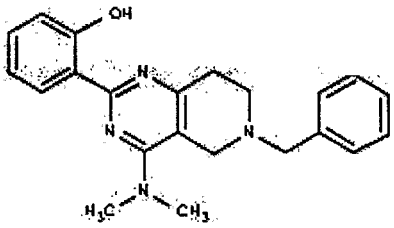
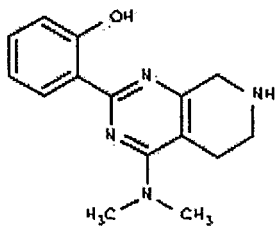
Cmpd	Structure
49	
50	
51	
52	

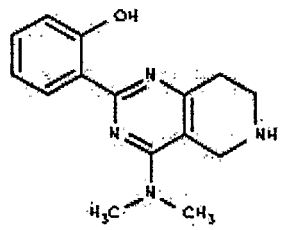
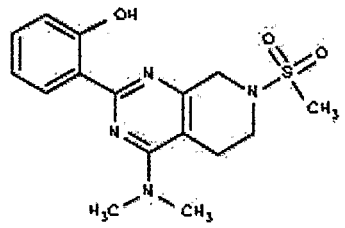
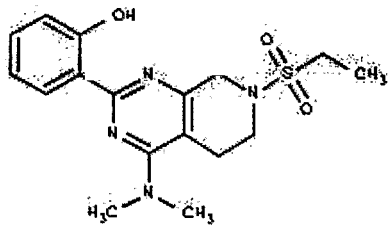
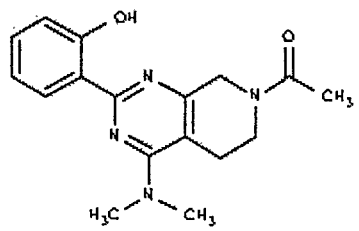
Cmpd	Structure
53	
54	
55	
56	

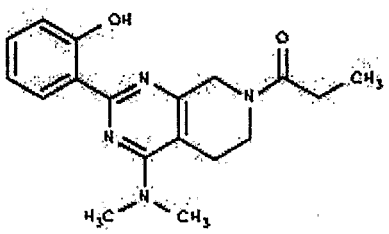
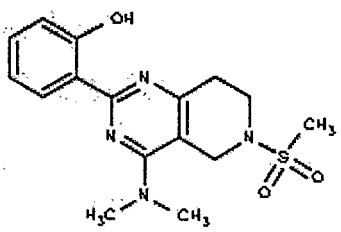
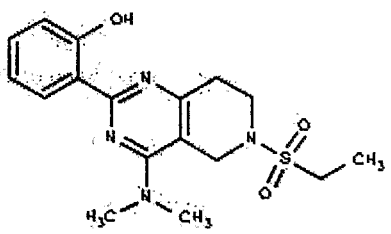
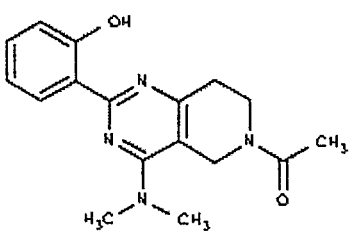
Cmpd	Structure
57	
58	
59	
60	

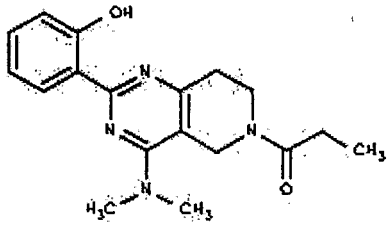
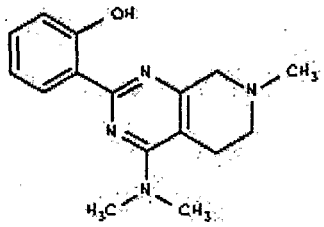
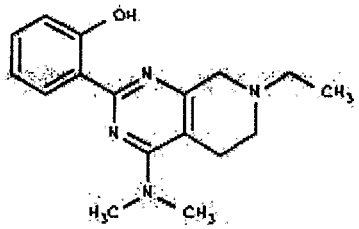
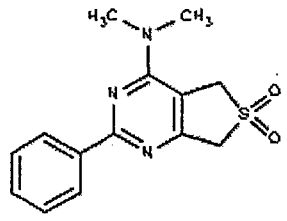
Cmpd	Structure
61	
62	
63	
64	

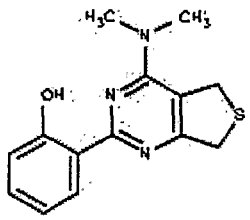
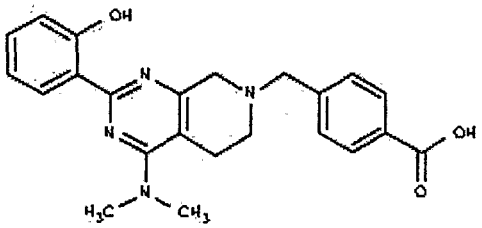
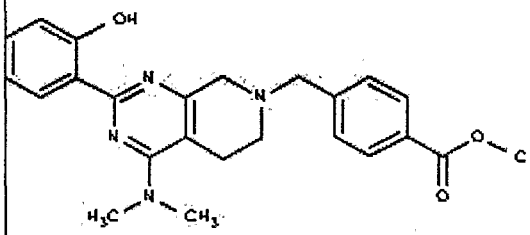
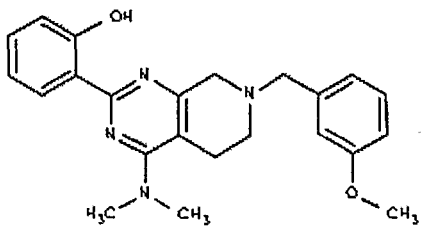
Cmpd	Structure
65	
66	
67	
68	

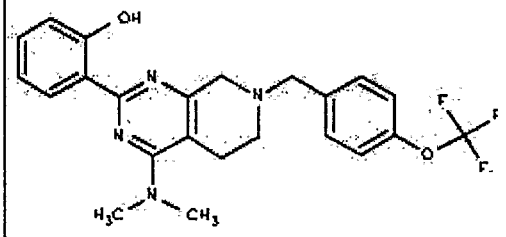
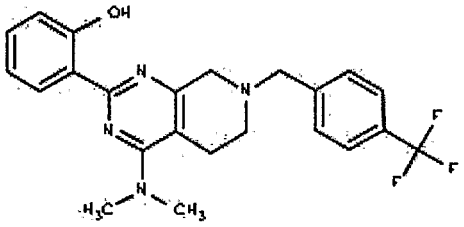
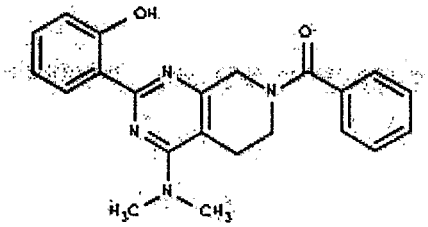
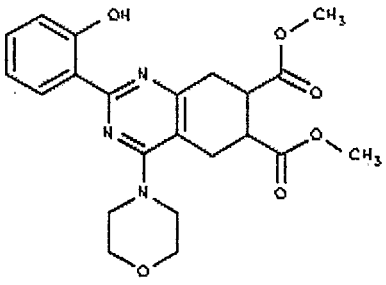
Cmpd	Structure
69	
70	
71	
72	

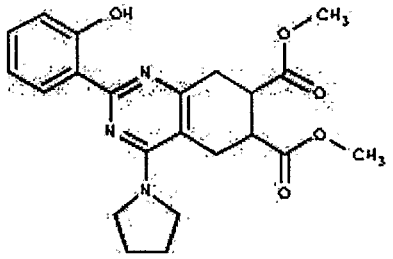
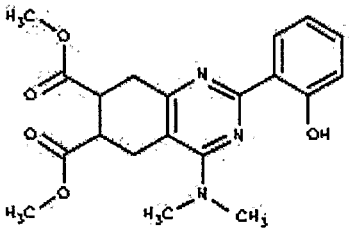
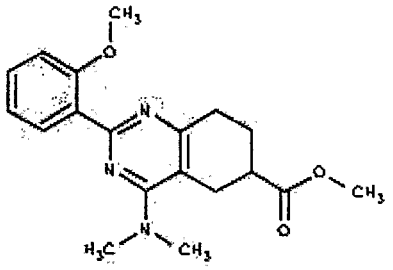
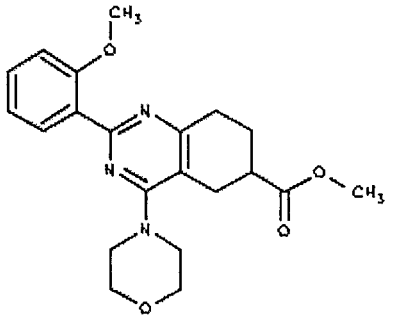
Cmpd	Structure
73	
74	
75	
76	

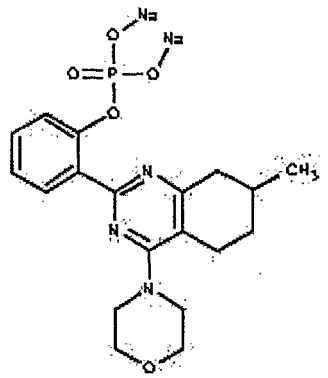
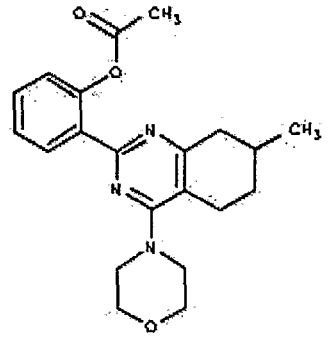
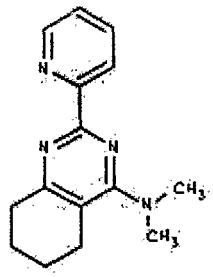
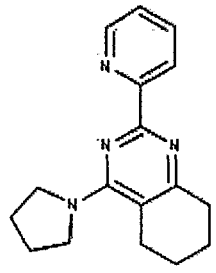
Cmpd	Structure
77	
78	
79	
80	

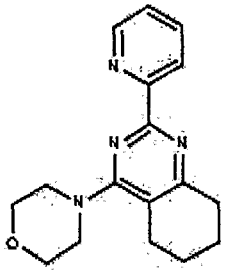
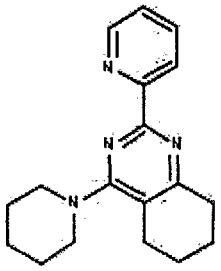
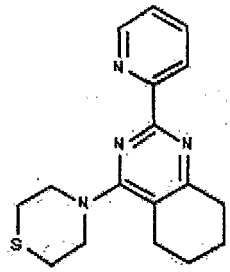
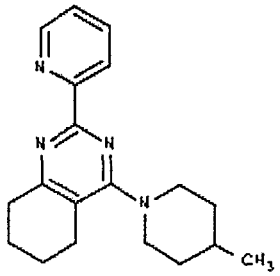
Cmpd	Structure
81	
82	
83	
84	

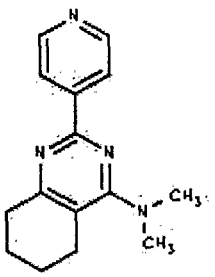
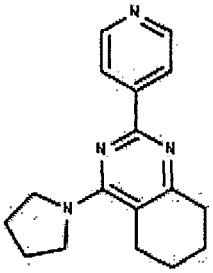
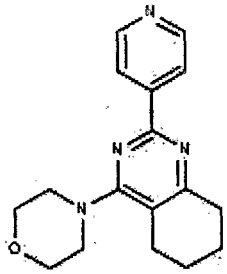
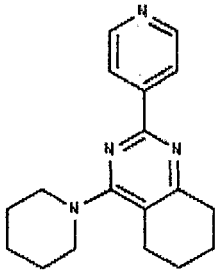
Cmpd	Structure
85	
86	
87	
88	

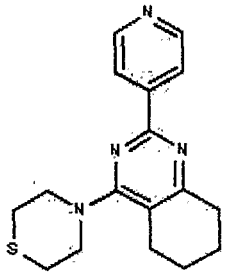
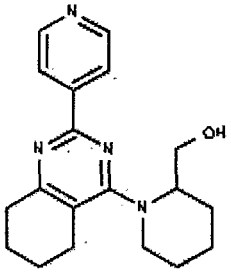
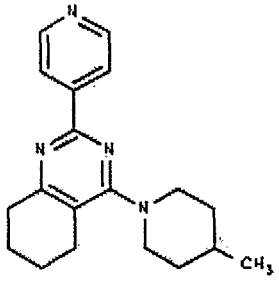
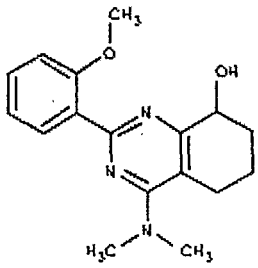
Cmpd	Structure
89	
90	
91	
92	

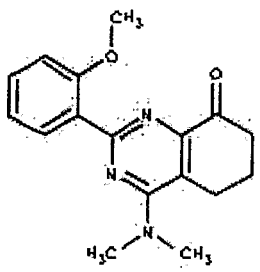
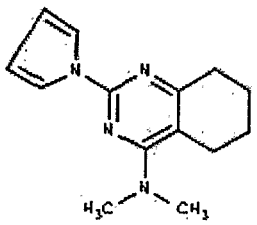
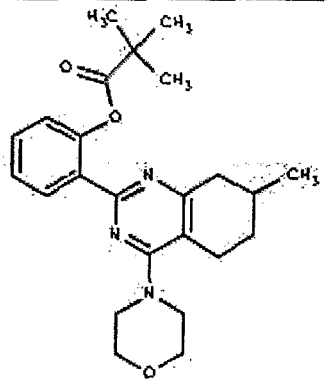
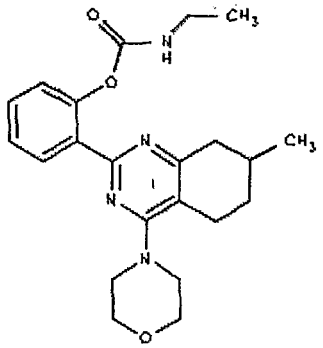
Cmpd	Structure
93	
94	
95	
96	

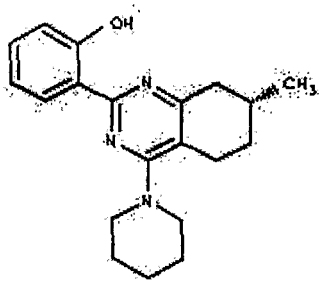
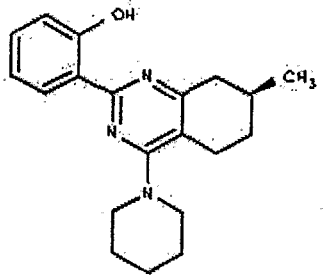
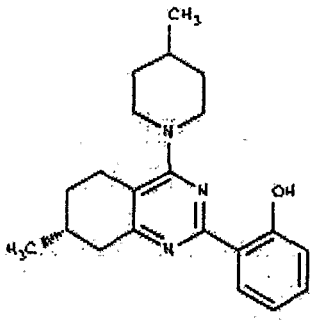
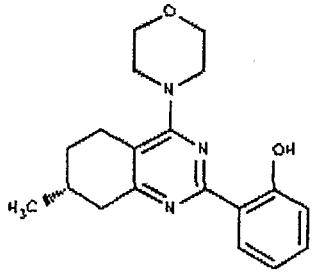
Cmpd	Structure
97	
98	
99	
100	

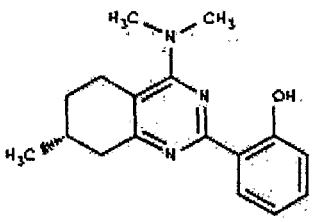
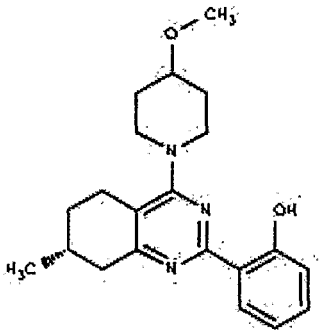
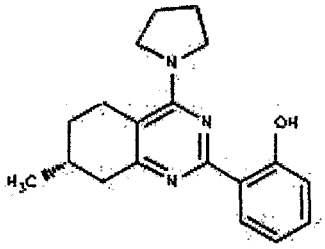
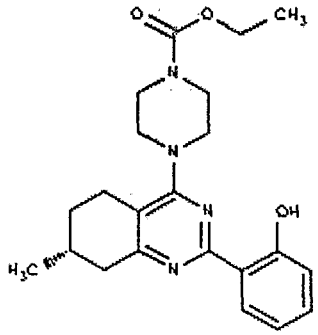
Cmpd	Structure
101	
102	
103	
104	

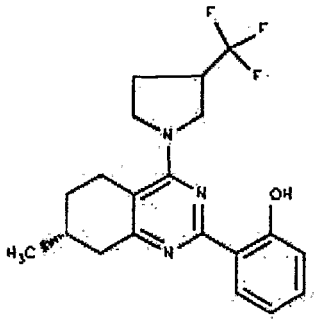
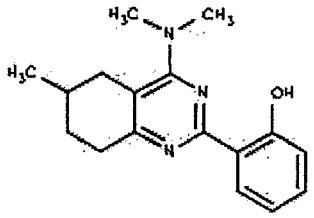
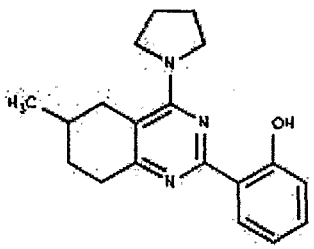
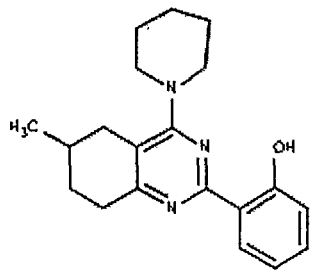
Cmpd	Structure
105	
106	
107	
108	

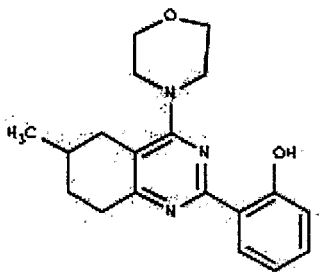
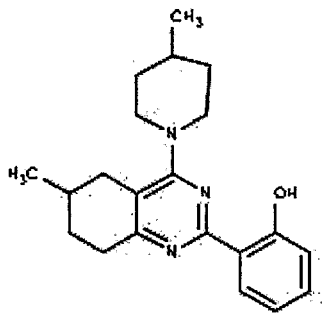
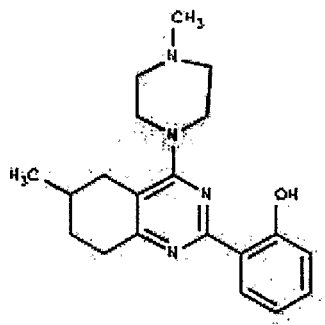
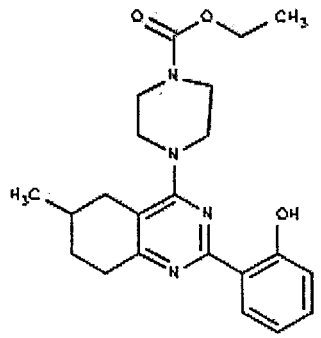
Cmpd	Structure
109	
110	
111	
112	

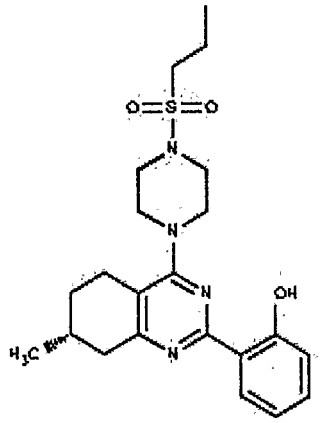
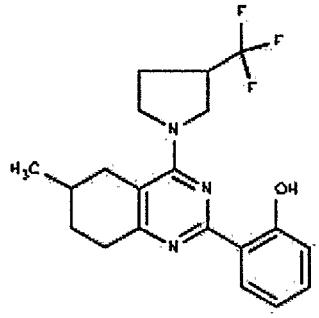
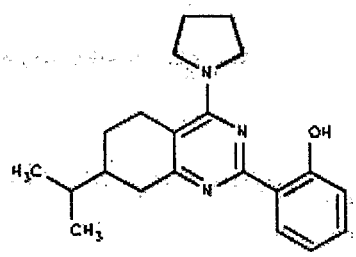
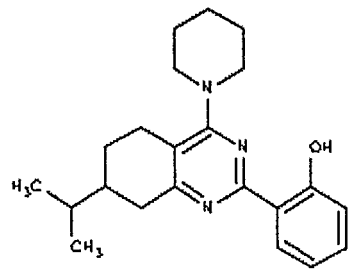
Cmpd	Structure
113	
114	
115	
116	

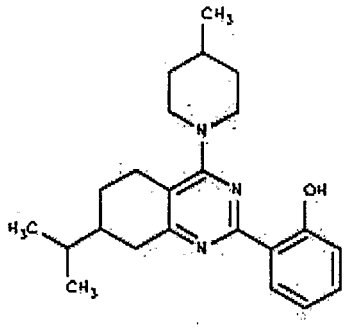
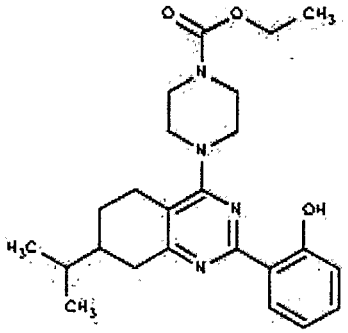
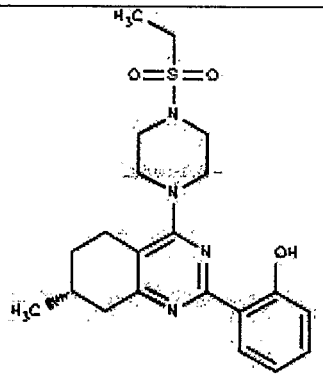
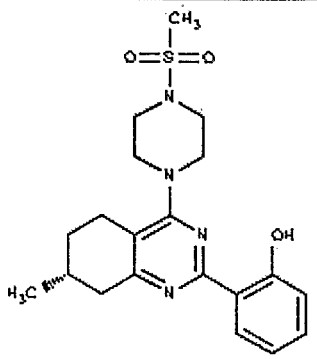
Cmpd	Structure
117	
118	
119	
120	

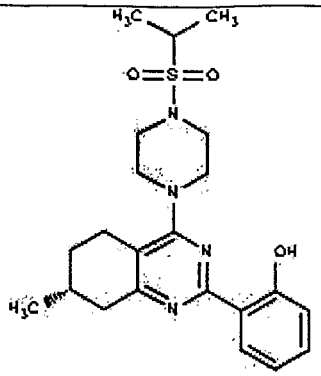
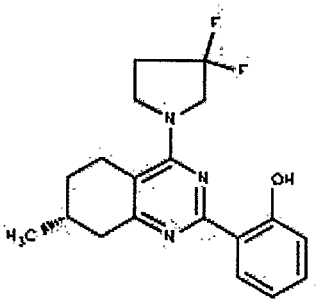
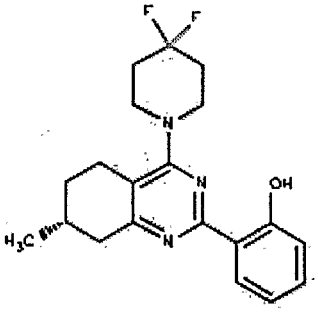
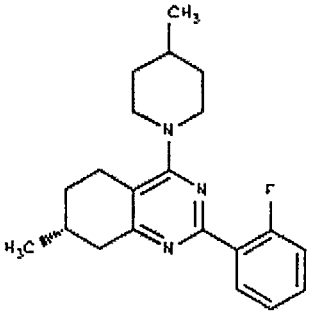
Cmpd	Structure
121	
122	
123	
124	

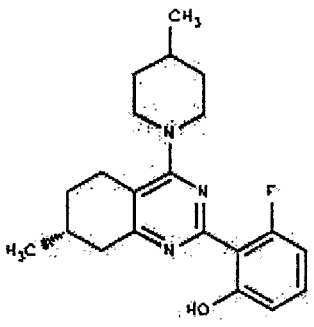
Cmpd	Structure
125	
126	
127	
128	

Cmpd	Structure
129	
130	
131	
132	

Cmpd	Structure
133	
134	
135	
136	

Cmpd	Structure
137	
138	
139	
140	

Cmpd	Structure
141	
142	
143	
144	

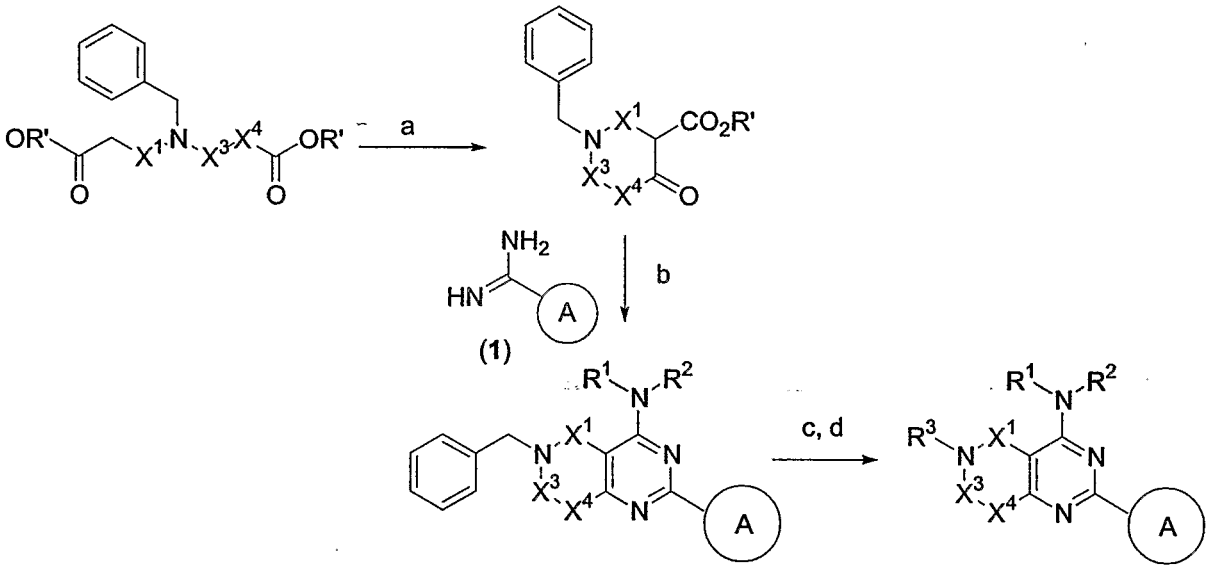
Cmpd	Structure
145	

[00158] *4. General Synthetic Methodology:*

[00159] The compounds of this invention may be prepared in general by methods known to those skilled in the art for analogous compounds, as illustrated by the general scheme below, and the preparative examples that follow.

[00160] As described in more detail in the Examples herein, and as shown generally in Scheme A below, reaction of a desired heterocyclohexanone-1-carboxylate and an amidine in ethanol with NaOEt at 0°C, and subsequent reaction with phosphorus oxychloride, boron tribromide and a desired amine, followed by debenzylation and reaction with an appropriate chloride generates compounds of general formula **I'**.

Scheme A: Preparation of C6_Aza_6 and Elaboration

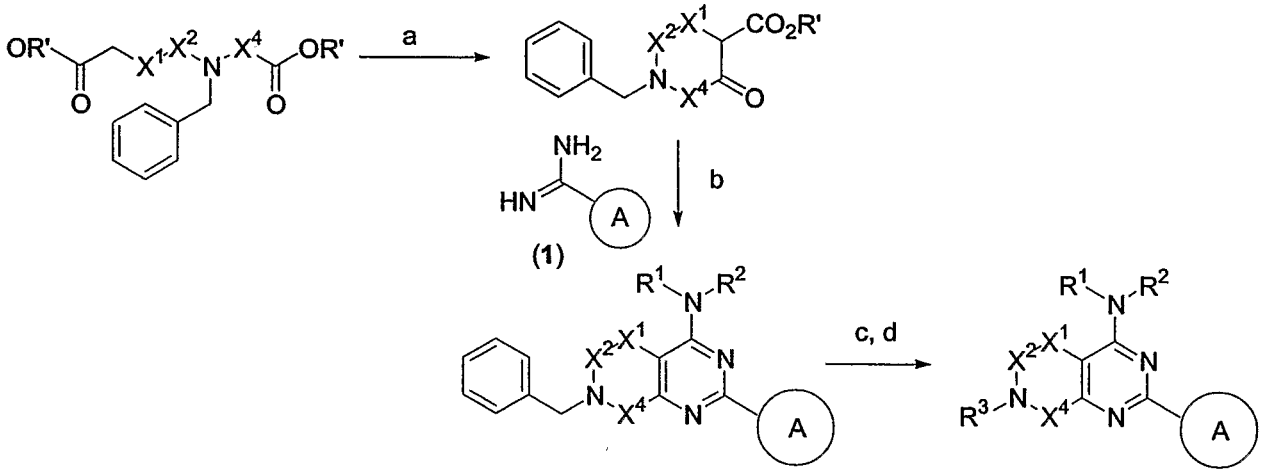


[00161] Conditions: a) i. $SnCl_4$, CH_2Cl_2; ii. Et_3N, CH_2Cl_2; b) i. 1, NaOEt, EtOH; ii. $POCl_3$, N,N-dimethylaniline, benzene, reflux; iii. R^1R^2NH, THF/CH_2Cl_2, RT; c) Pd/C, H_2, AcOH, 90 °C; d) R^3-Cl, Et_3N, CH_2Cl_2.

[00162] It will be appreciated that this method can be utilized to prepare a variety of compounds.

[00163] Scheme B below depicts the preparation of C7_Aza_6 compounds and elaboration:

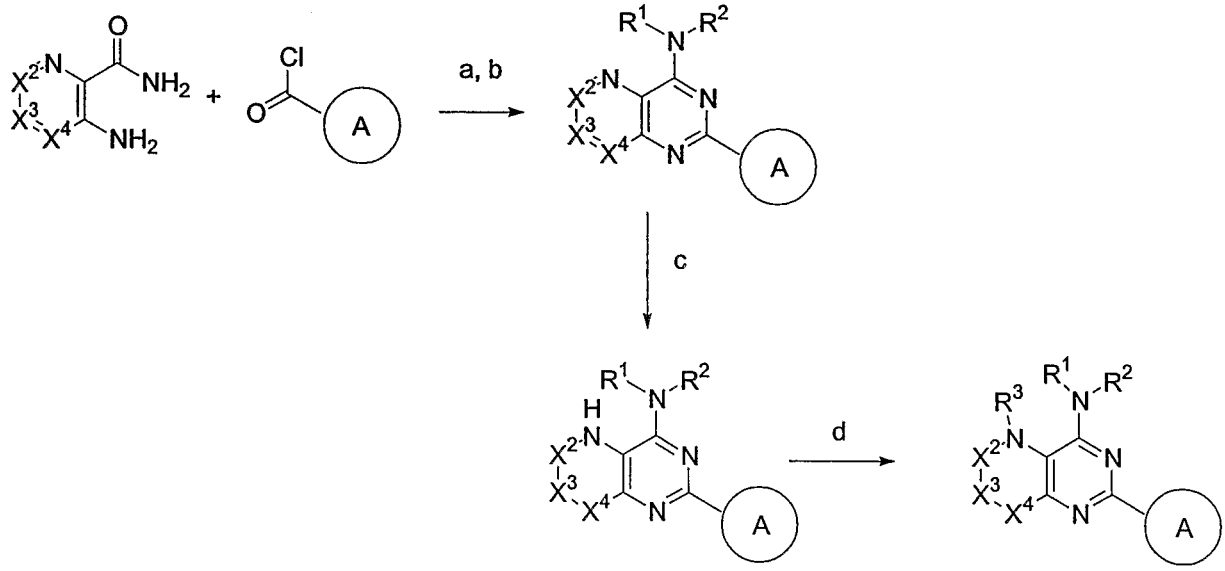
Scheme B: Preparation of C7_Aza_6 and Elaboration



[00164] Conditions: a) i. $SnCl_4$, CH_2Cl_2; ii. Et_3N, CH_2Cl_2; b) i. 1, NaOEt, EtOH; ii. $POCl_3$, N,N-dimethylaniline, benzene, reflux; iii. R^1R^2NH, THF/CH_2Cl_2, RT; c) Pd/C, H_2, AcOH, 90 °C; d) R^3-Cl, Et_3N, CH_2Cl_2.

[00165] Scheme C below depicts the preparation of C5_Aza_6 compounds:

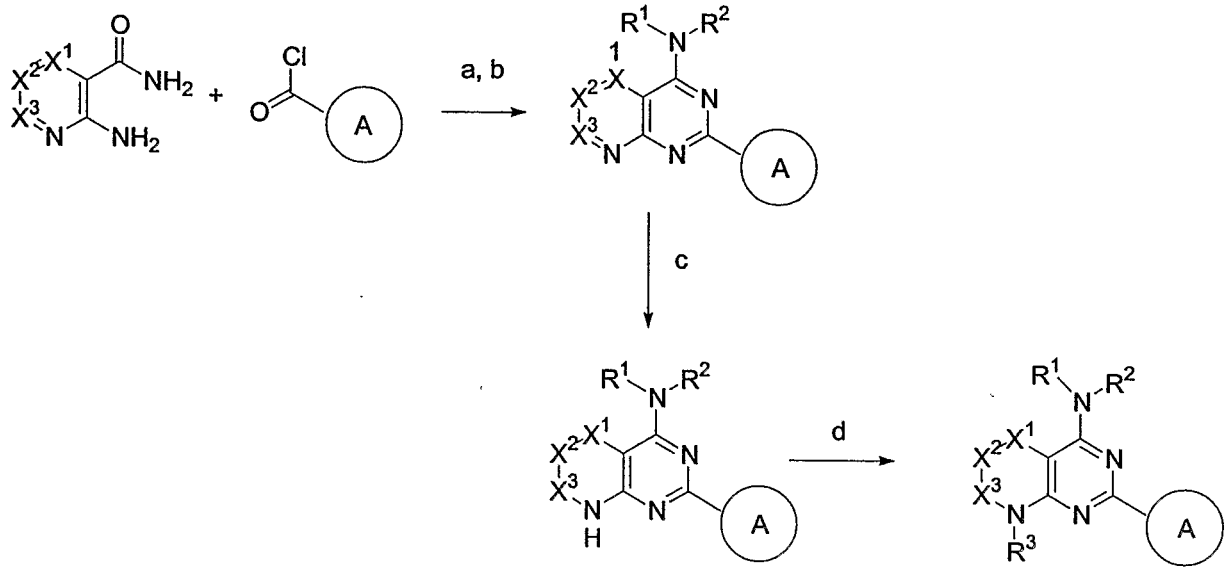
Scheme C: Preparation of C5-Aza_6 and Elaborations



[00166] Conditions: a) i. Et_3N, CH_2Cl_2; ii. NaOH, H_2O, reflux b) i. $POCl_3$, N,N-dimethylaniline, benzene, reflux; ii. R^1R^2NH, THF/CH_2Cl_2, RT; c) H_2, Pt_2O_2, TFA, EtOH; d) R^3-Cl, Et_3N, CH_2Cl_2.

[00167] Scheme D below depicts the preparation of C8_Aza_6 compounds and elaborations:

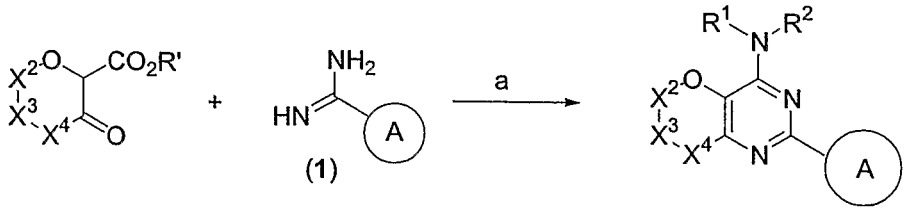
Scheme D: Preparation of C8-Aza_6 and Elaborations



[00168] Conditions: a) i. Et_3N, CH_2Cl_2; ii. NaOH, H_2O, reflux b) i. $POCl_3$, N,N-dimethylaniline, benzene, reflux; ii. R^1R^2NH, THF/CH_2Cl_2, RT; c) H_2, Pt_2O_2, TFA, EtOH; d) R^3-Cl, Et_3N, CH_2Cl_2.

[00169] Scheme E below depicts the preparation of C5_Oxa_6 compounds:

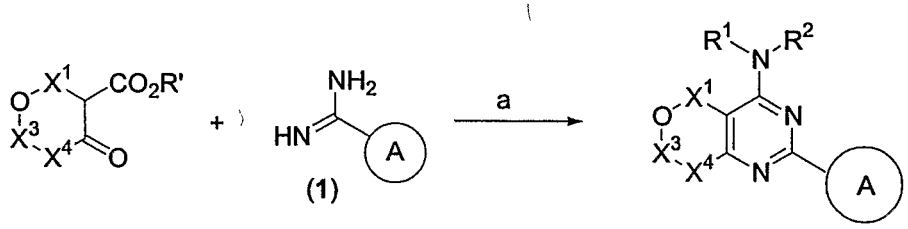
Scheme E: C5_Oxa_6 compounds



[00170] Conditions: a) i. 1, NaOEt, EtOH, reflux; ii. $POCl_3$, N,N-dimethylaniline, benzene, reflux; ii. R^1R^2NH, THF/CH_2Cl_2, RT.

[00171] Scheme F below depicts the preparation of C6_Oxa_6 compounds:

Scheme F: C6_Oxa_6 compounds

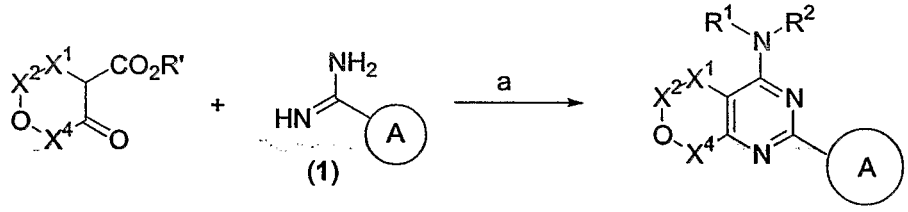


[00172] Conditions: a) i. 1, NaOEt, EtOH, reflux; ii. $POCl_3$, N,N-dimethylaniline, benzene, reflux; ii. R^1R^2NH, THF/CH_2Cl_2, RT.

[00173] Scheme G below depicts the preparation of C7_Oxa_6 compounds:

[00174]

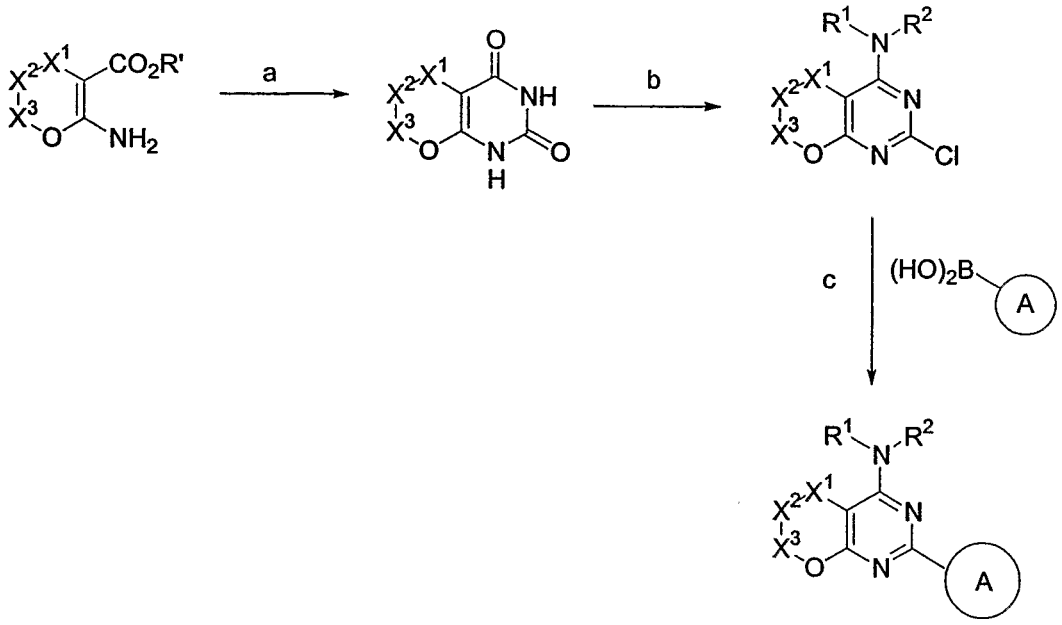
Scheme G: C7_Oxa_6 compounds



[00175] Conditions: a) i. 1, NaOEt, EtOH, reflux; ii. $POCl_3$, N,N-dimethylaniline, benzene, reflux; ii. R^1R^2NH, THF/CH_2Cl_2, RT.

[00176] Scheme H below depicts the preparation of C8_Oxa_6 compounds:

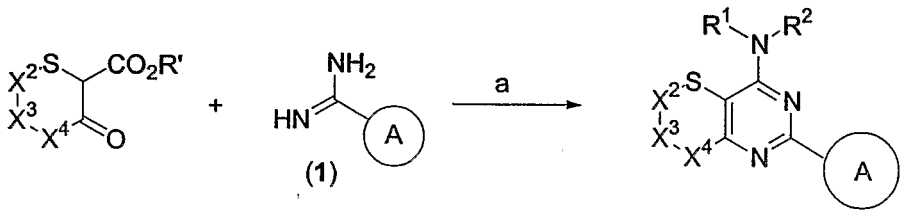
Scheme H: C8_Oxa_6 compounds



[00177] Conditions: a) i. $ClSO_2NCO$, CH_2Cl_2; ii. KOH, H_2O; b) i. $POCl_3$, N,N-dimethylaniline, benzene, reflux; ii. R^1R^2NH, THF/CH_2Cl_2, RT; c) $Pd(Ph_3)_4$, Na_2CO_3, CH_3CN, H_2O, reflux

[00178] Scheme I below depicts the preparation of C5_thia_6 compounds:

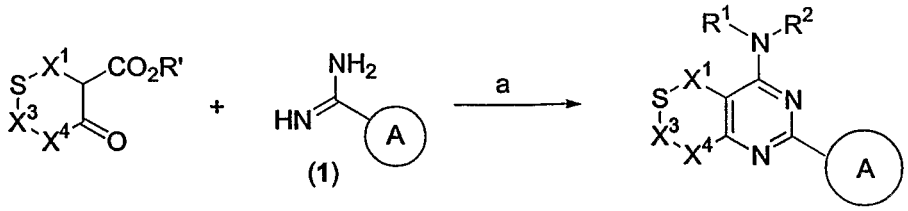
Scheme I: C5_Thia_6 compounds



[00179] Conditions: a) i. 1, NaOEt, EtOH, reflux; ii. $POCl_3$, N,N-dimethylaniline, benzene, reflux; ii. R^1R^2NH, THF/CH_2Cl_2, RT.

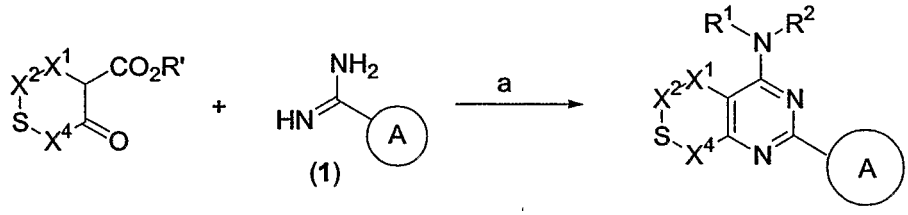
[00180] Scheme J below depicts the preparation of C6_Thia_6 compounds:

Scheme J: C6_Thia_6 compounds



[00181] Scheme K below depicts the preparation of C7_Thia_6 compounds:

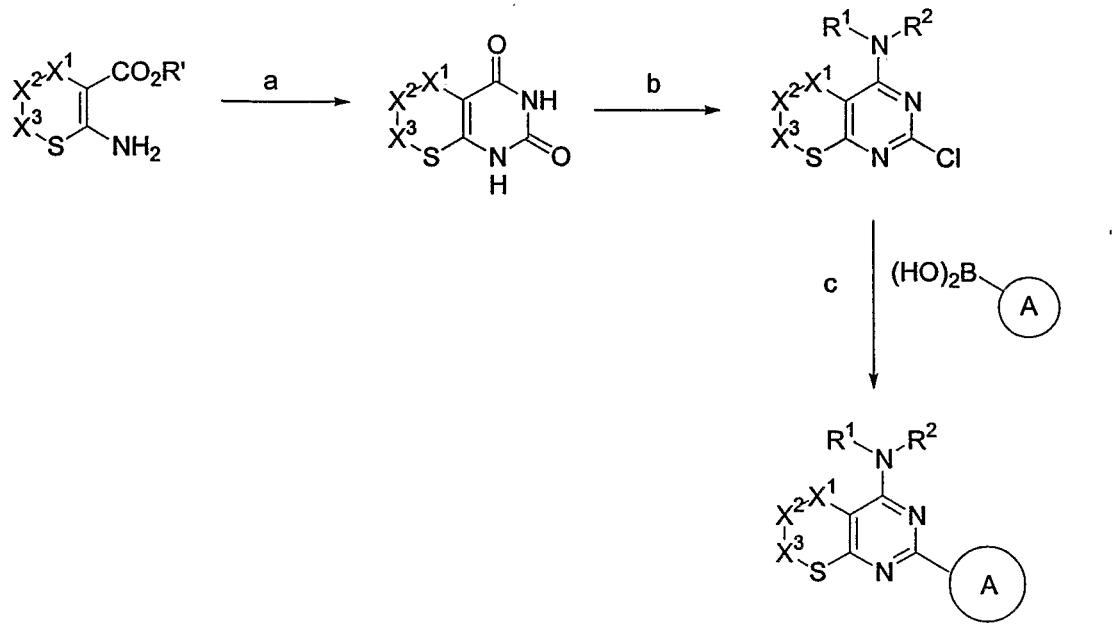
Scheme K: C7_Thia_6 compounds



[00182] Conditions: a) i. 1, NaOEt, EtOH, reflux; ii. $POCl_3$, N,N-dimethylaniline, benzene, reflux; ii. R^1R^2NH, THF/CH_2Cl_2, RT.

[00183] Scheme L below depicts the preparation of C8_Thia_6 compounds:

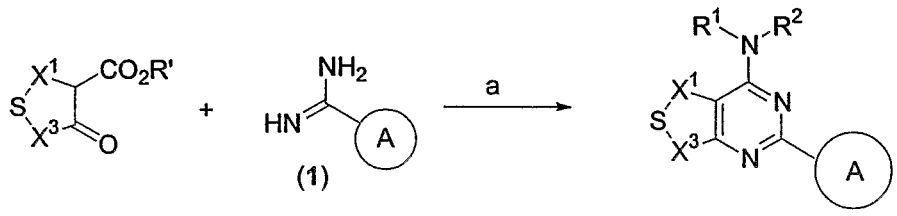
Scheme L: C8_Thia_6 compounds



[00184] Conditions: a) i. $ClSO_2NCO$, CH_2Cl_2; ii. KOH, H_2O; b) i. $POCl_3$, N,N-dimethylaniline, benzene, reflux; ii. R^1R^2NH, THF/CH_2Cl_2, RT; c) $Pd(Ph_3)_4$, Na_2CO_3, CH_3CN, H_2O, reflux

[00185] Scheme M below depicts the preparation of C6_thia_5 compounds:

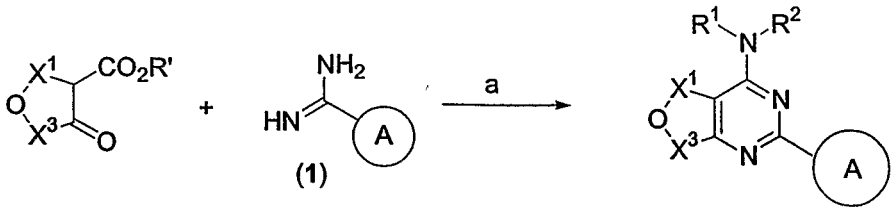
Scheme M: C6_Thia_5 compounds



[00186] Conditions: a) i. 1, NaOEt, EtOH, reflux; ii $POCl_3$, N,N-dimethylaniline, benzene, reflux; ii. R^1R^2NH, THF/CH_2Cl_2, RT.

[00187] Scheme N below depicts the preparation of C6_oxa_5 compounds:

Scheme N: C6_oxa_5 compounds

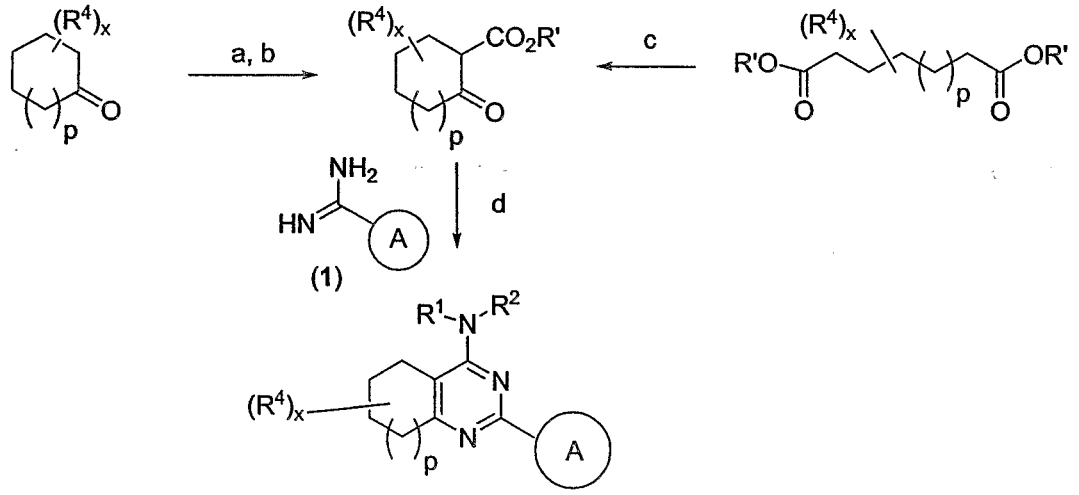


[00188] Conditions: a) i. 1, NaOEt, EtOH, reflux; ii $POCl_3$, N,N-dimethylaniline, benzene, reflux; ii. R^1R^2NH, THF/CH_2Cl_2, RT.

[00189]

[00190] As described in more detail in the Examples herein, and as shown generally in Scheme O below, reaction of a desired cyclohexanone-1-carboxylate and an amidine in ethanol with NaOEt at 0°C, and subsequent reaction with phosphorus oxychloride, boron tribromide, and a desired amine generates compounds of general formula **I'**.

Scheme O: Preparation of β-Ketoesters and Elaboration

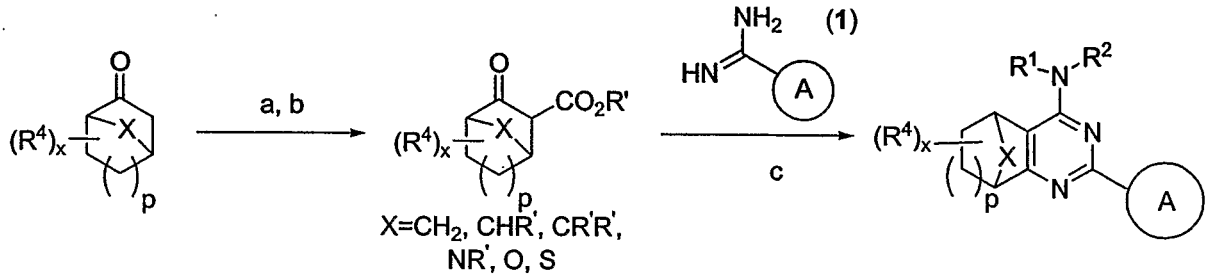


[00191] Conditions: a) LDA, R'OC(O)CN, THF; b) NaOR', R'OH, 48h, rt; c) NaOR', R'OH; d) i. 1, NaOEt, EtOH; ii. $POCl_3$, N,N-dimethylaniline, benzene, reflux; iii. R^1R^2NH, THF/CH_2Cl_2, RT.

[00192] It will be appreciated that this method can be utilized to prepare a variety of compounds.

[00193] Scheme P below depicts the preparation of bicyclic β-ketoesters:

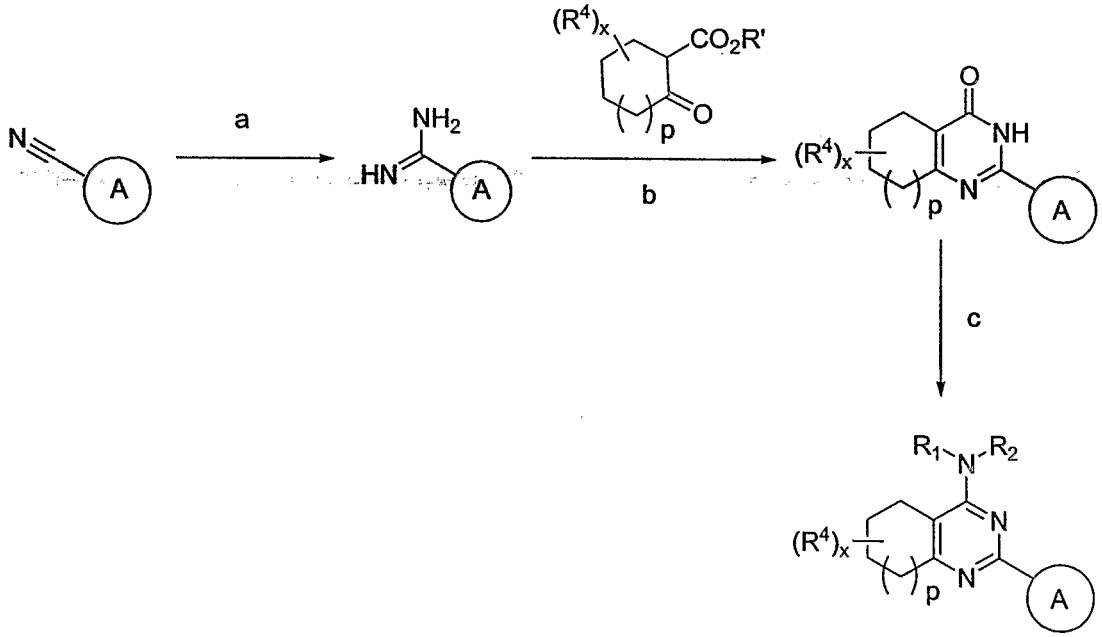
Scheme P: Preparation of Bicyclic β-Ketoesters and Elaboration



[00194] Conditions: a) i. LDA, R'OC(O)CN, THF; ii. b) NaOR', R'OH, 48h, rt; c) i. NaOEt, EtOH; ii. $POCl_3$, N,N-dimethylaniline, benzene, reflux; iii. R^1R^2NH, THF/CH_2Cl_2, RT.

[00195] Additional conditions for the preparation of compounds of formula **I'** and subsets thereof is presetned below in Scheme Q.

Scheme Q: Additional Amidine Syntheses and Elaborations

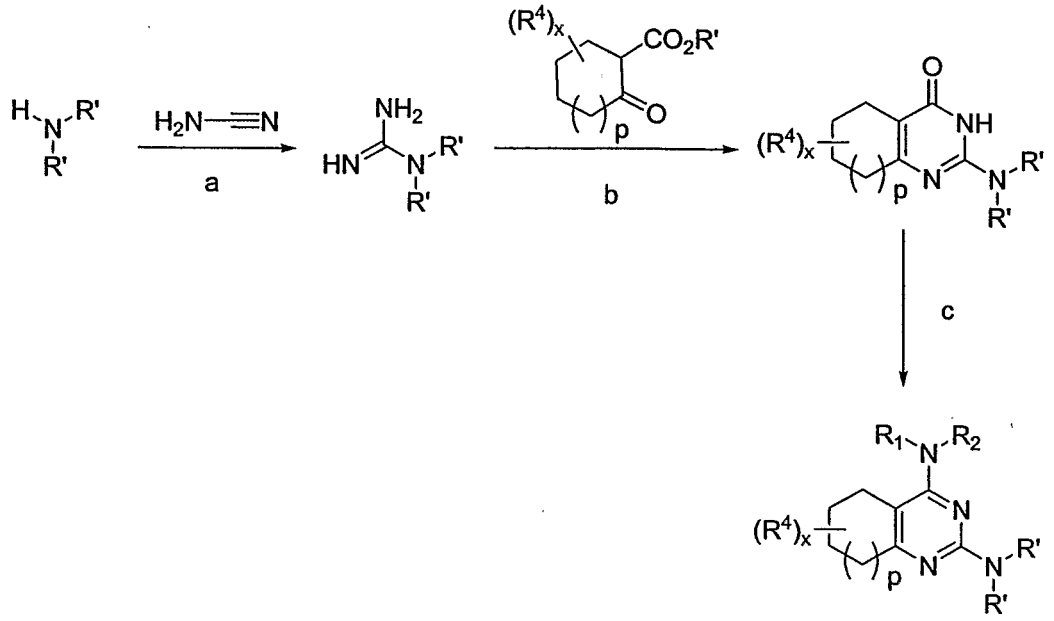


[00196] Conditions: a) i. LiHMDS; ii. HCl or i. HCl, MeOH; ii. NH_3; b) NaOEt, EtOH; c) i. $POCl_3$, N,N-dimethylaniline, benzene, reflux; ii. R^1R^2NH, THF/CH_2Cl_2, RT.

[00197] In certain other embodiments, Ring A represents an N-linked heteroaryl or heterocyclyl group (as depicted below in Scheme R, where two occurrences of R' are taken

together below to form an optionally substituted 5-8-membered cycloalkyl, heterocyclyl, aryl, or heteoaryl ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur).

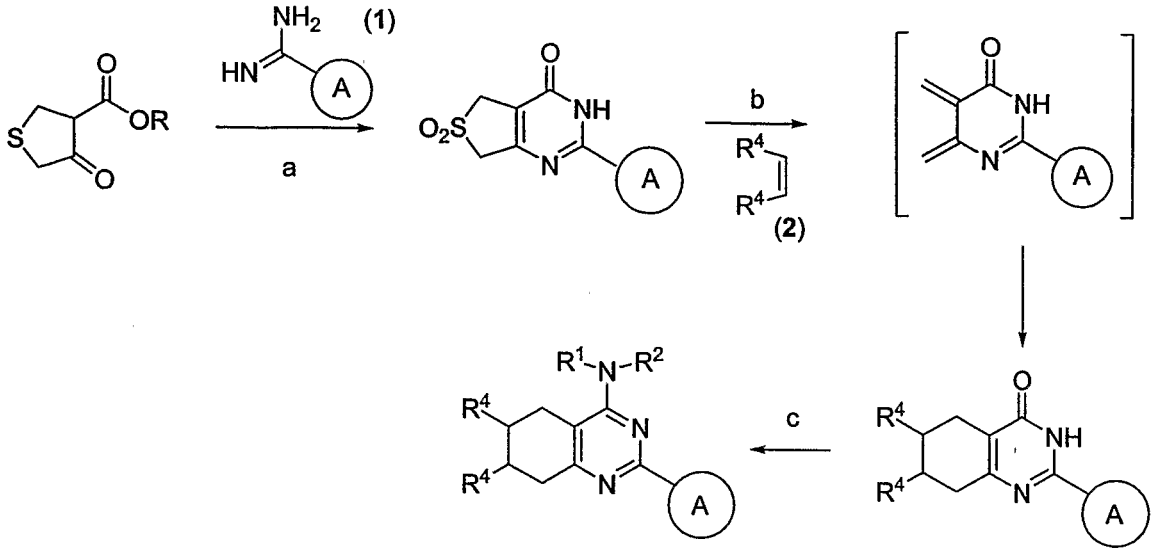
Scheme R: Amidine Synthesis and Elaboration: C2 Aza



[00198] Conditions: a) H_2O; b) NaOEt, EtOH; c) i. $POCl_3$, N,N-dimethylaniline, benzene, reflux; ii. R^1R^2NH, THF/CH_2Cl_2, RT.

[00199] In still other embodiments, compounds of the invention are prepared via Diels-Alder reactions to provide substituted tetrohydroquinazoline moieties as depicted in Scheme S below:

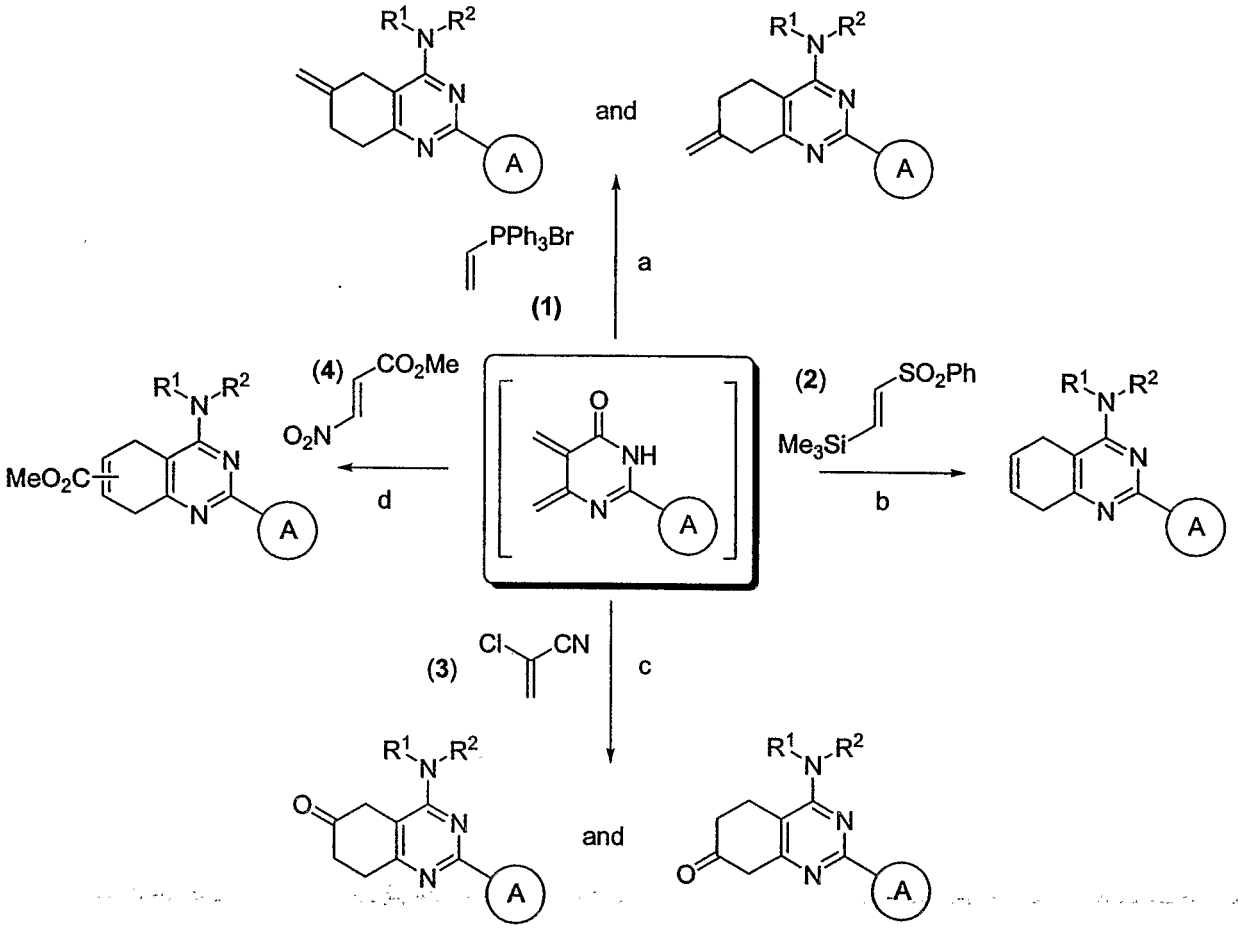
Scheme S: Diels-Alder Reactions



[00200] Conditions: a) i. 1, EtOH; ii. m-CPBA; b) 2, toluene, reflux, 18 h; c) i. $POCl_3$, N,N-dimethylaniline, benzene, reflux; ii. R^1R^2NH, THF/CH_2Cl_2, RT.

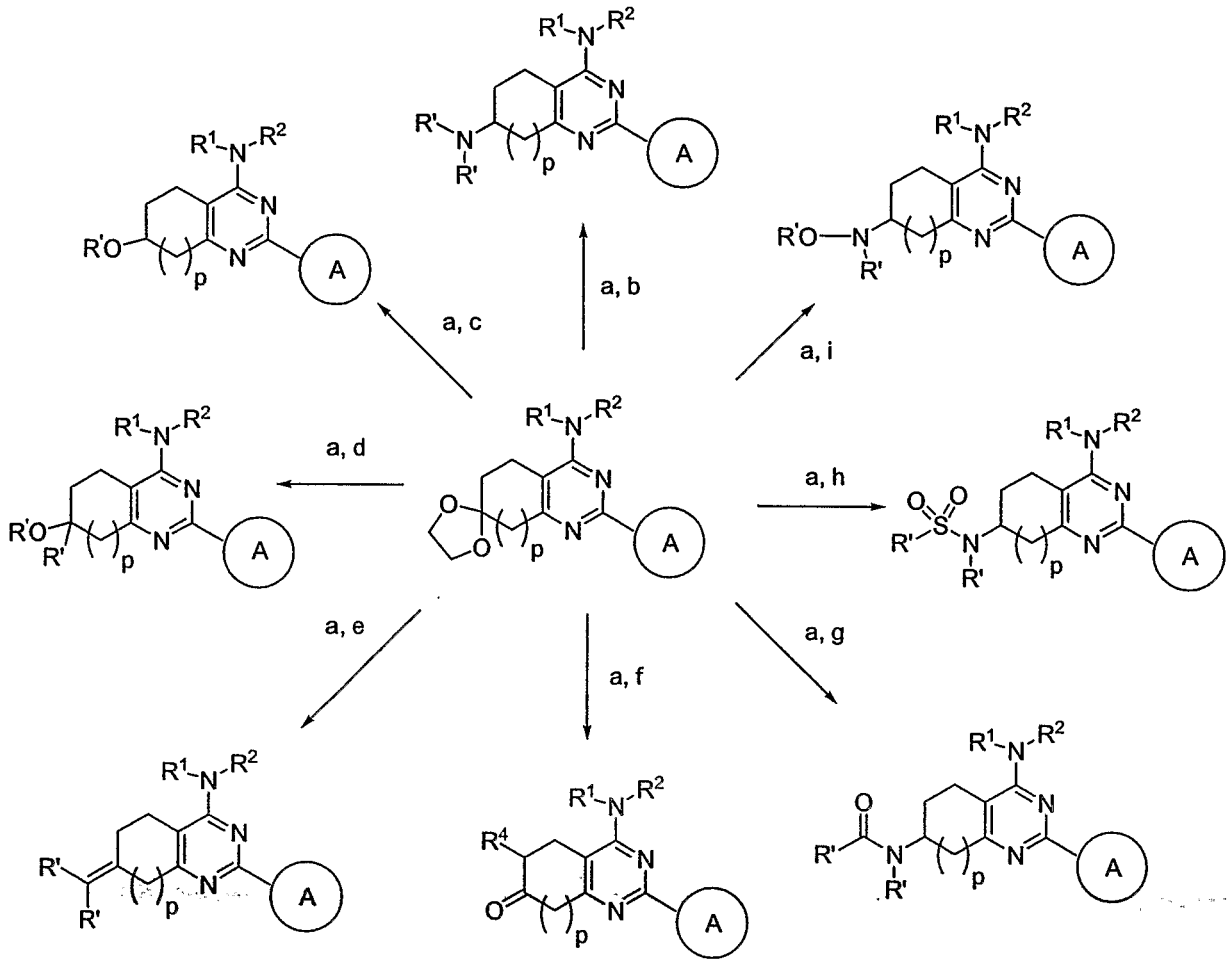
[00201] Further functionalization of inventive compounds can be achieved via exemplary reactions as depicted below in Schemes T and U:

Scheme T: Additional Diels Alder Reactions



[00202] Conditions: a) i. 1; ii. LDA, HCHO; iii. $POCl_3$; iv. R^1R^2NH; b) i. 2; ii. TBAF; iii. $POCl_3$; iv. R^1R^2NH; c) i. 3; ii. Na_2S; iii. $POCl_3$; iv. R^1R^2NH; d) i. 4; ii. DBU; iii. $POCl_3$; iv. R^1R^2NH.

Scheme U: Cycloalkanoyl Derivatization



[00203] Conditions: a) 25% H_2SO_4; b) $NaBH(OAc)_3$, AcOH, R'R'NH, DCE, rt; c) i. $NaBH_4$, MeOH; ii. NaH, R'X; d) i. R'MgBr; ii. R'X; e) R'R'C=P(Ph)$_3$; f) LDA, R^4X; g) i. $R'NH_2$, $NaBH(OAc)_3$, AcOH; ii. pyridine, R'C(O)Cl; h) i. $R'NH_2$, $NaBH(OAc)_3$, AcOH; ii. pyridine, $R'SO_2Cl$; i) NH_2OR', TsOH.

[00204] Although certain exemplary embodiments are depicted and described above and herein, it will be appreciated that a compounds of the invention can be prepared according to the methods described generally above using appropriate starting materials by methods generally available to one of ordinary skill in the art.

[00205] *5. Uses, Formulation and Administration*

[00206] *Pharmaceutically acceptable compositions*

[00207] As discussed above, the present invention provides compounds that are inhibitors of voltage-gated sodium ion 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.

[00208] 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.

[00209] 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.

[00210] 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.

[00211] 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.

[00212] *Uses of Compounds and Pharmaceutically Acceptable Compositions*

[00213] 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, or incontinence 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 preferred 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 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, 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, or incontinence.

[00214] 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, 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, or incontinence. 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.

[00215] 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.

[00216] 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.

[00217] 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.

[00218] 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.

[00219] 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.

[00220] 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.

[00221] 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.

[00222] 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.

[00223] 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.

[00224] 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.

[00225] 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.

[00226] 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.

[00227] In certain exemplary embodiments, compounds of the invention are useful as inhibitors of NaV1.8. In other embodiments, compounds of the invention are useful as inhibitors of NaV1.8 and CaV2.2. In still other embodiments, compounds of the invention are useful as inhibitors of CaV2.2.

[00228] 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".

[00229] 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.

[00230] 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.

[00231] Another aspect of the invention relates to inhibiting 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 the present invention 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.

[00232] Inhibition 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.

[00233] In order that the invention described herein may be more fully understood, the following examples are set forth. It should be understood that these examples are for illustrative purposes only and are not to be construed as limiting this invention in any manner.

EXAMPLES

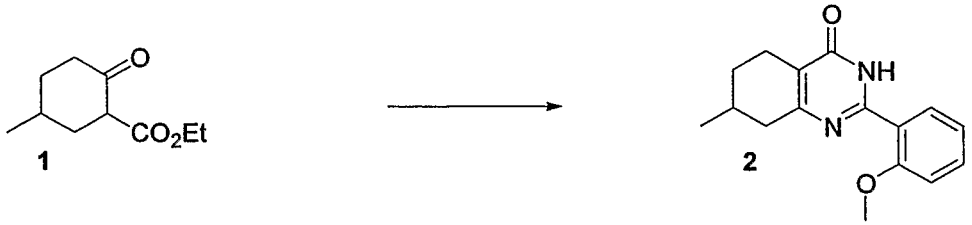
[00234] SYNTHESIS OF EXEMPLARY COMPOUNDS OF THE INVENTION

[00235] Methods:

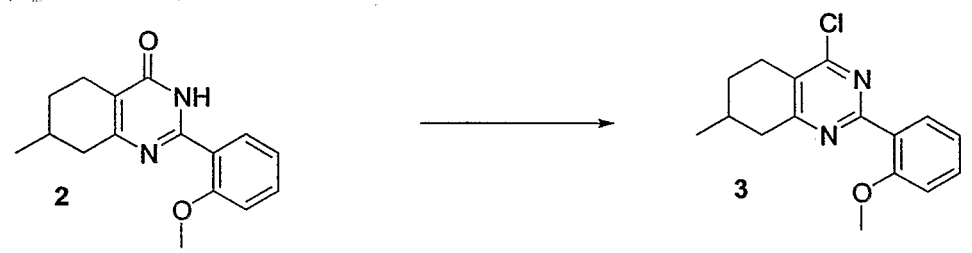
[00236] (A) Micromass MUX LCT 4 channel LC/MS, Waters 60F pump, Gilson 215 4 probe autosampler, Gilson 849 injection module, 1.5 mL/min/column flow rate, 10-99% CH_3CN (0.035 % TFA) / H_2O (0.05 % TFA) gradient, Phenomenex Luna 5u C18 columns (50 x 4.60 mm), Waters MUX UV-2488 UV detector, Cedex 75 ELSD detectors.

[00237] (B) PESciex API-150-EX LC/MS, Shimadzu LC-8A pumps, Gilson 215 autosampler, Gilson 819 injection module, 3.0 mL/min flow rate, 10-99% CH_3CN (0.035 % TFA) / H_2O (0.05 % TFA) gradient, Phenomenex Luna 5u C18 column (50 x 4.60 mm), Shimadzu SPD-10A UV/Vis detector, Cedex 75 ELSD detector.

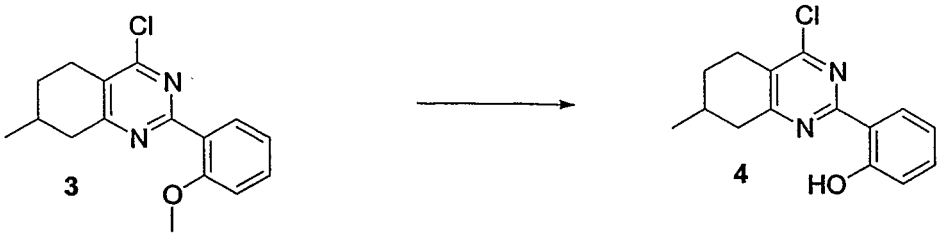
[00238] (C) PESciex API-150-EX LC/MS, Shimadzu LC-8A pumps, Gilson 215 autosampler, Gilson 819 injection module, 3.0 mL/min flow rate, 40-99% CH_3CN (0.035 % TFA) / H_2O (0.05 % TFA) gradient, Phenomenex Luna 5u C18 column (50 x 4.60 mm), Shimadzu SPD-10A UV/Vis detector, Cedex 75 ELSD detector.



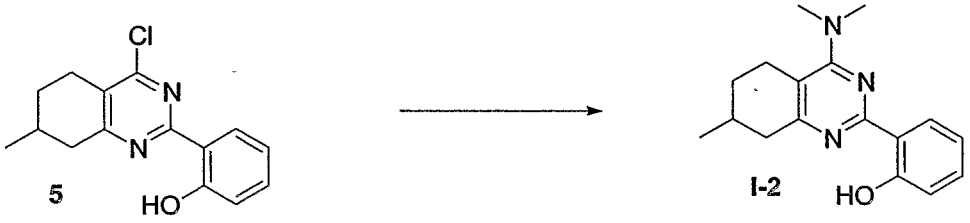
[00239] To a solution of ethyl 4-methyl-2-cyclohexanone-1-carboxylate **1** (4.7 g, 26.4 mmol) and 2-methoxy-benzamidine (5.7 g, 26.4 mmol) in ethanol (100 mL) was added NaOEt (21% in EtOH, 39.4 mL, 105.6 mmol) at 0°C. The reaction mixture was allowed to warm to room temperature and was then heated to 90°C for 12 hours. After cooling to room temperature, the solvent was removed, and the residue was taken up in ice water, extracted with DCM (50 mL x 2), dried (Na_2SO_4) and concentrated to give a crude yellow solid. The crude mixture was purified by silica gel chromatography (65% EtOAc/35% hexane) to afford **2** (2.7 g, 9.9 mmol, 38 % yield) as a white solid. LC/MS (Method C: 10-99% CH_3CN / H_2O) M+1 (obs) = 272.0 retention time 2.77 min.



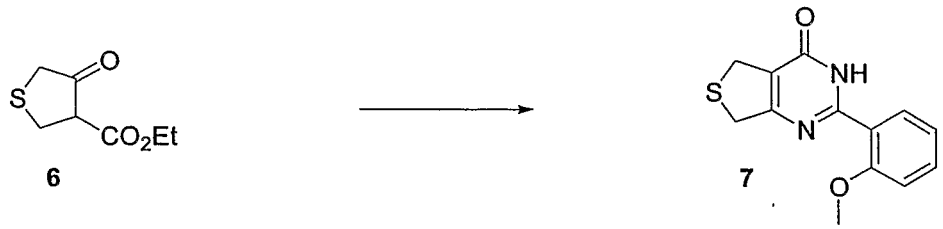
[00240] 2-(2-Methoxy-phenyl)-7-methyl-5,6,7,8-tetrahydro-3*H*-quinazolin-4-one **2** (2.2 g, 8.15 mmol) was dissolved in phosphorus oxychloride (50 mL) and heated to 90°C for 3 hours. The solution was cooled to room temperature and solvent removed in *vacuo*. The residue was taken up in ice water, neuralized with sat aqueous $NaHCO_3$, extracted with dichloromethane (150 mL) (PH = 10), and concentrated to afford **3** (2.2 g, 7.61 mmol, 93% yield) as light yellow solid. LC/MS (Method C: 10-99% CH_3CN / H_2O) M+1 (obs) = 290.0 retention time 3.73 min.



[00241] To a solution of 4-chloroquinazoline **3** (2.2 g, 7.86 mmol) in dichloromethane (100 mL) in a round-bottomed flask equipped with rubber septum, stirring bar and nitrogen balloon was added boron tribromide (1M in DCM, 39.3 mmol) dropwise at -78°C. The reaction was warmed to room temperature and allowed to stir for 3 hours at room temperature. Then the reaction mixture was cooled to -78°C and quenched with saturated aqueous $NaHCO_3$ (50 mL). After stirring for 1 hour at room temperature, the mixture was extracted with dichloromethane (2 x 100 mL), dried over Na_2SO_4 and concentrated to afford **4** (2.1 g, 7.76 mmol, 97 %yield) as a light pink solid. LC/MS, (Method C: 10-99% CH_3CN / H_2O) M+1 (obs) = 275.0 retention time 4.60 min.

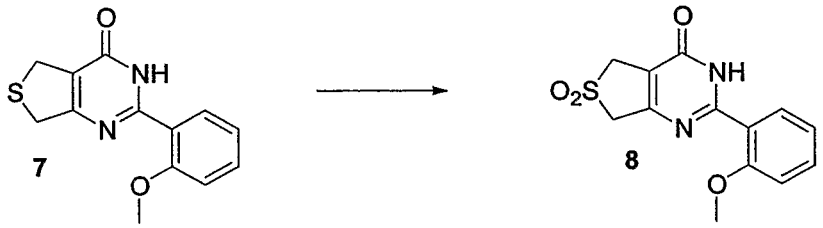


[00242] To a solution of 2-(4-chloro-7-methyl-5,6,7,8-tetrahydroquinazolin-2-yl)-phenol **4** (50 mg, 0.18 mmol) in THF (2 mL) was added triethylamine (0.072 mL, 0.54 mmol) and dimethylamine (1M in THF, 0.9 mL, 0.9 mmol). After stirring at room temperature overnight, the solvent was removed *in vacuo*. The crude mixture was purified by using Gilson HPLC to afford the TFA salt of **I-2** (47 mg, 0.12 mmol, 67% yield) as a white solid. LC/MS (Method C: 10-99% CH_3CN / H_2O) M+1 (obs) = 284.0 retention time 3.17 min.

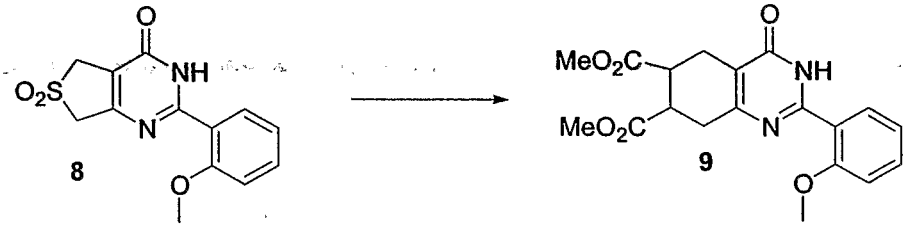


[00243] A solution of ethyl 4-oxo-tetranhydrothiophene-3-carboxylic acid ethyl ester **6** (1.0 g, 26.4 mmol) and 2-methoxy-benzamidine (5.7 g, 26.4 mmol) in ethanol (100 mL) was stirred at ambient temperature overnight, then heated at reflux for 4 hours. After cooling to

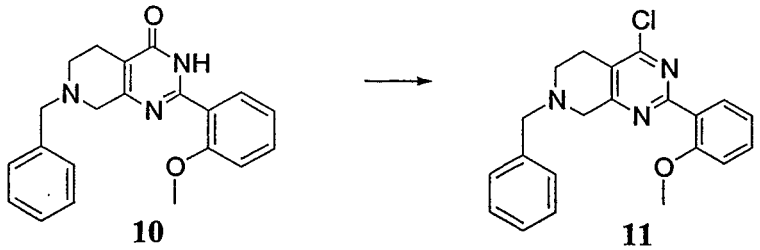
ambient temperature, the solvent was removed *in vacuo*. The crude mixture was purified by flash chromatography on silica (65% EtOAc/ 35% hexane) to afford **7** (2.7 g, 10.4 mmol, 39% yield) as a white solid. LC/MS (Method C: 10-99% CH_3CN / H_2O) M+1 (obs) = 261.0, retention time 2.89 min.



[00244] To a solution of 2-(2-methoxy-phenyl)-5,7-dihydro-3H-thieno[3,4-d]pyrimidine-4-one **7** (1.0 g, 3.94 mmol) in dichloromethane (100 mL) was added MCPBA (1.8 g, 7.9 mmol) in portions at ambient temperature. After stirring for 3 hours at ambient temperature, the reaction was quenched with saturated aqueous sodium thiosulfate, washed with aqueous sodium bicarbonate, water, and then extracted twice with 50 mL portions of dichloromethane. The combined organic layer was dried (Na_2SO_4) and concentrated *in vacuo* to give the crude product as a yellow solid. Purification by flash chromatography on silica gel (65% EtOAc/35% hexane) gave **8** (1.1 g, 3.8 mmol, 97% yield) as a white solid. LC/MS (Method C: 10-99% CH_3CN / H_2O) M+1 (obs) = 293.0, retention time 2.39 min.

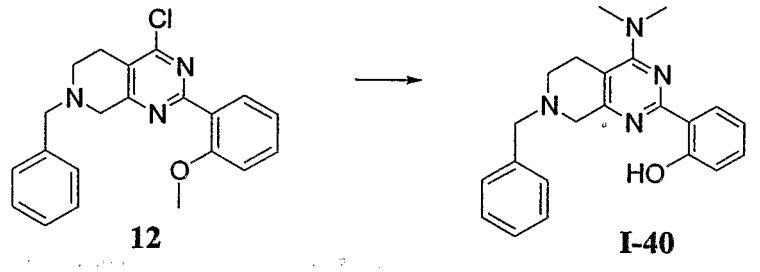


[00245] A solution of 2-(2-methoxy-phenyl)-6,6-dioxo-3,5,6,7-tetrahydro-6-thieno[3,4-d]pyrimidine-4-one **8** (1.0 g, 3.4 mmol) and diethyl maleate (4.3 mL, 34 mmol) in toluene (100 mL), was refluxed for 18 hours in a 150 mL round-bottomed flask equipped with a Dean-Stark trap. The solvent was removed *in vacuo* and the crude mixture purified by flash chromatography on silica gel to afford **9** (1.0 g, 2.7 mmol, 79% yield) as a white solid. LC/MS (Method C: 10-99% CH_3CN / H_2O) M+1 (obs) = 372.8, retention time 2.70 min.



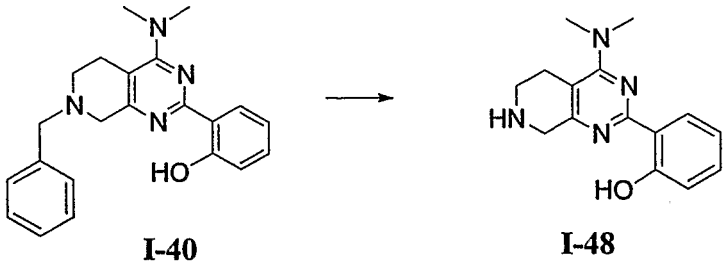
10 11

[00246] A 250 mL roundbottom flask, equipped with a reflux condenser, was charged with a mixture of **11** (2.0 g, 5.8 mmol), *N*, *N*-dimethylaniline (0.70 g, 5.8 mmol), and phosphoryl chloride (8.9g, 57.7 mmol). The mixture was heated, with stirring, at 95 °C for 10 minutes. The clear solution was concentrated under reduced pressure and the residue was poured onto ice (250 g) followed by the addition of CH_2Cl_2 (500 mL). The mixture was made strongly basic by the dropwise addition of 50% aqueous NaOH solution. The organic portion was dried ($MgSO_4$) and evaporated under reduced pressure. The residue was purified by silica gel chromatography using (70% hexanes, 30% ethyl acetate) to obtain **11** (1.6 g, 4.3 mmol, 75% yield) as a light yellow oil. LC/MS (Method C: 10-99% CH_3CN / H_2O) M+1 (obs) = 375.3; R_t = 1.90.



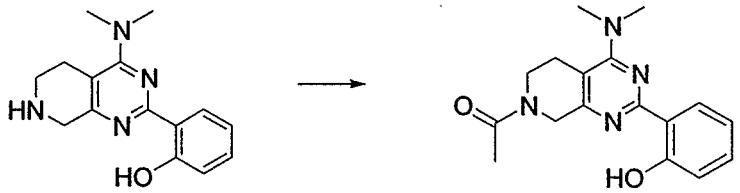
12 I-40

[00247] A 250 mL roundbottom flask was charged with a solution of **12** (3.5 g, 9.6 mmol), and CH_2Cl_2 (120 mL). To this solution was added boron tribromide (28.8 mL, 28.8 mmol, 1.0M in CH_2Cl_2) dropwise over a period of 5 minutes. The solution was stirred at 25 °C for 30 minutes. The mixture was poured into saturated aqueuous $NaHCO_3$ solution (500 mL) followed by the addition of CH_2Cl_2 (300 mL). The organic portion was dried ($MgSO_4$) and treated with triethylamine (1.4 mL, 10.0 mmol) followed by the addition of dimethylamine (14.4 mL, 28.8 mmol, 2.0 M in THF). The mixture was stirred at ambient temperature for 1 hour. The mixture was evaporated to dryness under reduced pressure. The residue was purified by silica gel chromatography using (70% hexanes, 30% ethyl acetate) to obtain **I-40** (1.3 g, 3.6 mmol, 39% yield) as a white solid. LC/MS (Method C: 10-99% CH_3CN / H_2O) M+1 (obs) = 361.2; R_t = 2.42.



I-40 I-48

[00248] A 250 mL roundbottom flask, equipped with a reflux condenser, was charged with a solution of **I-40** (1.3 g, 3.6 mmol), AcOH (50 mL), and 10% palladium on carbon (200 mg), under an atmosphere of N_2. A hydrogen balloon was introduced to the top of the reflux condenser via a needle pierced septa. The mixture was stirred and heated at 90 °C for 6 hours. The mixture was purged with N_2, cooled, filtered, and the filtrate evaporated to dryness under reduced pressure to obtain compound **I-48** (1.0 g, 3.6 mmol, 100% yield) as a white solid. LC/MS (Method C: 10-99% CH_3CN / H_2O) M+1 (obs) = 271.2; R_t = 2.00.



I-48 I-49

[00249] A 2 mL vial was charged with a solution of 4 (25 mg, 0.09 mmol), triethylamine (19 mg, 18 mmol), and CH_2Cl_2 (0.5 mL), under an atmosphere of N_2. To this solution was added acetyl chloride (7.0 mg, 0.09 mmol). The mixture was stirred at 25 °C for 20 minutes. The mixture was purified by HPLC to obtain compound **I-49** (32 mg, 0.07 mmol, 80% yield) as a trifluoroacetic acid salt. LC/MS (Method C: 10-99% CH_3CN / H_2O) M+1 (obs) = 313.2; R_t = 2.18.

[00250] Other compounds of formula I have been prepared by methods substantially similar to those described above. The characterization data for these compounds is summarized in Table 3 below and includes HPLC, LC/MS (observed) and ^1H NMR data. Compound numbers correspond to the compound *numbers* listed in Table 2.

[00251] Table 3. Characterization Data for Selected Compounds of Formula I

Cmd	LC-MS M+1 (obs)	LC-MS R_t

Cmd	LC-MS M+1 (obs)	LC-MS R_t

Cmd	LC-MS M+1 (obs)	LC-MS R_t
30	284.0	3.23
31	326.0	3.51
32	310.2	3.27
33	270.0	3.04
34	312.0	3.21
35	296.2	3.16
36	284.0	3.17
37	326.2	3.42
38	310.4	3.28
39	312.0	2.59
40	314.0	1.98
41	314.0	2.01
42	341.4	1.73
43	327.2	1.70
44	372.2	2.43
45	325.2	1.96
46	367.0	2.19
47	350.0	2.84
48	350.2	1.64
49	324.0	2.87
50	339.0	2.01
51	338.0	3.10
52	338.0	3.07
53	353.2	1.76
54	338.0	2.50
55	340.0	2.19
56	286.0	2.18
57	312.0	2.39
58	328.0	2.10
59	341.2	1.55
60	359.8	2.93
61	423.0	2.69
62	276.0	5.53
63	258.0	5.57
64	375.3	1.90
65	375.4	1.81
66	255.8	2.39
67	281.8	2.53
68	297.8	2.52
69	297.2	2.83
70	361.2	2.42
71	361.4	2.23
72	271.2	2.00
73	271.2	1.72
74	349.3	2.61
75	363.2	2.76
76	313.2	2.18
77	327.3	2.37
78	349.1	2.52
79	363.2	2.30
80	313.2	1.93

Cmd	LC-MS M+1 (obs)	LC-MS R_t
81	327.2	2.41
82	285.2	2.04
83	299.2	2.43
84	290.0	2.49
85	274.0	2.75
86	405.4	2.30
87	419.2	2.52
88	391.2	2.52
89	445.2	2.84
90	429.4	2.79
91	375.2	2.86
92	428.2	3.43
93	412.4	3.06
94	386.0	2.91
95	342.0	2.89
96	383.8	2.79
97	406.4	1.93
98	368.2	2.16
99	254.8	2.20
100	281.0	2.43
101	297.0	2.15
102	295.0	2.57
103	312.8	2.41
104	309.0	2.76
105	255.0	1.88
106	281.0	2.10
107	297.2	2.12
108	295.2	2.41
109	313.0	2.44
110	325.2	2.17
111	309.4	2.63
112	300.4	2.08
113	298.3	2.07
114	243.0	2.47
115	410.0	2.76
116	397.2	2.32
117	324.0	2.93
118	324.0	2.93
119	338.0	3.51
120	326.0	3.02
121	283.9	2.68
122	353.9	2.91
123	309.9	2.73
124	397.1	3.07
125	378.1	3.16
126	283.8	2.65
127	310.0	2.79
128	323.9	3.22
129	326.1	2.97
130	337.9	3.41
131	339.1	2.64

Cmd	LC-MS M+1 (obs)	LC-MS R_t
132	397.1	3.26
133	445.0	3.68
134	378.2	3.20
135	338.5	3.31
136	352.0	3.31
137	366.2	3.52
138	425.2	3.39

Cmd	LC-MS M+1 (obs)	LC-MS R_t
139	417.1	3.11
140	403.1	2.99
141	431.1	3.23
142	345.9	3.11
143	359.9	3.46
144	339.9	2.91
145	356.1	3.04

[00252] **ASSAYS FOR DETECTING AND MEASURING NaV INHIBITION PROPERTIES OF COMPOUNDS**

[00253] A) Optical methods for assaying NaV inhibition properties of compounds:

[00254] 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).

[00255] B) VIPR® optical membrane potential assay method with chemical stimulation

[00256] Cell Handling and Dye Loading

[00257] 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.

[00258] Analysis of VIPR® Data:

[00259] 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:

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

[00260] 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.

[00261] 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: NaCl 160, KCl 4.5, $CaCl_2$ 2, $MgCl_2$ 1, HEPES 10, pH 7.4 with NaOH

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

[00262] Cell Culture

[00263] 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.

[00264] C) VIPR® optical membrane potential assay method with electrical stimulation

[00265] 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.

[00266] 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.

[00267] ***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)

[00268] ***Loading protocol:***

[00269] **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.

[00270] **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 .

[00271] 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.

[00272] 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.

[00273] Reagents

[00274] 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

[00275] 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.

[00276] Data Analysis

[00277] 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:

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

[00278] 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.

[00279] 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.

[00280] ELECTROPHYSIOLOGY ASSAYS FOR NaV ACTIVITY AND INHBITION OF TEST COMPOUNDS

[00281] 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.

[00282] 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 (~22° 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.

[00285] Solutions

[00286] Intracellular solution (in mM): Cs-F (130), NaCl (10), $MgCl_2$ (1), EGTA (1.5), $CaCl_2$ (0.1), HEPES (10), glucose (2), pH = 7.42, 290 mOsm.

[00287] Extracellular solution (in mM): NaCl (138), $CaCl_2$ (1.26), KCl (5.33), KH_2PO_4 (0.44), $MgCl_2$ (0.5), $MgSO_4$ (0.41), $NaHCO_3$ (4), Na_2HPO_4 (0.3), glucose (5.6), HEPES (10), CdCl2 (0.4), NiCl2 (0.1), TTX (0.25×10^{-3}).

[00288] CURRENT-CLAMP assay for NaV channel inhibition activity of compounds

[00289] 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.

[00290] Compounds of the invention as depicted generally herein and in Table 2 were found to inhibit voltage-gated sodium channels at 25.0 μM or less.

[00291] **ASSAYS FOR DETECTING AND MEASURING CaV INHIBITION PROPERTIES OF COMPOUNDS**

[00292] A) Optical methods for assaying CaV inhibition properties of compounds:

[00293] Compounds of the invention are useful as antagonists of voltage-gated calcium ion channels. Antagonist properties of test compounds were assessed as follows. Cells expressing the CaV 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 electrical means to evoke a CaV 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).

[00294] VIPR® optical membrane potential assay method with electrical stimulation

[00295] The following is an example of how CaV2.2 inhibition activity is measured using the optical membrane potential method. Other subtypes are performed in an analogous mode in a cell line expressing the CaV of interest.

[00296] HEK293 cells stably expressing CaV2.2 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 $DiSBAC_6(3)$ (Aurora #00-100-010) in dry DMSO

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

200 mM Acid Yellow 17 (Aurora #VABSC) in H_20

370mM Barium Chloride (Sigma Cat# B6394) in H_20

Bath X

160mM NaCl (Sigma Cat# S-9888)

4.5mM KCl (Sigma Cat# P-5405)

1mM MgCl2 (Fluka Cat# 63064)

10mM HEPES (Sigma Cat# H-4034)

pH 7.4 using NaOH

[00297] Loading rotocol:

[00298] **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 added 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.

[00299] **2X CC2DMPE & $DISBAC_6(3)$ = 8 μM CC2DMPE & 2. 5 μM $DISBAC_6(3)$:** Vortex together both dyes with an equivalent volume of 10% pluronic (in DMSO). Vortex in required amount of Bath X with beta-cyclodextrin. Each 96well cell plate will require 5 ml of 2XCC2DMPE. Wash plate with ELx405 with Bath X, leaving a residual volume of 50 μL/well. Add 50 μL of 2XCC2DMPE & $DISBAC_6(3)$ to each well. Stain for 30 minutes in the dark at RT.

[00300] **1. 5X AY17 = 750 μM AY17 with 15mM $BaCl_2$:** Add Acid Yellow 17 to vessel containing Bath X. Mix well. Allow solution to sit for 10 minutes. Slowly mix in 370mM $BaCl_2$. This solution can be used to solvate compound plates. Note that compound plates are made at 1.5X drug concentration and not the usual 2X. Wash CC2 stained plate, again, leaving

residual volume of 50 µL. Add 100 uL/well of the AY17 solution. Stain for15 minutes in the dark at RT. Run plate on the optical reader.

[00301] 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.

[00302] Assay Protocol

[00303] Insert or use electrodes into each well to be assayed.

[00304] Use the current-controlled amplifier to deliver stimulation wave pulses for 3-5 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.

[00305] Data Analysis

[00306] 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:

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

[00307] 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.

[00308] Control responses are obtained by performing assays in the presence of a compound with the desired properties (positive control), such as mibefradil, 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.

[00309] ELECTROPHYSIOLOGY ASSAYS FOR CaV ACTIVITY AND INHBITION OF TEST COMPOUNDS

[00310] Patch clamp electrophysiology was used to assess the efficacy of calcium channel blockers expressed in HEK293 cells. HEK293 cells expressing CaV2.2 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 – 100 mV. The results of these experiments have contributed to the definition of the efficacy profile of the compounds.

[00311] VOLTAGE-CLAMP assay in HEK293 cells expressing CaV2.2

[00312] CaV2.2 calcium currents were recorded from HEK293 cells using the whole-cell variation of the patch clamp technique. Recordings were made at room temperature (~22° 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).

[00313] 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 +20mV for 50ms at frequencies of 0.1, 1, 5, 10, 15, and 20 Hz. Blocking effects were allowed to plateau before proceeding to the next test concentration.

[00314] Solutions

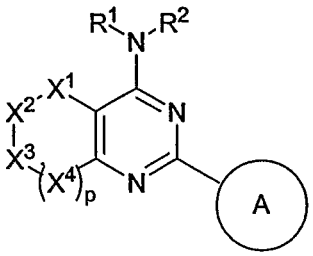
[00315] Intracellular solution (in mM): Cs-F (130), NaCl (10), $MgCl_2$ (1), EGTA (1.5), $CaCl_2$ (0.1), HEPES (10), glucose (2), pH = 7.42, 290 mOsm.

[00316] Extracellular solution (in mM): NaCl (138), $BaCl_2$ (10), KCl (5.33), KH_2PO_4 (0.44), $MgCl_2$ (0.5), $MgSO_4$ (0.41), $NaHCO_3$ (4), Na_2HPO_4 (0.3), glucose (5.6), HEPES (10).

[00317] Following these procedures, representative compounds of the present invention were found to possess desired N-type calcium channel modulation activity and selectivity.

Claims

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



I

or a pharmaceutically acceptable salt thereof, wherein:

p is 0, 1 or 2;

X^1, X^2, X^3 and X^4 are each independently selected from NR^3, C=O, CHR^4, S, O, S=O, or SO_2;

R^1 and R^2 are each independently hydrogen, or an optionally substituted group selected from C_{1-6} aliphatic, a 5-6 membered aryl ring having 0-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or a 3-7-membered saturated or partially unsaturated ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur; or R^1 and R^2, taken together with the nitrogen atom to which they are bound, form an optionally substituted 3-8 membered heterocyclyl or heteroaryl ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur, wherein R^1, R^2, or any ring formed by R^1 and R^2 taken together, are each independently optionally substituted at one or more carbon atoms with 0-4 occurrences of $-R^5$, and at one or more substitutable nitrogen atoms with $-R^6$;

Ring A is a 5-6 membered monocyclic or 8-10 membered bicyclic aryl ring having 0-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or a 3-7-membered saturated or partially unsaturated ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur, optionally substituted at one or more carbon atoms with 0-5 occurrences of $-R^7$, and at one or more substitutable nitrogen atoms with $-R^8$;

each occurrence of R^4, R^5, and R^7 is independently $Q\text{-}R^X$; wherein Q is a bond or is a C_1-C_6 alkylidene chain wherein up to two non-adjacent methylene units of Q are optionally and

independently replaced by CO, CO_2, COCO, CONR, OCONR, NRNR, NRNRCO, NRCO, $NRCO_2$, NRCONR, SO, SO_2, $NRSO_2$, SO_2NR, $NRSO_2NR$, O, S, or NR;

each occurrence of R^X is independently selected from R', halogen, NO_2, or CN;

each occurrence of R is independently selected from hydrogen or an optionally substituted C_{1-6} aliphatic group;

each occurrence of R' is independently selected from hydrogen or an optionally substituted group selected from C_{1-8} aliphatic, C_{6-10} aryl, a heteroaryl ring having 5-10 ring atoms, or a heterocyclyl ring having 3-10 ring atoms, or wherein R and R' taken together with the atom(s) to which they are bound, or two occurrences of R' taken together with the atom(s) to which they are bound, form a 5-8 membered cycloalkyl, heterocyclyl, aryl, or heteroaryl ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur; and

each occurrence of R^3, R^6 or R^8 is independently R', -COR', $-CO_2(C_{1-6}$ aliphatic), $-CON(R')_2$, or $-SO_2R'$;

provided that:

a) R^1 is not hydrogen when R^2 is optionally substituted indazol-3-yl;

b) R^1 is not hydrogen when R^2 is optionally substituted pyrazol-3-yl;

c) R^1 is not hydrogen when R^2 is 1,2,4-triazol-3-yl;

d) when p is 1, then:

i) when R^1 and R^2, taken together with the nitrogen atom, is N-morpholino, and Ring A is unsubstituted phenyl, then X^1, X^2, X^3 and X^4 are not, respectively:

1) CH_2, $CH(CH_2)Ph$, NR^3, and $CHCH_3$;

2) CH_2, CH_2, CH_2, and S;

3) CH_2, S, CH_2, and S;

4) CH_2, CH_2, S, and CH_2;

5) CH_2, CHMe, S, and CH_2; or

6) CHMe, CH_2, $N(CH_2)Ph$, and CH_2;

ii) R^1 is not hydrogen, and R^2 is not CH_2Ph, $(CH_2)_2O(CH_2)_2OH$, or $-CH_2$(1,3-benzodioxol-5-yl) when ring A is imidazol-1-yl;

iii) when R^1 and R^2, taken together with the nitrogen atom, is N-piperidinyl then:

1) when X^1, X^2 and X^3 are CH_2, and X^4 is S, then Ring A is not unsubstituted phenyl; and

2) when X^1, X^2 and X^4 are CH_2; and X^3 is S, then Ring A is not unsubstituted phenyl;

iv) when R^1 and R^2, taken together with the nitrogen atom, is N-piperizinyl, X^1, X^2 and X^3 are CH_2, and X^4 is S, then Ring A is not 3-NO_2Ph, 4-pyridinyl, or unsubstituted phenyl;

v) when one of X^1, X^2, X^3 or X^4 is NR^3 and the others of X^1, X^2, X^3 or X^4 are each CH_2, and R^1 and R^2 are each Me, H, CH_2Ph, or $(CH_2)_2NMe_2$, then Ring A is not pyrid-2-yl substituted at the 6-position;

vi) when X^1, X^2, and X^3 are each CH_2, X^4 is S, R^1 is H, and R^2 is $-CH_2-C\equiv CH$, then Ring A is not unsubstituted phenyl;

vii) when X^1 is NMe; X^2, X^3 and X^4 are each CH^2, R^1 is H, and R^2 is unsubstituted phenyl, then Ring A is not unsubstituted phenyl; and

viii) when X^1, X^2 and X^4 are each CH_2, X^3 is S, R^1 and R^2 are each Me, then Ring A is not unsubstituted phenyl; and

e) when p is 0, then:

i) when X^1 is CH_2, X^2 is NR^3, X^3 is C=O; or X^1 is C=O, X^2 is CHR^4, and X^3 is NR^3; or X^2 is NR^3, X^2 is C=O, and X^3 is CHR^4; or X^1 is CH_2, X^2 is O, and X^3 is C=O, then when R^1 is hydrogen and R^2 is unsubstituted phenyl or -CH_2CH_2Cl, or when R^1 and R^2, taken together form optionally substituted piperazinyl, morpholino, piperidinyl, or pyrrolidinyl, then Ring A is not optionally substituted piperidinyl, piperazinyl, morpholino, or pyrrolidinyl;

ii) when X^1 is CHR^4, X^2 is SO_2, and X^3 is CHR^4, and R^1 and R^2, taken together are piperazinyl, then Ring A is not unsubstituted phenyl;

iii) when X^1 and X^2 are CHR^4, X^3 is O, R^1 is hydrogen, and R^2 is $-C(=O)CH_3$, then Ring A is not substituted furyl;

iv) when X^1 is S, X^2 is CHR^4, X^3 is CHR^4; or X^1 is CHR^4, X^2 is S, and X^3 is CHR^4; or X^1 and X^2 are CHR^4 and X^3 is S, then Ring A is not optionally substituted N-linked morpholino, pyrrolidinyl, piperazinyl, piperidinyl, or is not unsubstituted phenyl or cyclopropyl;

v) when X^1 is CHR^4, X^2 is NR^3, X^3 is CHR^4, and R^1 and R^2 are both methyl, then Ring A is not 6-methyl-2-pyridyl;

vi) when X^1 is NR^3, X^2 is C=O, X^2 is NR^3, and R^1 and R^2 are both methyl, then Ring A is not unsubstituted phenyl; and

vii) when X^1 and X^2 are CHR^4, X^3 is NR^3, R^1 is hydrogen, and R^2 is unsubstituted phenyl, then Ring A is not unsubstituted phenyl; and

further provided that:

a) when each of X^1, X^2, X^3, and X^4 is CHR^4 and p is 0 or 1, then at least one R^4 is other than hydrogen;

b) when each of X^1, X^2, X^3, and X^4 is CHR^4 and Ring A is a substituted or unsubstituted piperizinyl group, then at least one R^4 is other than hydrogen;

c) when each of X^1, X^2, X^3, and X^4 is CHR^4, R^1 is hydrogen, and R^2 is 1H-indazol-3-yl, 7-fluoro-1H-indazol-3-yl, 5-fluoro-1H-indazol-3-yl, 5,7-difluoro-1H-indazol-3-yl or 5-methyl-1H-pyrazolyl, and Ring A is an unsubstituted phenyl group or is a phenyl group substituted in the ortho position with Cl or CF_3, then at least one R^4 is other than hydrogen; and

d) 5(6H)-quinazolinone, 4-anilino-7,8-dihydro-2,7-diphenyl- and 5(6H)-quinazolinone, 4-anilino-7,8-dihydro-7,7-dimethyl-2-phenyl- are excluded.

2. The compound according to claim 1, wherein p is 0 or 1.

3. The compound according to claim 1, wherein Ring A is a 5-6 membered aryl ring having 0-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or a 3-7-membered saturated or partially unsaturated ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur, optionally substituted at one or more carbon atoms with 0-5 occurrences of $-R^7$, and at one or more substitutable nitrogen atoms with $-R^8$, wherein R^7 and R^8 are as defined above.

4. The compound according to claim 1, wherein:

X^1, X^2, and X^4 are CH_2, and X^3 is CH-Me or N-(C_{1-4} alkyl), N-benzyl;

p is 0, 1 or 2;

R^1 is methyl and R^2 is furan-2-ylmethyl, dimethylaminoethyl, or methyl; or

R^1 and R^2 taken together form piperidinyl, piperazinyl, 4-methylpiperidinyl, 4-C_{1-4} alkoxypiperidinyl, morpholinyl, 4-carboxy-C_{1-4}alkylpiperazinyl, or 4-C_{1-4} alkylsulfonylpiperazinyl; and

ring A is 2-hydroxyphenyl, 2-hydroxy-6-fluorophenyl, phenyl-2-disodium phosphate, or pyrrolyl.

5. The compound according to claim 4, wherein:

X^1, X^2, and X^4 are CH_2, and X^3 is CH-Me or N-Me;

p is 1;

R^1 is methyl and R^2 is furan-2-ylmethyl or methyl; or

R^1 and R^2 taken together form piperidinyl, 4-methylpiperidinyl, morpholinyl, or 4-C_{1-4} alkylsulfonylpiperazinyl; and

ring A is 2-hydroxyphenyl or 2-hydroxy-6-fluorophenyl.

6. The compound according to claim 5, wherein:

X^1, X^2, and X^4 are CH_2, and X^3 is CH-Me;

p is 1;

R^1 is methyl and R^2 is furan-2-ylmethyl or methyl; or

R^1 and R^2 taken together form piperidinyl, 4-methylpiperidinyl, or 4-C_{1-4} alkylsulfonylpiperazinyl; and

ring A is 2-hydroxyphenyl or 2-hydroxy-6-fluorophenyl.

7. The compound according to claim 6, wherein:

X^1, X^2, and X^4 are CH_2, and X^3 is CH-Me;

p is 1;

R^1 and R^2 taken together form 4-methylpiperidinyl or 4-C_{1-4} alkylsulfonylpiperazinyl; and

ring A is 2-hyhdroxy or 2-hydroxy-6-fluorophenyl.

8. The compound according to claim 1, wherein:

X^1, and X^2 are CH_2, X^4 is CHOH or CH_2, and X^3 is CH_2, CH-Me, or C(O)-Me;

p is 1;

R^1 is methyl and R^2 methyl or methylaminoethyl; or

R^1 and R^2 taken together form 1-piperidinyl, 1-piperazinyl, or 4-methylpiperazinyl; and

ring A is 2-hydroxyphenyl, 2-fluorophenyl, or 1-pyrrolyl.

9. The compound according to claim 8, wherein:

X^1, X^2, and X^4 are CH_2, and X^3 is CH_2 or CH-Me;

p is 1;

R^1 is methyl and R^2 is methyl or methylaminoethyl; or

R^1 and R^2 taken together form 1-piperazinyl or 4-methylpiperazinyl; and

ring A is 2-hydroxyphenyl or 1-pyrrolyl.

10. The compound according to claim 1, wherein:

X^1 and X^4 are CH_2, X^2 is CH_2, CHMe, or C(O)OMe, and X^3 is N-benzyl, N-(3-methoxybenzyl), N-(4-carboxymethylbenzyl), CH_2, or CH-Me;

p is 1;

R^1 is methyl or benzyl and R^2 is methyl or dimethylaminoethyl; or

R^1 and R^2 taken together form a 1-piperazinyl, 1-piperidinyl, 4-carboxyethylpiperazinyl, 4-C_{1-4} alkylsulfonyl piperazinyl, 4-methylpiperidinyl, 4-methoxypiperidinyl, 4-methylpiperazinyl, 3-diethylaminocarbonylpiperidinyl, or morpholinyl; and

ring A is 2-hydroxyphenyl, 2-methoxyphenyl, or 1-pyrrolyl.

11. The compound according to claim 10, wherein:In one

X^1, X^2, and X^4 are CH_2, and X^3 is N-benzyl, N-(3-methoxybenzyl), N-(4-carboxymethylbenzyl), CH_2, or CH-Me;

p is 1;

R^1 is methyl or benzyl and R^2 is methyl or dimethylaminoethyl; or

R^1 and R^2 taken together form a 1-piperazinyl, 1-piperidinyl, 4-carboxyethylpiperazinyl, 4-C_{1-4} alkylsulfonyl piperazinyl, 4-methylpiperidinyl, 4-methoxypiperidinyl, 3-diethylaminocarbonylpiperidinyl, or morpholinyl; and

ring A is 2-hydroxyphenyl, 2-methoxyphenyl, or 1-pyrrolyl.

12. The compound according to claim 11, wherein:

X^1, X^2, and X^4 are CH_2, and X^3 is N-benzyl, N-(3-methoxybenzyl), N-(4-carboxymethylbenzyl), or CH-Me;

p is 1;

R^1 is methyl or benzyl and R^2 is methyl or dimethylaminoethyl; or

R^1 and R^2 taken together form a 4-C_{1-4} alkylsulfonyl piperazinyl, 4-methylpiperidinyl, or 3-diethylaminocarbonylpiperidinyl; and

ring A is 2-hydroxyphenyl or 2-methoxyphenyl.

13. The compound according to claim 12, wherein:

X^1, X^2, and X^4 are CH_2, and X^3 is N-(3-methoxybenzyl) or CH-Me;

p is 1;

R^1 and R^2 are both methyl; or

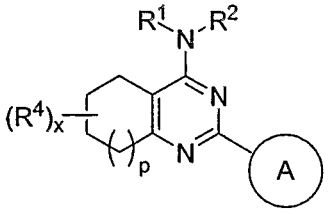
R^1 and R^2 taken together form a 4-methylsulfonylpiperazinyl or 4-ethylsulfonylpiperazinyl; and

ring A is 2-hydroxyphenyl or 2-methoxyphenyl.

14. The compound according to claim 9, wherein:

X^1, X^2, and X^4 are CH_2, and X^3 is CH_2 or CH-Me, p is 1, R^1 and R^2 each are methyl or R^1 and R^2 taken together form 1-piperazinyl, and ring A is 2-hydroxyphenyl or 1-pyrrolyl.

15. A compound of formula **I'**:



I'

or a pharmaceutically acceptable salt thereof, wherein:

R^1 and R^2 are each independently hydrogen, or an optionally substituted group selected from C_{1-6} aliphatic, a 5-6 membered aryl ring having 0-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or a 3-7-membered saturated or partially unsaturated ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur; or R^1 and R^2, taken together with the nitrogen atom to which they are bound, form an optionally substituted 3-8 membered heterocyclyl or heteroaryl ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur, wherein R^1, R^2, or any ring formed by R^1 and R^2 taken together, are each independently optionally substituted at one or more carbon atoms with 0-4 occurrences of $-R^5$, and at one or more substitutable nitrogen atoms with $-R^6$;

Ring A is a 5-6 membered monocyclic or 8-10 membered bicyclic aryl ring having 0-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or a 3-7-membered saturated or partially unsaturated ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur, optionally substituted at one or more carbon atoms with 0-5 occurrences of $-R^7$, and at one or more substitutable nitrogen atoms with $-R^8$;

x is 0-6;

p is 0, 1, or 2; and

each occurrence of R^4, R^5, and R^7 is independently $Q\text{-}R^X$; wherein Q is a bond or is a C_1-C_6 alkylidene chain wherein up to two non-adjacent methylene units of Q are optionally and independently replaced by CO, CO_2, COCO, CONR, OCONR, NRNR, NRNRCO, NRCO, $NRCO_2$, NRCONR, SO, SO_2, $NRSO_2$, SO_2NR, $NRSO_2NR$, O, S, or NR;

each occurrence of R is independently selected from hydrogen or an optionally substituted C_{1-6} aliphatic group;

each occurrence of R' is independently selected from hydrogen or an optionally substituted group selected from C_{1-8} aliphatic, C_{6-10} aryl, a heteroaryl ring having 5-10 ring atoms, or a heterocyclyl ring having 3-10 ring atoms, or wherein R and R' taken together with the atom(s) to which they are bound, or two occurrences of R' taken together with the atom(s) to which they are bound, form a 5-8 membered cycloalkyl, heterocyclyl, aryl, or heteroaryl ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur; and

each occurrence of R^6 or R^8 is independently R', -COR', $-CO_2(C_{1-6}$ aliphatic), $-CON(R')_2$, or $-SO_2R'$;

provided that:

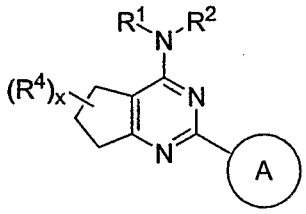
a) when p is 0 or 1, then at least one R^4 is other than hydrogen;

b) when Ring A is a substituted or unsubstituted piperizinyl group, then at least one R^4 is other than hydrogen;

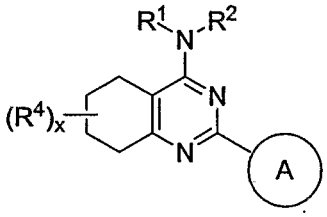
c) when R^1 is hydrogen and R^2 is 1H-indazol-3-yl, 7-fluoro-1H-indazol-3-yl, 5-fluoro-1H-indazol-3-yl, 5,7-difluoro-1H-indazol-3-yl or 5-methyl-1H-pyrazolyl, and Ring A is an unsubstituted phenyl group or is a phenyl group substituted in the ortho position with Cl or CF_3, then at least one R^4 is other than hydrogen; and

d) 5(6H)-quinazolinone, 4-anilino-7,8-dihydro-2,7-diphenyl- and 5(6H)-quinazolinone, 4-anilino-7,8-dihydro-7,7-dimethyl-2-phenyl- are excluded.

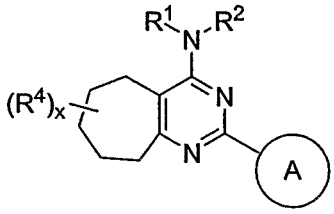
16. The compound according to claim 15, wherein said compound has formula **I-A, I-B,** or **I-C**:



I-A



I-B



I-C.

17. The compound according to claim 16, having formula **I-B.**

18. The compound according to claim 17, wherein:

(i) ring A is pyrrolyl, pyridyl, fluorophenyl, hydroxyphenyl, acyloxyphenyl, hydroxy-fluorophenyl, methoxyphenyl, phenyl-phosphate disodium salt, methylpiperidyl, ethyl-carbamic acid phenyl ester;

(ii) x is 0-2, and R^4 is C_{1-4} alkyl optionally substituted with hydroxy,C_{1-4} alkoxy, or halo, hydroxy, C_{1-4} alkylcarbonyloxy or carbo(C_{1-4}alkoxy);

(iii) R^1 is hydrogen, C_{1-4} alkyl, or benzyl, and R^2 is C_{1-4} alkyl, di(C_{1-4} alkyl)amino-C_{1-4} alkyl, 2-(2'-tetrahydrofuranyl)methyl, 2-hydroxy-1-methyl-ethyl, or imidazol-5-yl-ethyl; or

(iv) R^1 and R^2 taken together form a ring selected from N-pyrrolidinyl, N-piperidinyl, N-piperazinyl, morpholinyl, thiomorpholinyl, (C_{1-4} alkyl)sulfonylpiperazinyl, wherein said ring is optionally substituted with up to 3 substituents selected from halo, oxo, hydroxy, trifluoromethyl,

-O- C_{1-4} alkyl, C_{1-4} alkyl optionally substituted with hydroxy, amino, aminocarbonyl, di(C_{1-4}alkyl)aminocarbonyl, or carboxy.

19. The compound according to claim 17, wherein:

(i) ring A is 1-pyrrolyl, 2-pyridyl, 2-fluorophenyl, 2-hydroxyphenyl, 2-acyloxyphenyl, 2-hydroxy-6-fluorophenyl, 2-methoxyphenyl, phenyl-2-phosphate disodium salt, or 4-methylpiperidyl, 2- ethyl-carbamic acid phenyl ester

(ii) x is 0, or x is 1 and R^4 is 6-methyl, 7-methyl, 8-hydroxy, or 2-t-butylcarbonyloxy, or x is 2, and R^4 is 6-carboxymethyl and 7-carboxymethyl;

(iii) R^1 is hydrogen, methyl, ethyl, or benzyl, and R^2 is methyl, ethyl, dimethylaminoethyl, 2-(2'-tetrahydrofuranyl)methyl, 2-hydroxy-1-methyl-ethyl, methylaminoethyl, imidazol-5-yl-ethyl, or

(vii) R^1 and R^2 taken together form 4-methoxypiperidinyl, N-pyrrolidinyl, 3-trifluoromethyl-1-pyrrolidinyl, 4-butylsulfonyl-piperazinyl, 1-piperidinyl, 1-piperazinyl, 4-methylpiperidinyl, 4-hydroxypiperidinyl, 4-morpholinyl, 4-methylsulfonylpiperazinyl, 4-ethylsulfonylpiperazinyl, 4-isopropylsulfonylpiperazinyl, N-piperidinyl, 3-diethylaminocarbonyl-1-piperidinyl, 4-oxo-piperidinyl, 3-aminocarbonyl-piperidinyl, 4-methylpiperazinyl, or 4-carboxyethyl-piperazinyl.

20. The compound according to claim 17, wherein:

(i) ring A is 2-pyridyl, 2-fluorophenyl, 2-hydroxyphenyl, 2-acyloxyphenyl, 2-hydroxy-6-fluorophenyl, 2-methoxyphenyl, or 4-methylpiperidyl,

(ii) x is 0, or x is 1 and R^4 is 6-methyl, 7-methyl, or 8-hydroxy,

(iii) R^1 is methyl, ethyl, or benzyl, and R^2 is methyl, ethyl, dimethylaminoethyl, or 2-(2'-tetrahydrofuranyl)methyl, or R^1 and R^2 taken together form 4-methoxypiperidinyl, N-pyrrolidinyl, 4-butylsulfonyl-piperazinyl, piperidinyl, 4-methylpiperidinyl, 4-hydroxypiperidinyl, 4-morpholinyl, 4-methylsulfonylpiperazinyl, 4-ethylsulfonylpiperazinyl, N-piperidinyl, 3-diethylaminocarbonyl-1-piperidinyl, or 4-carboxyethyl-piperazinyl.

21. The compound according to claim 17, wherein:

(i) ring A is 2-pyridyl, 2-hydroxyphenyl, 2-acyloxyphenyl, 2-hydroxy-6-fluorophenyl, or 4-methylpiperidyl;

(ii) x is 0, or x is 1 and R^4 is 7-methyl;

(iii) R^1 is methyl and R^2 is methyl or 2-(2'-tetrahydrofuranyl)methyl, or R^1 and R^2 taken together form 4-butylsulfonyl-piperazinyl, piperidinyl, 4-methylpiperidinyl, 4-morpholinyl, 4-methylsulfonylpiperazinyl, 4-ethylsulfonylpiperazinyl, 4-piperidinyl, or 4-carboxyethyl-piperazinyl.

22. The compound according to claim 17, wherein:

ring A is 2-hydroxyphenyl, R^1 and R^2, taken together, form a 1-piperidinyl ring, x is 1, and R^4 is 7-methyl.

23. The compound according to claim 15 or 16, wherein neither R^1 nor R^2 is hydrogen, and R^1 and R^2 are each independently selected from a 5- or 6-membered aryl ring having 0-5 heteroatoms independently selected from N, O, or S, a 3-7-membered saturated or partially unsaturated ring having 0-3 heteroatoms independently selected from N, O, or S, or an optionally substituted C_{1-4} aliphatic group, wherein one or more methylene units in the C_{1-4} aliphatic group are optionally and independently replaced with NR, O, (CO)O, O(CO), NR(CO), (CO)NR, SO_2(NR), or (NR)SO_2.

24. The compound according to claim 23, wherein R^1 and R^2 are each independently an optionally substituted C_{1-4} aliphatic group, wherein one or more methylene units in the C_{1-4} aliphatic group are optionally and independently replaced with NR, O, (CO)O, O(CO), NR(CO), (CO)NR, SO_2(NR), or (NR)SO_2.

25. The compound according to claim 24, wherein when R^1 and R^2 are each independently an optionally substituted C_{1-4} aliphatic group, wherein one or more methylene units in the C_{1-4} aliphatic group are optionally and independently replaced with NR, O, (CO)O, O(CO), NR(CO), (CO)NR, SO_2(NR), or (NR)SO_2.

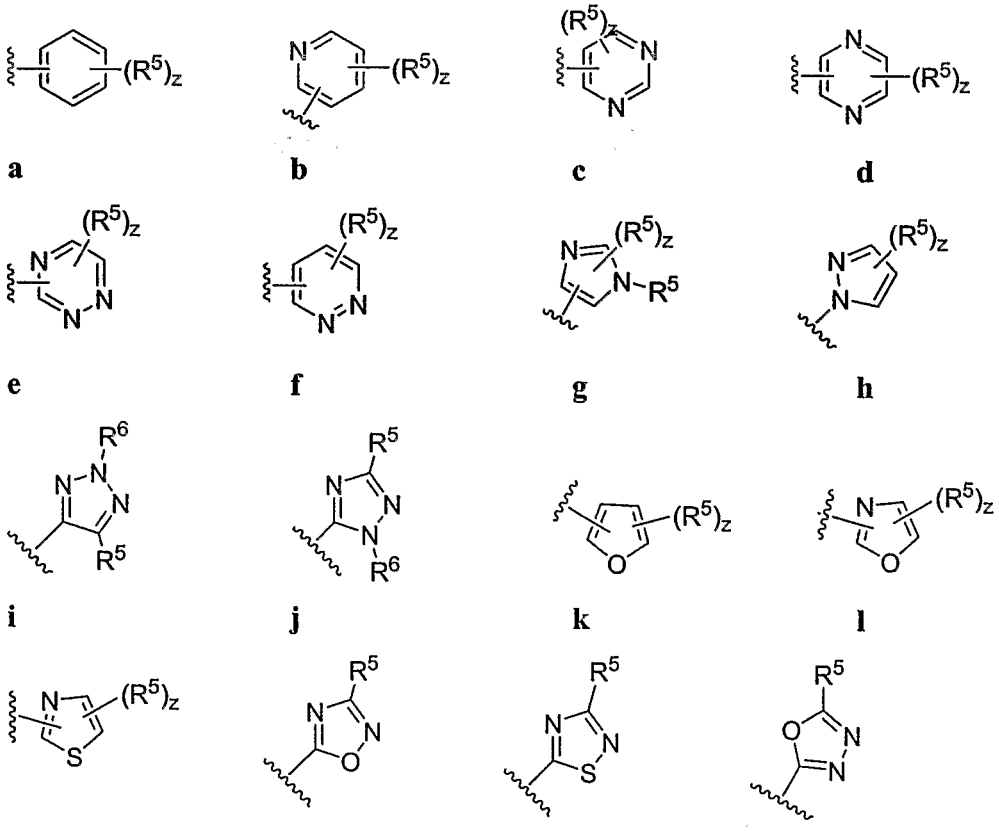
26. The compound according to claim 25, R^1 and R^2 groups are each independently optionally substituted methyl, ethyl, cyclopropyl, n-propyl, propenyl, cyclobutyl, $(CO)OCH_2CH_3$, $(CH_2)_2OCH_3$, $CH_2(CO)OCH_2CH_3$, $CH_2(CO)OCH_3$, $CH(CH_3)CH_2CH_3$, or t-butyl, or n-butyl.

27. The compound according to claim 15 or 16, wherein:

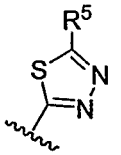
(i) one of R^1 or R^2 is hydrogen and the other of R^1 or R^2 is a 5-6 membered aryl ring having 0-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or a 3-7-membered saturated or partially unsaturated ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur; or

(ii) one of R^1 or R^2 is hydrogen, and the other of R^1 or R^2 is an optionally substituted C_{1-4} aliphatic group, wherein one or more methylene units in the C_{1-4} aliphatic group are optionally and independently replaced with NR, O, (CO)O, O(CO), NR(CO), (CO)NR, $SO_2(NR)$, or $(NR)SO_2$.

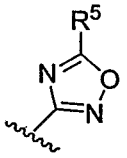
28. The compound according to claim 23, wherein R^1 or R^2 is selected from:



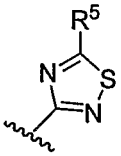
m



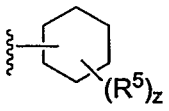
n



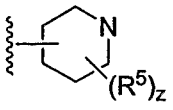
o



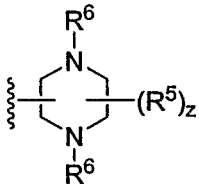
p



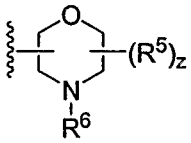
q



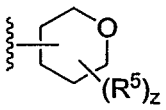
r



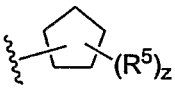
s



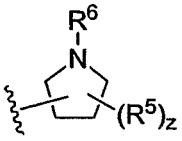
t



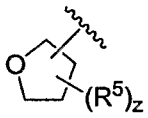
u



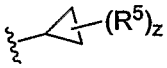
v



w



x



y

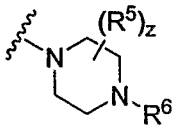
z

aa

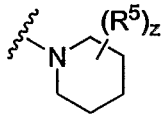
bb.

29. The compound according to claim 15 or 16, wherein R^1 and R^2, taken together with the nitrogen atom to which they are bound, form an optionally substituted 3-8 membered heterocyclyl ring having 1-3 heteroatoms independently selected from nitrogen or oxygen.

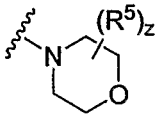
30. The compound according to claim 29, R^1 and R^2 are taken together with the nitrogen atom to which they are bound and form a ring selected from:



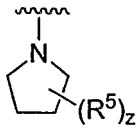
cc



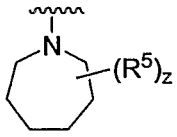
dd



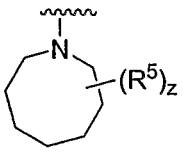
ee



ff



gg



hh.

31. The compound according to claim 30, wherein R^1 and R^2 taken together are optionally substituted pyrrolidin-1-yl (**ff**), piperidin1-yl (**dd**), piperazin-1-yl (**cc**), or morpholin-4-yl (**ee**).

32. The compound according to claim 31, wherein z is 0-2.

33. The compound according to claim 31, wherein z is 0.

34. The compound according to claim 30, wherein R^5 is independently selected from halogen, CN, NO_2, or an optionally substituted group selected from C_{1-6} alkyl, aryl, aryl(C_{1-6})alkyl, -N(R')$_2$, -CH_2N(R')$_2$, OR', -CH_2OR', SR', -CH_2SR', COOR', -NRCOR', -(CH_2)$_2$N(R')$_2$, -(CH_2)$_2$OR', -(CH_2)$_2$SR', -COR', -CON(R')$_2$, or -S(O)$_2$N(R')$_2$.

35. The compound according to claim 34, wherein R^5 is independently selected from Cl, Br, F, CF_3, Me, Et, CN, NO_2, -COOH, NH_2, –N(CH_3)$_2$, -N(Et)$_2$, -N(iPr)$_2$, -O(CH_2)$_2$$OCH_3$, -$CONH_2$, -$COOCH_3$, -OH, -$CH_2$OH, -$NHCOCH_3$, -$SO_2NH_2$, SO_2N(CH_3)$_2$, piperidinyl, piperizinyl, morpholino, or an optionally substituted group selected from C_{1-4} alkoxy, phenyl, phenyloxy, benzyl, or benzyloxy.

36. The compound according to claim 28, wherein R^6 is independently selected from hydrogen, or an optionally substituted group selected from C_{1-6} alkyl, aryl, aryl(C_{1-6})alkyl, -N(R')$_2$, -CH_2N(R')$_2$, -CH_2OR', -CH_2SR', -(CH_2)$_2$N(R')$_2$, -(CH_2)$_2$OR', -(CH_2)$_2$SR', -COR', -CON(R')$_2$, or -S(O)$_2$N(R')$_2$.

37. The compound according to claim 36, wherein R^6 is independently selected from H, Me, CF_3, ethyl, propyl, butyl, pentyl, CO(C_1-C_4alkyl), -$CONH_2$, -COO(C_1-C_4alkyl), -CH_2OH, -SO_2NH_2, SO_2N(CH_3)$_2$, or optionally substituted phenyl.

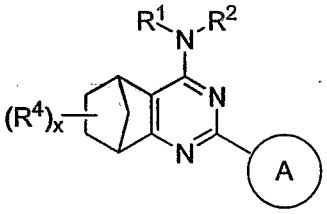
38. The compound according to claim 15 or 16, wherein:
x is 0, 1, or 2; and

each R^4 independently hydrogen, halogen, CN, NO_2, or an optionally substituted group selected from C_{1-6} alkyl, aryl, aryl(C_{1-6})alkyl, -N(R')$_2$, -CH_2N(R')$_2$, OR', -CH_2OR', SR', -CH_2SR', COOR', -NRCOR', -(CH_2)$_2$N(R')$_2$, -(CH_2)$_2$OR', -(CH_2)$_2$SR', -COR', -CON(R')$_2$, or -S(O)$_2$N(R')$_2$.

39. The compound according to claim 38, wherein each R^4 is independently H, Cl, Br, F, CF_3, Me, Et, CN, NO_2, -COOH, NH_2, –N(CH_3)$_2$, -N(Et)$_2$, -N(iPr)$_2$, -O(CH_2)$_2$OCH_3, -$CONH_2$, -$COOCH_3$, -OH, -CH_2OH, -NHCOCH_3, -SO_2NH_2, SO_2N(CH_3)$_2$, piperidinyl, piperizinyl, morpholino, or an optionally substituted group selected from C_{1-4} alkoxy, phenyl, phenyloxy, benzyl, or benzyloxy.

40. The compound according to claim 15 or 16, wherein two occurrences of R^4, taken together form an optionally substituted 3-7-membered saturated or partially unsaturated ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

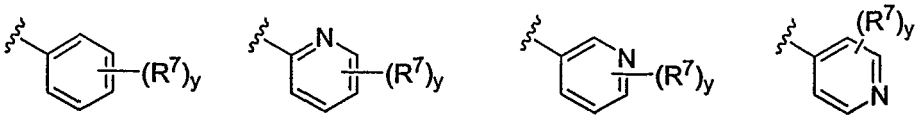
41. The compound according to claim 15 or 16, two occurrences of R^4, taken together form a cycloalkyl group and compounds have the structure as shown in formula **I-B-i**:



I-B-i.

42. The compound according to claim 15 or 16, wherein Ring A is a phenyl, pyridinyl, pyrimidinyl, pyridazinyl, pyrazinyl, pyrrolyl, piperidinyl, indolyl, indazolyl, benzotriazolyl, pyrazolyl, benzopyrazolyl, imidazolyl, benzimidazolyl, thiazolyl, benzthizolyl, oxazolyl, benzoxazolyl, isoxazolyl, benzisoxazolyl, isothiazolyl, benzisothiazolyl, triazolyl, benzotriazolyl, thiadiazolyl, thienyl, benzothienyl, furanoyl, benzofuranoyl, or triazinyl ring, each optionally substituted at one or more carbon atoms with 0-5 occurrences of –R^7, and at one or more substitutable nitrogen atoms with –R^8.

43. The compound according to claim 15 or 16, wherein Ring A is optionally substituted phenyl, 2-pyridyl, 3-pyridyl, or 4-pyridyl:



a **b** **c** **d**

wherein each y is independently 0-5.

44. The compound according to claim 43, wherein y is 0-2.

45. The compound according to claim 44, wherein y is 0 and Ring A is unsubstituted.

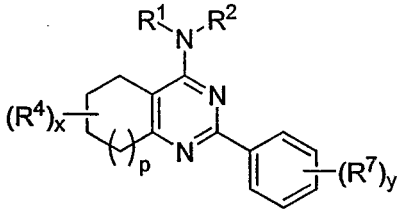
46. The compound according to claim 15 or 16, wherein R^7 groups are independently hydrogen, halogen, CN, NO_2, or an optionally substituted group selected from C_{1-6} alkyl, aryl, aryl(C_{1-6})alkyl, -N(R')$_2$, -CH_2N(R')$_2$, OR', -CH_2OR', SR', -CH_2SR', COOR', -NRCOR', -(CH_2)$_2$N(R')$_2$, -(CH_2)$_2$OR', -(CH_2)$_2$SR', -COR', -CON(R')$_2$, or -S(O)$_2$N(R')$_2$.

47. The compound according to claim 46, wherein R^7 is independently H, Cl, Br, F, CF_3, Me, Et, CN, NO_2, -COOH, NH_2, –N(CH_3)$_2$, -N(Et)$_2$, -N(iPr)$_2$, -O(CH_2)$_2$OCH_3, -$CONH_2$, -$COOCH_3$, -OH, -CH_2OH, -NHCOCH_3, -SO_2NH_2, SO_2N(CH_3)$_2$, piperidinyl, piperizinyl, morpholino, or an optionally substituted group selected from C_{1-4} alkoxy, phenyl, phenyloxy, benzyl, or benzyloxy.

48. The compound according to claim 15 or 16, R^8 is independently hydrogen, or an optionally substituted group selected from C_{1-6} alkyl, aryl, aryl(C_{1-6})alkyl, -N(R')$_2$, -CH_2N(R')$_2$, -CH_2OR', -CH_2SR', -(CH_2)$_2$N(R')$_2$, -(CH_2)$_2$OR', -(CH_2)$_2$SR', -COR', -CON(R')$_2$, or -S(O)$_2$N(R')$_2$.

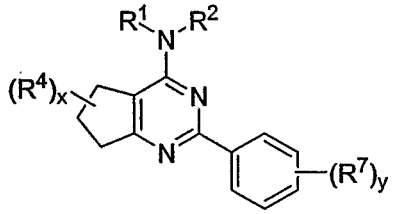
49. The compound according to claim 48, R^8 is independently H, Me, CF_3, ethyl, propyl, butyl, pentyl, CO(C_1-C_4 alkyl), -$CONH_2$, -COO(C_1-C_4 alkyl), -CH_2OH, -SO_2NH_2, SO_2N(CH_3)$_2$, or optionally substituted phenyl.

50. A compound according to claim 15, having formula **II**:

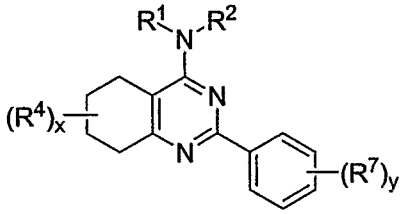


II.

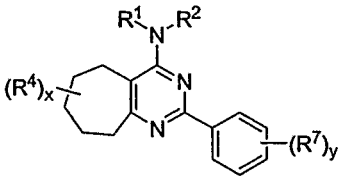
51. The compound according to claim 50, having formula **II-A**, formula **II-B**, or formula **II-C**:



II-A



II-B



II-C.

52. The compound according to claim 51, wherein neither R^1 nor R^2 is hydrogen, and R^1 and R^2 are each independently selected from a 5- or 6-membered aryl ring having 0-5 heteroatoms independently selected from N, O, or S; a 3-7 membered saturated or partially unsaturated ring having 0-3 heteroatoms independently selected from N, O, or S, or an optionally substituted C_{1-4} aliphatic group, wherein one or more methylene units in the C_{1-4} aliphatic group are optionally and independently replaced with NR, O, (CO)O, O(CO), NR(CO), (CO)NR, SO_2(NR), or (NR)SO_2.

53. The compound according to claim 51, wherein both R^1 and R^2 are an optionally substituted C_{1-4} aliphatic group, wherein one or more methylene units in the C_{1-4} aliphatic group are optionally and independently replaced with NR, O, (CO)O, O(CO), NR(CO), (CO)NR, SO_2(NR), or (NR)SO_2.

54. The compound according to claim 53, wherein R^1 and R^2 are an optionally substituted C_{1-4} aliphatic group, wherein one or more methylene units in the C_{1-4} aliphatic group

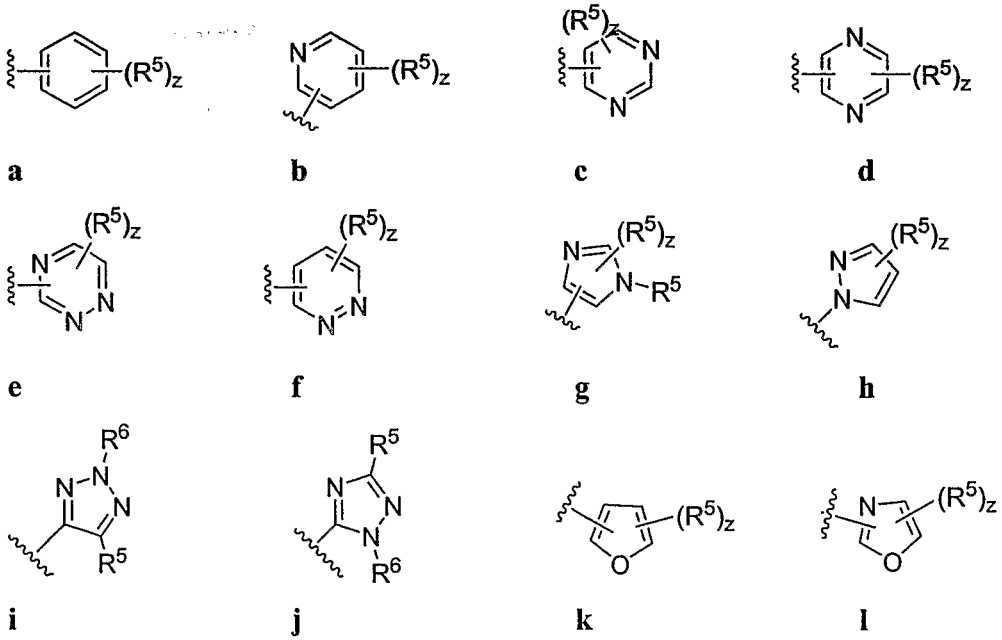
are optionally and independently replaced with NR, O, (CO)O, O(CO), NR(CO), (CO)NR, $SO_2(NR)$, or $(NR)SO_2$.

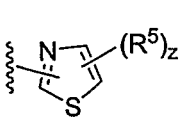
55. The compound according to claim 54, wherein R^1 and R^2 are optionally substituted methyl, ethyl, cyclopropyl, n-propyl, propenyl, cyclobutyl, $(CO)OCH_2CH_3$, $(CH_2)_2OCH_3$, $CH_2(CO)OCH_2CH_3$, $CH_2(CO)OCH_3$, $CH(CH_3)CH_2CH_3$, or t-butyl, or n-butyl.

56. The compound according to claim 51, wherein one of R^1 or R^2 is hydrogen and the other of R^1 or R^2 is a 5-6 membered aryl ring having 0-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or a 3-7-membered saturated or partially unsaturated ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

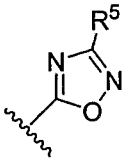
57. The compound according to claim 51, wherein one of R^1 or R^2 is hydrogen, and the other of R^1 or R^2 is an optionally substituted C_{1-4} aliphatic group, wherein one or more methylene units in the C_{1-4} aliphatic group are optionally and independently replaced with NR, O, (CO)O, O(CO), NR(CO), (CO)NR, $SO_2(NR)$, or $(NR)SO_2$.

58. The compound according to claim 51, wherein R^1 or R^2 is selected from:

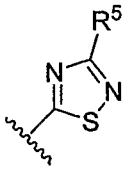




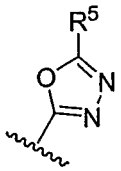
m



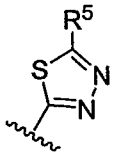
n



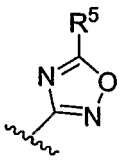
o



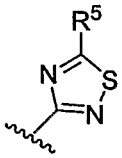
p



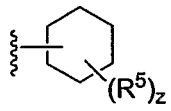
q



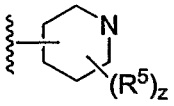
r



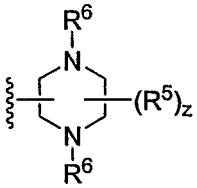
s



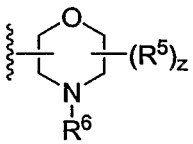
t



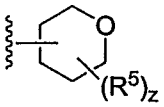
u



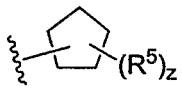
v



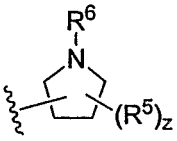
w



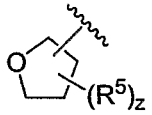
x



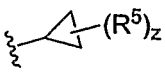
y



z



aa

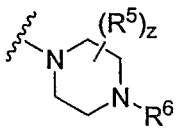


bb

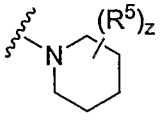
wherein each z is independently 0-4.

59. The compound according to claim 51, wherein R^1 and R^2, taken together with the nitrogen atom to which they are bound, form an optionally substituted 3-8 membered heterocyclyl ring having 1-3 heteroatoms independently selected from nitrogen or oxygen.

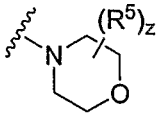
60. The compound according to claim 59, wherein R^1 and R^2 are taken together form a ring selected from:



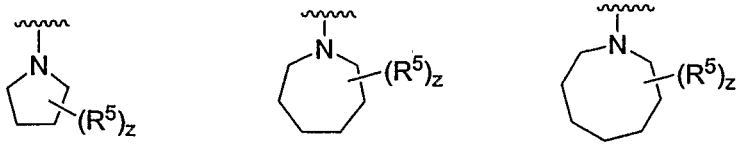
cc



dd



ee



ff **gg** **hh**

wherein each z is independently 0-4.

61. The compound according to claim 60, wherein R^1 and R^2 taken together are optionally substituted pyrrolidin-1-yl (**ff**), piperidin1-yl (**dd**), piperazin-1-yl (**cc**), or morpholin-4-yl (**ee**).

62. The compound according to claim 61, wherein z is 0-2.

63. The compound according to claim 62, wherein z is 0 and the ring is unsubstituted.

64. The compound according to claim 61, wherein R^5 is independently halogen, CN, NO_2, or an optionally substituted group selected from C_{1-6} alkyl, aryl, aryl(C_{1-6})alkyl, -N(R')$_2$, -CH_2N(R')$_2$, OR', -CH_2OR', SR', -CH_2SR', COOR', -NRCOR', -(CH_2)$_2$N(R')$_2$, -(CH_2)$_2$OR', -(CH_2)$_2$SR', -COR', -CON(R')$_2$, or -S(O)$_2$N(R')$_2$.

65. The compound according to claim 64, wherein R^5 is independently Cl, Br, F, CF_3, Me, Et, CN, NO_2, -COOH, NH_2, –N(CH_3)$_2$, -N(Et)$_2$, -N(iPr)$_2$, -O(CH_2)$_2$$OCH_3$, -$CONH_2$, -$COOCH_3$, -OH, -$CH_2$OH, -$NHCOCH_3$, -$SO_2NH_2$, SO_2N(CH_3)$_2$, piperidinyl, piperizinyl, morpholino, or an optionally substituted group selected from C_{1-4} alkoxy, phenyl, phenyloxy, benzyl, or benzyloxy.

66. The compound according to claim 51, wherein R^6 is independently hydrogen, or an optionally substituted group selected from C_{1-6} alkyl, aryl, aryl(C_{1-6}) alkyl, -N(R')$_2$, -CH_2N(R')$_2$, -CH_2OR', -CH_2SR', -(CH_2)$_2$N(R')$_2$, -(CH_2)$_2$OR', -(CH_2)$_2$SR', -COR', -CON(R')$_2$, or -S(O)$_2$N(R')$_2$.

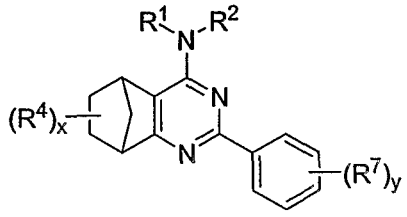
67. The compound according to claim 66, wherein R^6 is independently H, Me, CF_3, ethyl, propyl, butyl, pentyl, $CO(C_1\text{-}C_4$ alkyl), $-CONH_2$, $-COO(C_1\text{-}C_4$ alkyl), $-CH_2OH$, $-SO_2NH_2$, $SO_2N(CH_3)_2$, or optionally substituted phenyl.

68. The compound according to claim 51, wherein x is 0, 1, or 2 and each R^4 is independently hydrogen, halogen, CN, NO_2, or an optionally substituted group selected from $C_{1\text{-}6}$ alkyl, aryl, aryl($C_{1\text{-}6}$)alkyl, $-N(R')_2$, $-CH_2N(R')_2$, OR', $-CH_2OR'$, SR', $-CH_2SR'$, COOR', -NRCOR', $-(CH_2)_2N(R')_2$, $-(CH_2)_2OR'$, $-(CH_2)_2SR'$, -COR', $-CON(R')_2$, or $-S(O)_2N(R')_2$.

69. The compound according to claim 51, wherein each R^3 is independently H, Cl, Br, F, CF_3, Me, Et, CN, NO_2, -COOH, NH_2, $-N(CH_3)_2$, $-N(Et)_2$, $-N(iPr)_2$, $-O(CH_2)_2OCH_3$, $-CONH_2$, $-COOCH_3$, -OH, $-CH_2OH$, $-NHCOCH_3$, $-SO_2NH_2$, $SO_2N(CH_3)_2$, piperidinyl, piperizinyl, morpholino, or an optionally substituted group selected from $C_{1\text{-}4}$ alkoxy, phenyl, phenyloxy, benzyl, or benzyloxy.

70. The compound according to claim 51, wherein two occurrences of R^4, taken together form an optionally substituted 3-7-membered saturated or partially unsaturated ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

71. The compound according to claim 70, wherein two occurrences of R^4, taken together form a cycloalkyl group to form compound of formula **II-B-i**:



II-B-i.

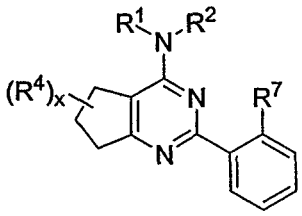
72. The compound according to claim 51, wherein y is 0-2.

73. The compound according to claim 72, wherein y is 0 and Ring A is unsubstituted.

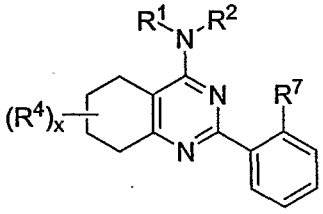
74. The compound according to claim 51, wherein R^7 is independently hydrogen, halogen, CN, NO_2, or an optionally substituted group selected from C_{1-6} alkyl, aryl, aryl(C_{1-6})alkyl, -N(R')$_2$, -CH_2N(R')$_2$, OR', -CH_2OR', SR', -CH_2SR', COOR', -NRCOR', -(CH_2)$_2$N(R')$_2$, -(CH_2)$_2$OR', -(CH_2)$_2$SR', -COR', -CON(R')$_2$, or -S(O)$_2$N(R')$_2$.

75. The compound according to claim 74, wherein R^7 is independently H, Cl, Br, F, CF_3, Me, Et, CN, NO_2, -COOH, NH_2, –N(CH_3)$_2$, -N(Et)$_2$, -N(iPr)$_2$, -O(CH_2)$_2$OCH_3, -$CONH_2$, -$COOCH_3$, -OH, -CH_2OH, -NHCOCH_3, -SO_2NH_2, SO_2N(CH_3)$_2$, piperidinyl, piperizinyl, morpholino, or an optionally substituted group selected from C_{1-4} alkoxy, phenyl, phenyloxy, benzyl, or benzyloxy.

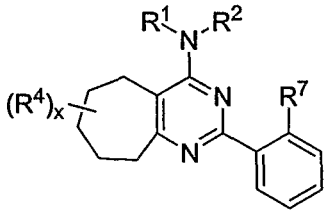
76. The compound according to any one of claims 51 to 75, having formula **III-A**, formula **III-B**, or formula **III-C**:



III-A



III-B



III-C

wherein each R^7 is independently halogen, CN, NO_2, or an optionally substituted group selected from C_{1-4} alkyl, aryl, aralkyl, -N(R')$_2$, -CH_2N(R')$_2$, -OR', -CH_2OR', -SR', -CH_2SR', -COOR', -NRCOR', -CON(R')$_2$, or -S(O)$_2$N(R')$_2$.

77. The compound according to claim 76, having formula **III-B**.

78. The compound according to claim 76, having formula **III-A**.

79. The compound according to claim 78, wherein:

x is 0, R^7 is hydroxy, R^1 and R^2 are both C_{1-4} alkyl, or R^1 and R^2, taken together, form a pyrrolidyl, piperidinyl, or morpholinyl ring.

80. The compound according to claim 79, wherein x is 0, R^7 is hydroxy, R^1 and R^2 are both methyl, or R^1 and R^2, taken together, form a pyrrolidyl or piperidinyl ring.

81. The compound according to claim 80, wherein x is 0, R^7 is hydroxy, R^1 and R^2 are both methyl, or R^1 and R^2, taken together, form a pyrrolidyl ring.

82. The compound according to claim 76, wherein:

a) R^1 and R^2 are each independently selected from a 5- or 6-membered aryl ring having 0-5 heteroatoms independently selected from N, O, or S, a 3-7-membered saturated or partially unsaturated ring having 0-3 heteroatoms independently selected from N, O, or S, or an optionally substituted C_{1-4} aliphatic group, wherein one or more methylene units in the C_{1-4} aliphatic group are optionally and independently replaced with NR, O, (CO)O, O(CO), NR(CO), (CO)NR, SO_2(NR), or (NR)SO_2; and

b) x is 0, 1, or 2, and R^4 is hydrogen, halogen, CN, NO_2, or an optionally substituted group selected from C_{1-6} alkyl, aryl, aryl(C_{1-6})alkyl, -N(R')$_2$, -CH_2N(R')$_2$, OR', -CH_2OR', SR', -CH_2SR', COOR', -NRCOR', -(CH_2)$_2$N(R')$_2$, -(CH_2)$_2$OR', -(CH_2)$_2$SR', -COR', -CON(R')$_2$, or -S(O)$_2$N(R')$_2$.

83. The compound according to claim 76, wherein:

a) R^1 and R^2 are each independently optionally substituted methyl, ethyl, cyclopropyl, n-propyl, propenyl, cyclobutyl, (CO)OCH_2CH_3, (CH_2)$_2$OCH_3, CH_2(CO)OCH_2CH_3, CH_2(CO)OCH_3, CH(CH_3)CH_2CH_3, or t-butyl, or n-butyl; and

b) x is 0, 1, or 2, and each R^4 is independently H, Cl, Br, F, CF_3, Me, Et, CN, NO_2, -COOH, NH_2, –N(CH_3)$_2$, -N(Et)$_2$, -N(iPr)$_2$, -O(CH_2)$_2$OCH_3, -$CONH_2$, -$COOCH_3$, -OH, -CH_2OH, -NHCOCH_3, -SO_2NH_2, SO_2N(CH_3)$_2$, piperidinyl, piperizinyl, morpholino, or an optionally substituted group selected from C_{1-4} alkoxy, phenyl, phenyloxy, benzyl, or benzyloxy.

84. The compound according to claim 76, wherein:

a) R^1 and R^2 are each independently optionally substituted methyl, ethyl, cyclopropyl, n-propyl, propenyl, cyclobutyl, (CO)OCH_2CH_3, (CH_2)$_2$OCH_3, CH_2(CO)OCH_2CH_3, CH_2(CO)OCH_3, CH(CH_3)CH_2CH_3, or t-butyl, or n-butyl;

b) x is 0, 1, or 2, and each R^4 is independently H, Cl, Br, F, CF_3, Me, Et, CN, NO_2, -COOH, NH_2, $-N(CH_3)_2$, $-N(Et)_2$, $-N(iPr)_2$, $-O(CH_2)_2OCH_3$, $-CONH_2$, $-COOCH_3$, -OH, $-CH_2OH$, $-NHCOCH_3$, $-SO_2NH_2$, $SO_2N(CH_3)_2$, piperidinyl, piperizinyl, morpholino, or an optionally substituted group selected from C_{1-4} alkoxy, phenyl, phenyloxy, benzyl, or benzyloxy; and

c) R^7 is Cl, Br, F, CF_3, Me, Et, CN, NO_2, -COOH, NH_2, $-N(CH_3)_2$, $-N(Et)_2$, $-N(iPr)_2$, $-O(CH_2)_2OCH_3$, $-CONH_2$, $-COOCH_3$, -OH, $-CH_2OH$, $-NHCOCH_3$, $-SO_2NH_2$, $SO_2N(CH_3)_2$, piperidinyl, piperizinyl, morpholino, or an optionally substituted group selected from C_{1-4} alkoxy, phenyl, phenyloxy, benzyl, or benzyloxy.

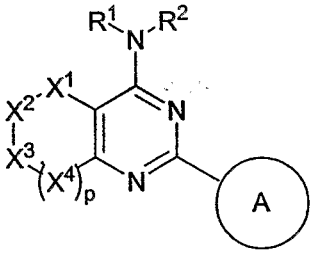
85. The compound according to claim 76 having formula **III-C:**

(i) R^7 is hydroxy;

(ii) R^1 and R^2 are both C_{1-4} alkyl, preferably, methyl, or R^1 and R^2, taken together, form a pyrrolinyl ring or morpholinyl ring; and

(iii) x is 0.

86. The compound according to claim 1, having formula **IV**:



IV

or a pharmaceutically acceptable salt thereof, wherein:

p is 0, 1 or 2;

X^1, X^2, X^3 and X^4 are each independently selected from NR^3, C=O, CHR^4, S, O, S=O, or SO_2, as valency and stability permit, provided that that X^1, X^2, X^3 and X^4 are not each simultaneously CHR^4;

R^1 and R^2 are each independently hydrogen, or an optionally substituted group selected from C_{1-6} aliphatic, a 5-6 membered aryl ring having 0-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or a 3-7-membered saturated or partially unsaturated ring

having 0-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur; or R^1 and R^2, taken together with the nitrogen atom to which they are bound, form an optionally substituted 3-8 membered heterocyclyl or heteroaryl ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur, wherein R^1, R^2, or any ring formed by R^1 and R^2 taken together, are each independently optionally substituted at one or more carbon atoms with 0-4 occurrences of $-R^5$, and at one or more substitutable nitrogen atoms with $-R^6$;

Ring A is a 5-6 membered monocyclic or 8-10 membered bicyclic aryl ring having 0-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or a 3-7-membered saturated or partially unsaturated ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur, optionally substituted at one or more carbon atoms with 0-5 occurrences of $-R^7$, and at one or more substitutable nitrogen atoms with $-R^8$;

each occurrence of R^4, R^5, and R^7 is independently $Q\text{-}R^X$; wherein Q is a bond or is a C_{1-6} alkylidene chain wherein up to two non-adjacent methylene units of Q are optionally and independently replaced by CO, CO_2, COCO, CONR, OCONR, NRNR, NRNRCO, NRCO, $NRCO_2$, NRCONR, SO, SO_2, $NRSO_2$, SO_2NR, $NRSO_2NR$, O, S, or NR;

each occurrence of R^X is independently selected from R', halogen, NO_2, or CN;

each occurrence of R is independently selected from hydrogen or an optionally substituted C_{1-6} aliphatic group;

each occurrence of R' is independently selected from hydrogen or an optionally substituted group selected from C_{1-8} aliphatic, C_{6-10} aryl, a heteroaryl ring having 5-10 ring atoms, or a heterocyclyl ring having 3-10 ring atoms, or wherein R and R' taken together with the atom(s) to which they are bound, or two occurrences of R' taken together with the atom(s) to which they are bound, form a 5-8 membered cycloalkyl, heterocyclyl, aryl, or heteroaryl ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur; and

each occurrence of R^3, R^6 or R^8 is independently R', -COR', $-CO_2(C_{1-6}$ aliphatic), $-CON(R')_2$, or $-SO_2R'$;

provided that:

a) R^1 is not hydrogen when R^2 is optionally substituted indazol-3-yl;

b) R^1 is not hydrogen when R^2 is optionally substituted pyrazol-3-yl;

c) R^1 is not hydrogen when R^2 is 1,2,4-triazol-3-yl;

d) when p is 1, then:

i) when R^1 and R^2, taken together with the nitrogen atom, is N-morpholino, and Ring A is unsubstituted phenyl, then X^1, X^2, X^3 and X^4 are not, respectively:

1) CH_2, $CH(CH_2)Ph$, NR^3, and $CHCH_3$;

2) CH_2, CH_2, CH_2, and S;

3) CH_2, S, CH_2, and S;

4) CH_2, CH_2, S, and CH_2;

5) CH_2, CHMe, S, and CH_2; or

6) CHMe, CH_2, $N(CH_2)Ph$, and CH_2;

ii) R^1 is not hydrogen, and R^2 is not CH_2Ph, $(CH_2)_2O(CH_2)_2OH$, or $-CH_2$(1,3-benzodioxol-5-yl) when Ring A is imidazol-1-yl;

iii) when R^1 and R^2, taken together with the nitrogen atom, is N-piperidinyl then:

1) when X^1, X^2 and X^3 are CH_2, and X^4 is S, then Ring A is not unsubstituted phenyl;and

2) when X^1, X^2 and X^4 are CH_2; and X^3 is S, then Ring A is not unsubstituted phenyl;

iv) when R^1 and R^2, taken together with the nitrogen atom, is N-piperizinyl, X^1, X^2 and X^3 are CH_2; and X^4 is S, then Ring A is not 3-NO_2Ph, 4-pyridinyl, or unsubstituted phenyl;

v) when one of X^1, X^2, X^3 or X^4 is NR^3 and the others of X^1, X^2, X^3 or X^4 are each CH_2, and R^1 and R^2 are each Me, H, CH_2Ph, or $(CH_2)_2NMe_2$, then Ring A is not pyrid-2-yl substituted at the 6-position;

vi) when X^1, X^2, and X^3 are each CH_2, X^4 is S, R^1 is H, and R^2 is $-CH_2$-C≡CH, then Ring A is not unsubstituted phenyl;

vii) when X^1 is NMe; X^2, X^3 and X^4 are each CH^2, R^1 is H, and R^2 is unsubstituted phenyl, then Ring A is not unsubstituted phenyl; and

viii) when X^1, X^2 and X^4 are each CH_2; X^3 is S, R^1 and R^2 are each Me, then Ring A is not unsubstituted phenyl; and

e) when p is 0, then:

i) when X^1 is CH_2, X^2 is NR^3, X^3 is C=O; or X^1 is C=O, X^2 is CHR^4, and X^3 is NR^3; or X^2 is NR^3, X^2 is C=O, and X^3 is CHR^4; or X^1 is CH_2, X^2 is O, and X^3 is C=O, then when R^1 is hydrogen and R^2 is unsubstituted phenyl or $-CH_2CH_2Cl$, or

when R^1 and R^2, taken together form optionally substituted piperazinyl, morpholino, piperidinyl, or pyrrolidinyl, then Ring A is not optionally substituted piperidinyl, piperazinyl, morpholino, or pyrrolidinyl;

ii) when X^1 is CHR^4, X^2 is SO_2, and X^3 is CHR^4, and R^1 and R^2, taken together are piperazinyl, then Ring A is not unsubstituted phenyl;

iii) when X^1 and X^2 are CHR^4, X^3 is O, R^1 is hydrogen, and R^2 is $-C(=O)CH_3$, then Ring A is not substituted furyl;

iv) when X^1 is S, X^2 is CHR^4, X^3 is CHR^4; or X^1 is CHR^4, X^2 is S, and X^3 is CHR^4; or X^1 and X^2 are CHR^4 and X^3 is S, then Ring A is not optionally substituted N-linked morpholino, pyrrolidinyl, piperazinyl, piperidinyl, or is not unsubstituted phenyl or cyclopropyl;

v) when X^1 is CHR^4, X^2 is NR^3, X^3 is CHR^4, and R^1 and R^2 are both methyl, then Ring A is not 6-methyl-2-pyridyl;

vi) when X^1 is NR^3, X^2 is C=O, X^2 is NR^3, and R^1 and R^2 are both methyl, then Ring A is not unsubstituted phenyl; and

vii) when X^1 and X^2 are CHR^4, X^3 is NR^3, R^1 is hydrogen, and R^2 is unsubstituted phenyl, then Ring A is not unsubstituted phenyl; and

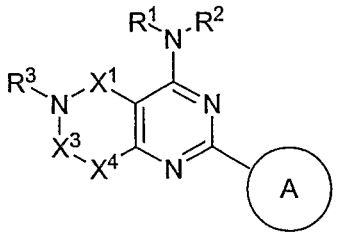
further provided that:

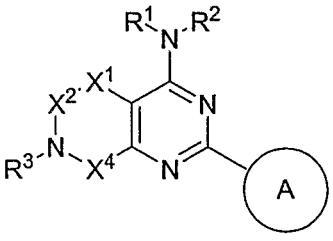
when p is 1, X^1, X^2, X^3 and X^4 are not each simultaneously CHR^4, or when p is 0, X^1, X^2, and X^3 are not each simultaneously CHR^4.

87. The compound according to claim 86, wherein p is 0 or 1.

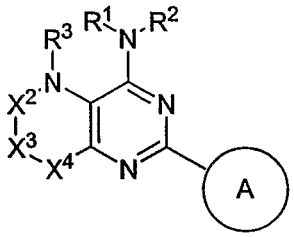
88. The compound according to claim 86, wherein one or two of X^1, X^2, X^3, or X^4 is NR^3, S, O, S=O, or SO_2, and the remainder each is CHR^4.

89. The compound according to claim 86, selected from:

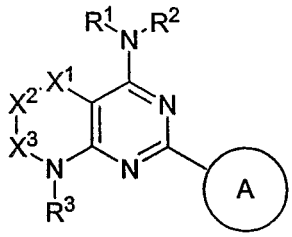




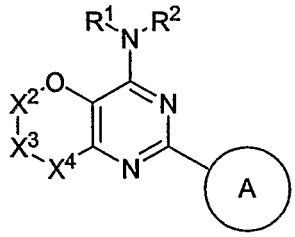
IV-A



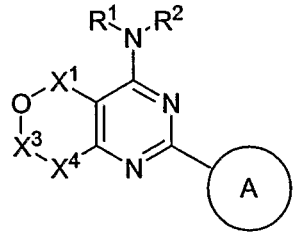
IV-B



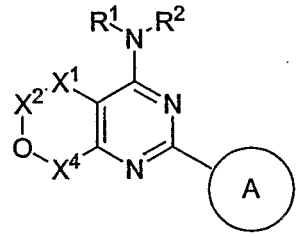
IV-C



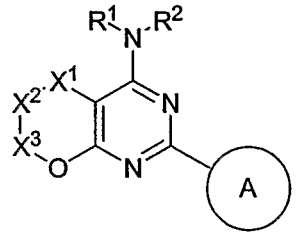
IV-D



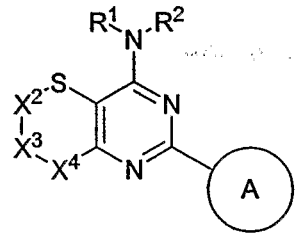
IV-E



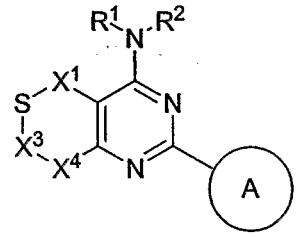
IV-F



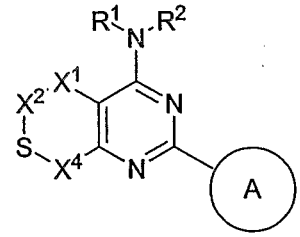
IV-G



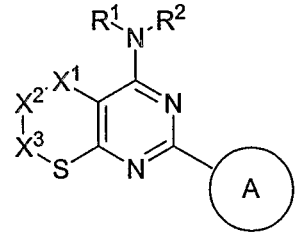
IV-H



IV-I

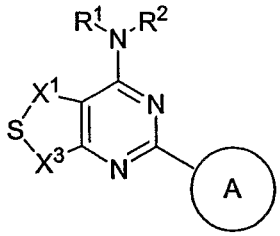


IV-J

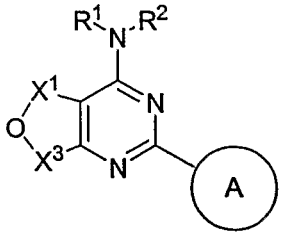


IV-K

IV-L



IV-M



IV-N.

90. The compound according to claim 89, having formula IV-I, formula IV-J, formula IV-K, formula IV-L, or formula IV-M, wherein the sulfur ring atom is replaced with sulfoxy or sulfonyl.

91. The compound according to claim 86, wherein neither R^1 nor R^2 is hydrogen, and R^1 and R^2 are each independently selected from a 5- or 6-membered aryl ring having 0-5 heteroatoms independently selected from N, O, or S, a 3-7-membered saturated or partially unsaturated ring having 0-3 heteroatoms independently selected from N, O, or S, or an optionally substituted C_{1-4} aliphatic group, wherein one or more methylene units in the C_{1-4} aliphatic group are optionally and independently replaced with NR, O, (CO)O, O(CO), NR(CO), (CO)NR, SO_2(NR), or (NR)SO_2.

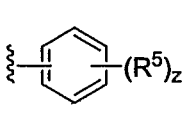
92. The compound according to claim 86, wherein both R^1 and R^2 are an optionally substituted C_{1-4} aliphatic group, wherein one or more methylene units in the C_{1-4} aliphatic group are optionally and independently replaced with NR, O, (CO)O, O(CO), NR(CO), (CO)NR, SO_2(NR), or (NR)SO_2.

93. The compound according to claim 92, wherein R^1 and R^2 are an optionally substituted C_{1-4} aliphatic group, wherein one or more methylene units in the C_{1-4} aliphatic group are optionally and independently replaced with NR, O, (CO)O, O(CO), NR(CO), (CO)NR, SO_2(NR), or (NR)SO_2, preferred R^1 and R^2 groups are optionally substituted methyl, ethyl, cyclopropyl, n-propyl, propenyl, cyclobutyl, (CO)OCH_2CH_3, $(CH_2)_2OCH_3$, CH_2(CO)OCH_2CH_3, CH_2(CO)OCH_3, $CH(CH_3)CH_2CH_3$, or t-butyl, or n-butyl.

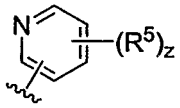
94. The compound according to claim 86, wherein one of R^1 or R^2 is hydrogen and the other of R^1 or R^2 is a 5-6 membered aryl ring having 0-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or a 3-7-membered saturated or partially unsaturated ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

95. The compound according to claim 94, wherein one of R^1 or R^2 is hydrogen, and the other of R^1 or R^2 is an optionally substituted C_{1-4} aliphatic group, wherein one or more methylene units in the C_{1-4} aliphatic group are optionally and independently replaced with NR, O, (CO)O, O(CO), NR(CO), (CO)NR, SO_2(NR), or (NR)SO_2.

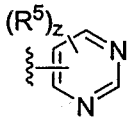
96. The compound according to claim 86 or 94, wherein R^1 or R^2 is selected from:



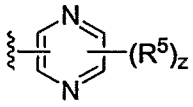
a



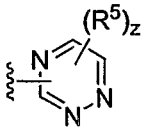
b



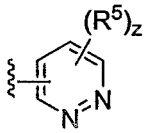
c



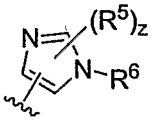
d



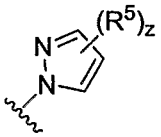
e



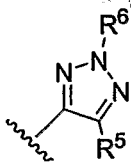
f



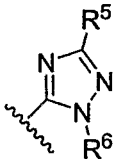
g



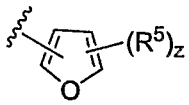
h



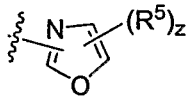
i



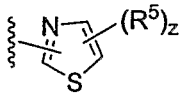
j



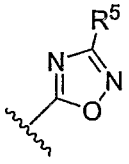
k



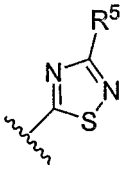
l



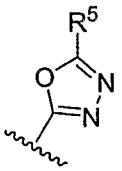
m



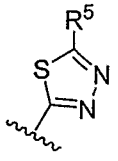
n

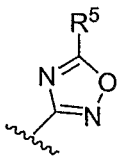


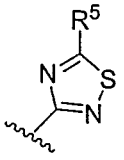
o

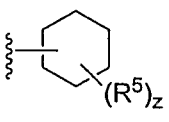


p

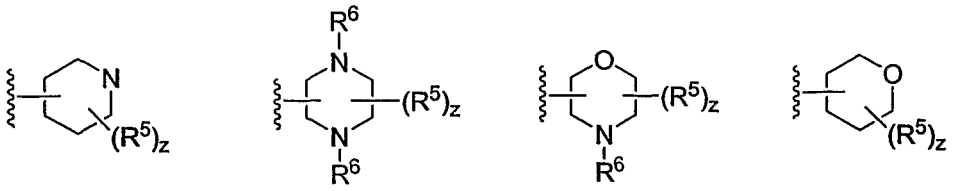




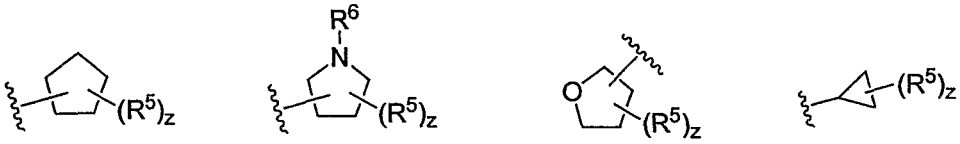




q r s t



u v w x

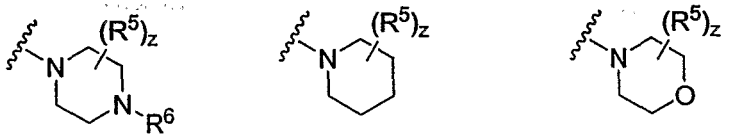


y z aa bb

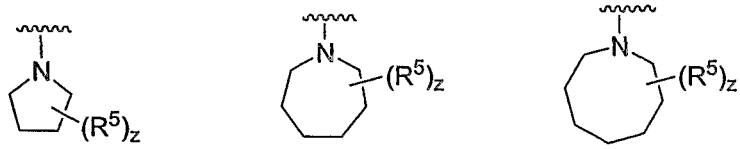
wherein each z is independently 0-4.

97. The compound according to claim 86, wherein R^1 and R^2, taken together with the nitrogen atom to which they are bound, form an optionally substituted 3-8 membered heterocyclyl ring having 1-3 heteroatoms independently selected from nitrogen or oxygen.

98. The compound according to claim 97, wherein R^1 and R^2 are taken together with the nitrogen atom to which they are bound and form a 3-8 membered heterocyclyl group selected from:



cc dd ee



ff gg hh

wherein each z is independently 0-4.

99. The compound according to claim 98, wherein R^1 and R^2 taken together are optionally substituted pyrrolidin-1-yl (**ff**), piperidin1-yl (**dd**), piperazin-1-yl (**cc**), or morpholin-4-yl (**ee**).

100. The compound according to claim 99, wherein z is 0-2.

101. The compound according to claim 100, wherein z is 0 and the ring is unsubstituted.

102. The compound according to claim 86, wherein R^5 is independently halogen, CN, NO_2, or an optionally substituted group selected from C_{1-6} alkyl, aryl, aryl(C_{1-6})alkyl, -N(R')$_2$, -CH_2N(R')$_2$, OR', -CH_2OR', SR', -CH_2SR', COOR', -NRCOR', -(CH_2)$_2$N(R')$_2$, -(CH_2)$_2$OR', -(CH_2)$_2$SR', -COR', -CON(R')$_2$, SO_2R', or -SO_2N(R')$_2$.

103. The compound according to claim 102, wherein R^5 is independently Cl, Br, F, CF_3, Me, Et, CN, NO_2, -COOH, NH_2, -N(CH_3)$_2$, -N(Et)$_2$, -N(iPr)$_2$, -O(CH_2)$_2$OCH_3, -CO(C_1-C_4 alkyl), -$CONH_2$, -$COOCH_3$, -OH, -CH_2OH, -NHCOCH_3, -SO_2(C_1-C_4 alkyl), -SO_2NH_2, -SO_2N(CH_3)$_2$, piperidinyl, piperizinyl, morpholino, or an optionally substituted group selected from C_{1-4} alkoxy, phenyl, phenyloxy, benzyl, or benzyloxy.

104. The compound according to claim 86, wherein R^6 is independently hydrogen, or an optionally substituted group selected from C_{1-6} alkyl, aryl, aryl(C_{1-6})alkyl, -N(R')$_2$, -CH_2N(R')$_2$, -CH_2OR', -CH_2SR', -(CH_2)$_2$N(R')$_2$, -(CH_2)$_2$OR', -(CH_2)$_2$SR', -COR', -CON(R')$_2$, SO_2R', or -S(O)$_2$N(R')$_2$.

105. The compound according to claim 104, wherein R^6 is independently H, Me, CF_3, ethyl, propyl, butyl, pentyl, CO(C_1-C_4 alkyl), -$CONH_2$, -COO(C_1-C_4 alkyl), -CH_2OH, -SO_2(C_1-C_4alkyl), -SO_2NH_2, SO_2N(CH_3)$_2$, or optionally substituted phenyl or benzyl.

106. The compound according to claim 86, wherein R^4 is independently hydrogen, halogen, CN, NO_2, or an optionally substituted group selected from C_{1-6} alkyl, aryl, aryl(C_1-

$_6$)alkyl, -N(R')$_2$, -CH_2N(R')$_2$, OR', -CH_2OR', SR', -CH_2SR', COOR', -NRCOR', -$(CH_2)_2$N(R')$_2$, -$(CH_2)_2$OR', -$(CH_2)_2$SR', -COR', -CON(R')$_2$, SO_2R', or -SO_2N(R')$_2$.

107. The compound according to claim 86, wherein R^4 is independently H, Cl, Br, F, CF_3, Me, Et, CN, NO_2, -COOH, NH_2, –N$(CH_3)_2$, -N$(Et)_2$, -N$(iPr)_2$, -O$(CH_2)_2OCH_3$, -CO(C_1-C_4alkyl), -$CONH_2$, -$COOCH_3$, -OH, -CH_2OH, -$NHCOCH_3$, -SO_2(C_1-C_4alkyl), -SO_2NH_2, -$SO_2N(CH_3)_2$, piperidinyl, piperizinyl, mórpholino, or an optionally substituted group selected from C_{1-4} alkoxy, phenyl, phenyloxy, benzyl, or benzyloxy.

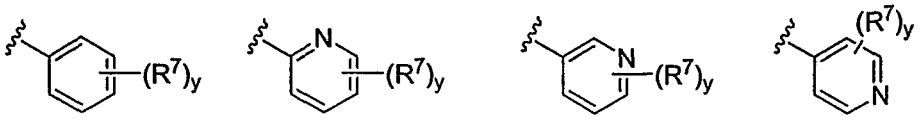
108. The compound according to claim 86, wherein R^3 is independently hydrogen, or an optionally substituted group selected from C_{1-6} alkyl, aryl, aryl(C_{1-6})alkyl, -N(R')$_2$, -CH_2N(R')$_2$, -CH_2OR', -CH_2SR', -$(CH_2)_2$N(R')$_2$, -$(CH_2)_2$OR', -$(CH_2)_2$SR', -COR', -CON(R')$_2$, SO_2R', or -$S(O)_2$N(R')$_2$.

109. The compound according to claim 108, wherein R^3 is independently H, Me, CF_3, ethyl, propyl, butyl, pentyl, CO(C_1-C_4alkyl), -$CONH_2$, -COO(C_1-C_4alkyl), -CH_2OH, -SO_2(C_1-C_4alkyl), -SO_2NH_2, $SO_2N(CH_3)_2$, or optionally substituted phenyl or benzyl.

110. The compound according to claim 86, wherein Ring A is a 5-6 membered aryl ring having 0-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or a 3-7-membered saturated or partially unsaturated ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur, optionally substituted at one or more carbon atoms with 0-5 occurrences of –R^7, and at one or more substitutable nitrogen atoms with –R^8.

111. The compound according to claim 110, wherein Ring A is a phenyl, pyridinyl, pyrimidinyl, pyridazinyl, pyrazinyl, pyrrolyl, piperidinyl, indolyl, indazolyl, benzotriazolyl, pyrazolyl, benzopyrazolyl, imidazolyl, benzimidazolyl, thiazolyl, benzthizolyl, oxazolyl, benzoxazolyl, isoxazolyl, benzisoxazolyl, isothiazolyl, benzisothiazolyl, triazolyl, benzotriazolyl, thiadiazolyl, thienyl, benzothienyl, furanoyl, benzofuranoyl, or triazinyl ring, each optionally substituted at one or more carbon atoms with 0-5 occurrences of –R^7, and at one or more substitutable nitrogen atoms with –R^8.

112. The compound according to claim 111, wherein Ring A is optionally substituted phenyl, 2-pyridyl, 3-pyridyl, or 4-pyridyl:



a **b** **c** **d**

wherein each y is independently 0-5.

113. The compound according to claim 86, wherein R^7 is independently hydrogen, halogen, CN, NO_2, or an optionally substituted group selected from C_{1-6} alkyl, aryl, aryl(C_{1-6})alkyl, -N(R')$_2$, -CH_2N(R')$_2$, OR', -CH_2OR', SR', -CH_2SR', COOR', -NRCOR', -(CH_2)$_2$N(R')$_2$, -(CH_2)$_2$OR', -(CH_2)$_2$SR', -COR', -CON(R')$_2$, SO_2R', or -SO_2N(R')$_2$.

114. The compound according to claim 113, wherein R^7 is independently H, Cl, Br, F, CF_3, Me, Et, CN, NO_2, -COOH, NH_2, –N(CH_3)$_2$, -N(Et)$_2$, -N(iPr)$_2$, -O(CH_2)$_2$OCH_3, -CO(C_1-C_4alkyl), -$CONH_2$, -$COOCH_3$, -OH, -CH_2OH, -NHCOCH_3, -SO_2(C_1-C_4alkyl), -SO_2NH_2, -SO_2N(CH_3)$_2$, piperidinyl, piperizinyl, morpholino, or an optionally substituted group selected from C_{1-4} alkoxy, phenyl, phenyloxy, benzyl, or benzyloxy.

115. The compound according to claim 86, wherein R^8 is independently hydrogen, or an optionally substituted group selected from C_{1-6} alkyl, aryl, aryl(C_{1-6})alkyl, -N(R')$_2$, -CH_2N(R')$_2$, -CH_2OR', -CH_2SR', -(CH_2)$_2$N(R')$_2$, -(CH_2)$_2$OR', -(CH_2)$_2$SR', -COR', -CON(R')$_2$, SO_2R', or -$S(O)_2$N(R')$_2$.

116. The compound according to claim 115, wherein R^8 is independently H, Me, CF_3, ethyl, propyl, butyl, pentyl, CO(C_1-C_4alkyl), -$CONH_2$, -COO(C_1-C_4alkyl), -CH_2OH, -SO_2(C_1-C_4alkyl), -SO_2NH_2, SO_2N(CH_3)$_2$, or optionally substituted phenyl or benzyl.

117. The compound of formula IV-A according to claim 89, wherein:

R^1 hydrogen or methyl, and R^2 is methyl, 5-methyl-pyrazol-3-yl, 5-fluoro-benzopyrazol-3-yl, or benzopyrazol-3-yl, X^1, X^3, and X^4 each is CH_2, R^3 is hydrogen, acyl, 1-oxo-2-methoxy-

ethyl, 1-oxo-propyl, methylsulfonyl, ethylsulfonyl, benzyl, and ring A is phenyl optionally substituted with halo, trifluoromethyl, hydroxy, C_{1-4} alkyl, or C_{1-4} alkoxy, preferably, methoxy, or ring A is 2,3-Dihydro-benzo[1,4]dioxin-3-yl.

118. The compound of formula **IV-A** according to claim 89, wherein:

R^1 hydrogen or methyl, and R^2 is methyl, 5-methyl-pyrazol-3-yl, 5-fluoro-benzopyrazol-3-yl, or benzopyrazol-3-yl, X^1, X^3, and X^4 each is CH_2, R^3 is hydrogen or benzyl, and ring A is phenyl optionally substituted with halo, trifluoromethyl, hydroxy, C_{1-4} alkyl, or C_{1-4} alkoxy, preferably, methoxy, or ring A is 2,3-Dihydro-benzo[1,4]dioxin-3-yl.

119. The compound of formula **IV-A** according to claim 89, wherein:

R^1 hydrogen or methyl, and R^2 is methyl, 5-methyl-pyrazol-3-yl, 5-fluoro-benzopyrazol-3-yl, or benzopyrazol-3-yl, X^1, X^3, and X^4 each is CH_2, R^3 is hydrogen or benzyl, and ring A is phenyl optionally substituted with halo, hydroxy or C_{1-4} alkoxy, preferably, methoxy.

120. The compound of formula **IV-B** according to claim 89, wherein:

R^1 is hydrogen or methyl, R^2 is methyl or 5-fluorobenzimidazol-3-yl, 5-methylimidazol-3-yl, X^1, X^3, and X^4 each is CH_2, R^3 is hydrogen, C_{1-4} alkyl, benzyl optionally substituted with carboxy-C_{1-4} alkyl, C_{1-4} alkylsulfonyl, acyl, methylcarboxyethyl, C_{1-4} alkylcarbonyl, methoxymethylcarbonyl, or benzoyl, and ring A is phenyl substituted with 2-hydroxy, 2-trifluoromethyl, 4-methyl, 4-carboxylic acid, 4-trifluoromethyloxy, or 2-C_{1-4} alkoxy, preferably, methoxy.

121. The compound of formula **IV-A** according to claim 89, wherein:

R^1 is hydrogen or methyl, R^2 is methyl or 5-fluorobenzimidazol-3-yl, X^1, X^3, and X^4 each is CH_2, R^3 is C_{1-4} alkyl, benzyl optionally substituted with carboxy-C_{1-4} alkyl, C_{1-4} alkylsulfonyl, acyl, methylcarboxyethyl, C_{1-4} alkylcarbonyl, or benzoyl, and ring A is phenyl substituted with 2-hydroxy, 2-trifluoromethyl, or 2-C_{1-4} alkoxy, preferably, methoxy.

122. The compound of formula **IV-B** according to claim 89, wherein:

R^1 and R^2, each is methyl, X^1, X^3, and X^4 each is CH_2, R^3 is C_{1-4} alkyl, benzyl optionally substituted with carboxy-C_{1-4} alkyl, C_{1-4} alkylsulfonyl, or benzoyl, and ring A is phenyl substituted with 2-hydroxy or 2-C_{1-4} alkoxy, preferably, methoxy.

123. The compound of formula **IV-B** according to claim 89, wherein:

R^1 and R^2, each is methyl, X^1, X^3, and X^4 each is CH_2, R^3 is C_{1-4} alkyl, or benzyl optionally substituted with carboxy-C_{1-4} alkyl, and ring A is phenyl substituted with 2-hydroxy or 2-C_{1-4} alkoxy, preferably, methoxy.

124. The compound of formula **IV-B** according to claim 89, wherein:

R^1 and R^2, each is methyl, X^1, X^3, and X^4 each is CH_2, R^3 is C_{1-4} alkyl, benzyl optionally substituted with carboxy-C_{1-4} alkyl, C_{1-4} alkoxy, and ring A is 2-hydroxy phenyl or 2-C_{1-4} alkoxyphenyl.

125. The compound of formula **IV-B** according to claim 89, wherein:

R^1 and R^2, each is methyl, X^1, X^3, and X^4 each is CH_2, R^3 is benzyl optionally substituted with carboxy-C_{1-4} alkyl, C_{1-4} alkoxy, and ring A is 2-hydroxy phenyl.

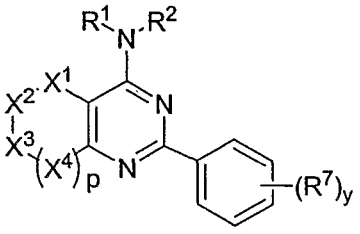
126. The compound of formula **IV-M** according to claim 89, wherein:

R^1 is hydrogen or methyl, and R^2 is methyl, benzimidazol-3-yl, 5-methyl-imidazol-3-yl, ring A is 2-hydroxyphenyl, 2-fluorophenyl, 2-trifluoromethylphenyl or phenyl.

127. The compound of formula **IV-M** according to claim 89, wherein:

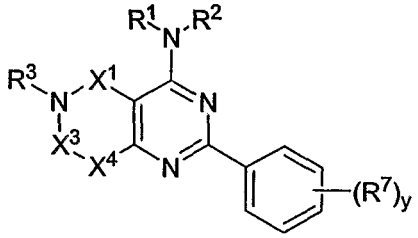
R^1 is hydrogen or methyl, and R^2 is methyl, benzimidazol-3-yl, 5-methyl-imidazol-3-yl, ring A is 2-trifluoromethylphenyl or phenyl.

128. The compound according to claim 87, wherein said compound has formula **V**:

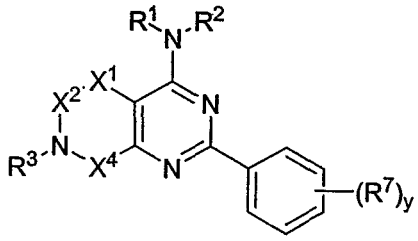


V.

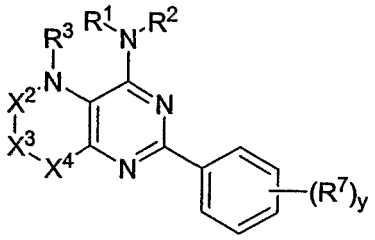
129. The compound according to claim 128, wherein said compound has one of the following structures:



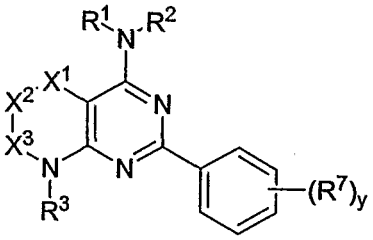
V-A



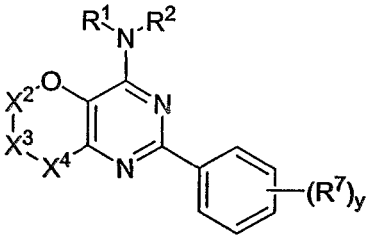
V-B



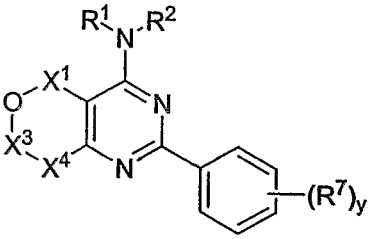
V-C



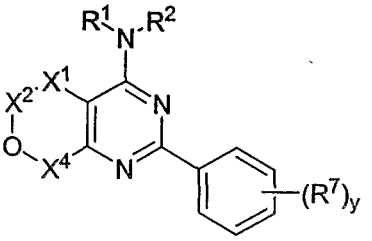
V-D



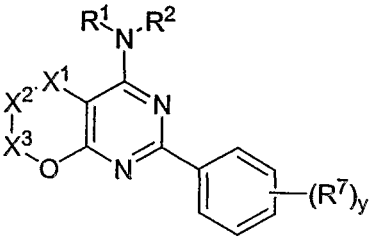
V-E



V-F

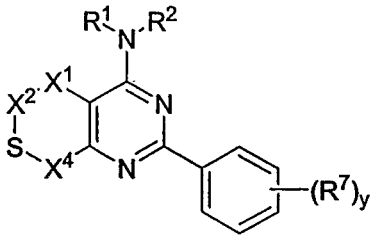


V-G

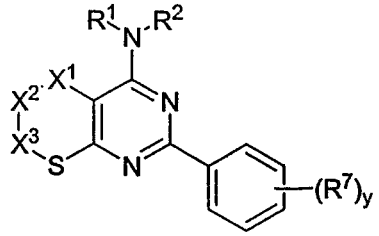


V-H

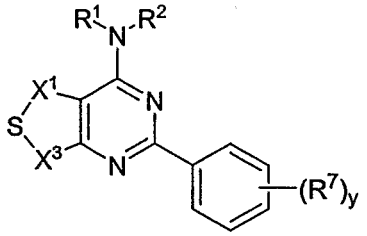
V-I



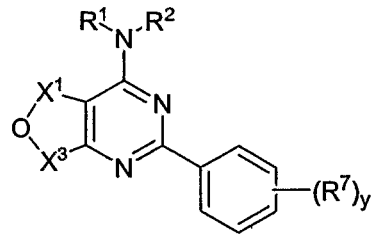
V-J



V-K



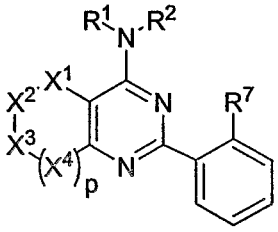
V-L



V-M

V-N.

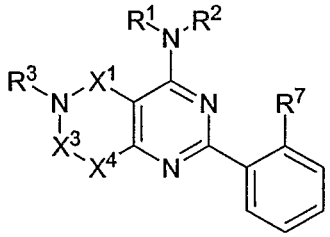
130. The compound according to claim 128, wherein said compound has formula **VI**:

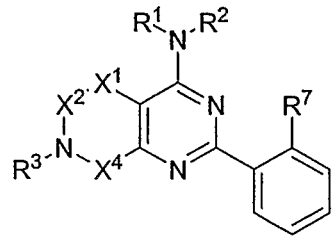


VI

wherein R^7 is halogen, CN, NO_2, or an optionally substituted group selected from C_{1-4} alkyl, aryl, aralkyl, $-N(R')_2$, $-CH_2N(R')_2$, $-OR'$, $-CH_2OR'$, $-SR'$, $-CH_2SR'$, $-COOR'$, $-NRCOR'$, $-CON(R')_2$, or $-S(O)_2N(R')_2$.

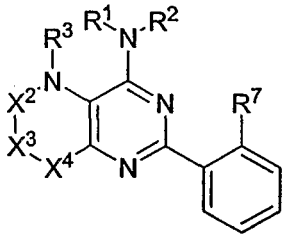
131. The compound according to claim 130, wherein said compound has a structure selected from formulae **VI-A** through **VI-N**:



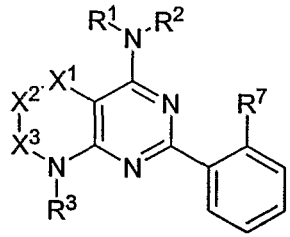


VI-A

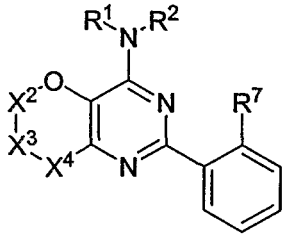
VI-B



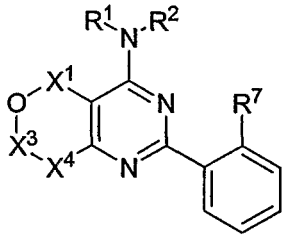
VI-C



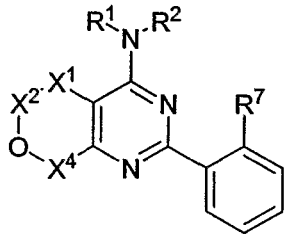
VI-D



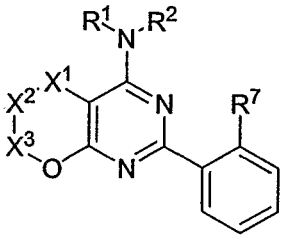
VI-E



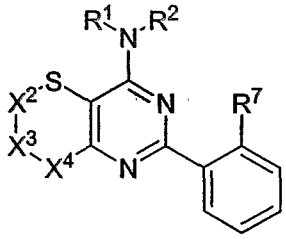
VI-F



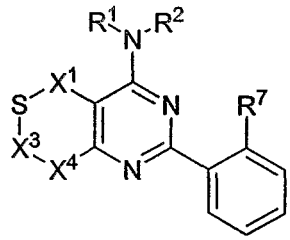
VI-G



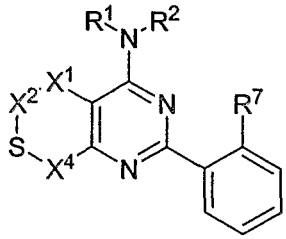
VI-H



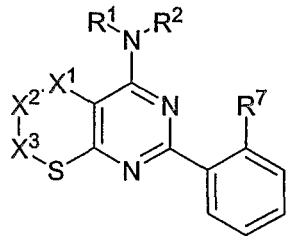
VI-I



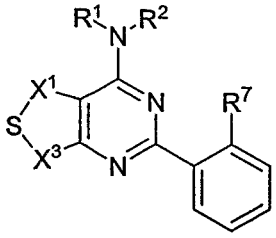
VI-J



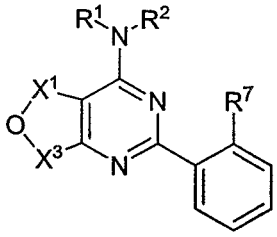
VI-K



VI-L



VI-M



VI-N.

132. The compound to claim 131, wherein:

a. R^1 and R^2 are each independently selected from a 5- or 6-membered aryl ring having 0-5 heteroatoms independently selected from N, O, or S; a 3-7-membered saturated or partially unsaturated ring having 0-3 heteroatoms independently selected from N, O, or S; or an optionally substituted C_{1-4} aliphatic group, wherein one or more methylene units in the C_{1-4} aliphatic group are optionally and independently replaced with NR, O, (CO)O, O(CO), NR(CO), (CO)NR, $SO_2(NR)$, or $(NR)SO_2$;

b. each occurrence of R^3 is independently hydrogen, or an optionally substituted group selected from C_{1-6} alkyl, aryl, aryl(C_{1-6})alkyl, -N(R')$_2$, -CH_2N(R')$_2$, -CH_2OR', -CH_2SR', -$(CH_2)_2$N(R')$_2$, -$(CH_2)_2$OR', -$(CH_2)_2$SR', -COR', -CON(R')$_2$, SO_2R', or -$S(O)_2$N(R')$_2$; and

c. each occurrence of R^4 is independently hydrogen, halogen, CN, NO_2, or an optionally substituted group selected from C_{1-6} alkyl, aryl, aryl(C_{1-6})alkyl, -N(R')$_2$, -CH_2N(R')$_2$, OR', -CH_2OR', SR', -CH_2SR', COOR', -NRCOR', -$(CH_2)_2$N(R')$_2$, -$(CH_2)_2$OR', -$(CH_2)_2$SR', -COR', -CON(R')$_2$, SO_2R', or -SO_2N(R')$_2$.

133. The compound according to claim 131, wherein:

a. R^1 and R^2 are each independently optionally substituted methyl, ethyl, cyclopropyl, n-propyl, propenyl, cyclobutyl, $(CO)OCH_2CH_3$, $(CH_2)_2OCH_3$, $CH_2(CO)OCH_2CH_3$, $CH_2(CO)OCH_3$, $CH(CH_3)CH_2CH_3$, or t-butyl, or n-butyl;

b. each occurrence of R^3 is independently H, Me, CF_3, ethyl, propyl, butyl, pentyl, CO(C_1-C_4alkyl), -$CONH_2$, -COO(C_1-C_4alkyl), -CH_2OH, -SO_2(C_1-C_4alkyl), -SO_2NH_2, $SO_2N(CH_3)_2$, or optionally substituted phenyl or benzyl; and

c. each occurrence of R^4 is independently H, Cl, Br, F, CF_3, Me, Et, CN, NO_2, -COOH, NH_2, $-N(CH_3)_2$, $-N(Et)_2$, $-N(iPr)_2$, $-O(CH_2)_2OCH_3$, $-CO(C_1\text{-}C_4alkyl)$, $-CONH_2$, $-COOCH_3$, -OH, $-CH_2OH$, $-NHCOCH_3$, $-SO_2(C_1\text{-}C_4alkyl)$, $-SO_2NH_2$, $-SO_2N(CH_3)_2$, piperidinyl, piperizinyl, morpholino, or an optionally substituted group selected from $C_{1\text{-}4}$ alkoxy, phenyl, phenyloxy, benzyl, or benzyloxy.

134. The compound according to claim 131, wherein:

a. R^1 and R^2 are each independently optionally substituted methyl, ethyl, cyclopropyl, n-propyl, propenyl, cyclobutyl, $(CO)OCH_2CH_3$, $(CH_2)_2OCH_3$, $CH_2(CO)OCH_2CH_3$, $CH_2(CO)OCH_3$, $CH(CH_3)CH_2CH_3$, or t-butyl, or n-butyl;

b. each occurrence of R^3 is independently H, Me, CF_3, ethyl, propyl, butyl, pentyl, $CO(C_1\text{-}C_4alkyl)$, $-CONH_2$, $-COO(C_1\text{-}C_4alkyl)$, $-CH_2OH$, $-SO_2(C_1\text{-}C_4alkyl)$, $-SO_2NH_2$, $SO_2N(CH_3)_2$, or optionally substituted phenyl or benzyl;

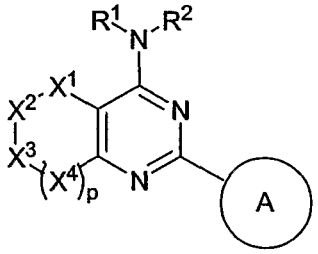
c. each occurrence of R^4 is independently H, Cl, Br, F, CF_3, Me, Et, CN, NO_2, -COOH, NH_2, $-N(CH_3)_2$, $-N(Et)_2$, $-N(iPr)_2$, $-O(CH_2)_2OCH_3$, $-CO(C_1\text{-}C_4alkyl)$, $-CONH_2$, $-COOCH_3$, -OH, $-CH_2OH$, $-NHCOCH_3$, $-SO_2(C_1\text{-}C_4alkyl)$, $-SO_2NH_2$, $-SO_2N(CH_3)_2$, piperidinyl, piperizinyl, morpholino, or an optionally substituted group selected from $C_{1\text{-}4}$ alkoxy, phenyl, phenyloxy, benzyl, or benzyloxy; and

d. R^7 is Cl, Br, F, CF_3, Me, Et, CN, NO_2, -COOH, NH_2, $-N(CH_3)_2$, $-N(Et)_2$, $-N(iPr)_2$, $-O(CH_2)_2OCH_3$, $-CO(C_1\text{-}C_4alkyl)$, $-CONH_2$, $-COOCH_3$, -OH, $-CH_2OH$, $-NHCOCH_3$, $-SO_2(C_1\text{-}C_4alkyl)$, $-SO_2NH_2$, $-SO_2N(CH_3)_2$, piperidinyl, piperizinyl, morpholino, or an optionally substituted group selected from $C_{1\text{-}4}$ alkoxy, phenyl, phenyloxy, benzyl, or benzyloxy.

135. A pharmaceutical composition comprising a compound according to claim 1 or 15, and a pharmaceutically acceptable carrier or adjuvant.

136. 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, or cancer pain, comprising the step of administering to said patient an effective amount of a compound according of formula **I**:



I

or a pharmaceutically acceptable salt thereof, wherein:

p is 0, 1 or 2;

X^1, X^2, X^3 and X^4 are each independently selected from NR^3, C=O, CHR^4, S, O, S=O, or SO_2;

R^1 and R^2 are each independently hydrogen, or an optionally substituted group selected from C_{1-6} aliphatic, a 5-6 membered aryl ring having 0-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or a 3-7-membered saturated or partially unsaturated ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur; or R^1 and R^2, taken together with the nitrogen atom to which they are bound, form an optionally substituted 3-8 membered heterocyclyl or heteroaryl ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur, wherein R^1, R^2, or any ring formed by R^1 and R^2 taken together, are each independently optionally substituted at one or more carbon atoms with 0-4 occurrences of $-R^5$, and at one or more substitutable nitrogen atoms with $-R^6$;

Ring A is a 5-6 membered monocyclic or 8-10 membered bicyclic aryl ring having 0-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or a 3-7-membered saturated or partially unsaturated ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur, optionally substituted at one or more carbon atoms with 0-5 occurrences of $-R^7$, and at one or more substitutable nitrogen atoms with $-R^8$;

each occurrence of R^4, R^5, and R^7 is independently Q-R^X; wherein Q is a bond or is a C_1-C_6 alkylidene chain wherein up to two non-adjacent methylene units of Q are optionally and independently replaced by CO, CO_2, COCO, CONR, OCONR, NRNR, NRNRCO, NRCO, $NRCO_2$, NRCONR, SO, SO_2, $NRSO_2$, SO_2NR, $NRSO_2NR$, O, S, or NR;

each occurrence of R^X is independently selected from R', halogen, NO_2, or CN;

each occurrence of R is independently selected from hydrogen or an optionally substituted C_{1-6} aliphatic group;

each occurrence of R' is independently selected from hydrogen or an optionally substituted group selected from C_{1-8} aliphatic, C_{6-10} aryl, a heteroaryl ring having 5-10 ring atoms, or a heterocyclyl ring having 3-10 ring atoms, or wherein R and R' taken together with the atom(s) to which they are bound, or two occurrences of R' taken together with the atom(s) to which they are bound, form a 5-8 membered cycloalkyl, heterocyclyl, aryl, or heteroaryl ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur; and

each occurrence of R^3, R^6 or R^8 is independently R', -COR', -CO_2(C_{1-6} aliphatic), -$CON(R')_2$, or -SO_2R'.

137. The method according to claim 136, wherein said compound is according to claim 1 or 15.

138. The method according to claim 136, wherein the disease, condition, or disorder is implicated in the activation or hyperactivity of voltage-gated sodium channels.

139. The method according to claim 136, wherein the disease, condition, or disorder is implicated in the activation or hyperactivity of voltage-gated calcium channels.

140. The method according to claim 139, wherein the disease, condition, or diorder is acute, chronic, neuropathic, or inflammatory pain.

141. The method according to claim 136, wherein the disease, condition, or disorder is radicular pain, sciatica, back pain, head pain, or neck pain.

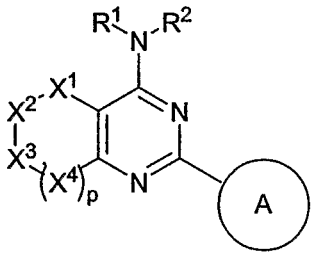
142. The method according to claim 136, wherein the disease, condition, or disorder is severe or intractable pain, acute pain, post-surgical pain, back pain, or cancer pain.

143. 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;

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



I

or a pharmaceutically acceptable salt thereof, wherein:

p is 0, 1 or 2;

X^1, X^2, X^3 and X^4 are each independently selected from NR^3, C=O, CHR^4, S, O, S=O, or SO_2;

R^1 and R^2 are each independently hydrogen, or an optionally substituted group selected from C_{1-6} aliphatic, a 5-6 membered aryl ring having 0-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or a 3-7-membered saturated or partially unsaturated ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur; or R^1 and R^2, taken together with the nitrogen atom to which they are bound, form an optionally substituted 3-8 membered heterocyclyl or heteroaryl ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur, wherein R^1, R^2, or any ring formed by R^1 and R^2 taken together, are each independently optionally substituted at one or more carbon atoms with 0-4 occurrences of $-R^5$, and at one or more substitutable nitrogen atoms with $-R^6$;

Ring A is a 5-6 membered monocyclic or 8-10 membered bicyclic aryl ring having 0-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or a 3-7-membered saturated or partially unsaturated ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur, optionally substituted at one or more carbon atoms with 0-5 occurrences of $-R^7$, and at one or more substitutable nitrogen atoms with $-R^8$;

each occurrence of R^4, R^5, and R^7 is independently $Q\text{-}R^X$; wherein Q is a bond or is a C_1-C_6 alkylidene chain wherein up to two non-adjacent methylene units of Q are optionally and independently replaced by CO, CO_2, COCO, CONR, OCONR, NRNR, NRNRCO, NRCO, $NRCO_2$, NRCONR, SO, SO_2, $NRSO_2$, SO_2NR, $NRSO_2NR$, O, S, or NR;

each occurrence of R^X is independently selected from R', halogen, NO_2, or CN;

each occurrence of R is independently selected from hydrogen or an optionally substituted C_{1-6} aliphatic group;

each occurrence of R' is independently selected from hydrogen or an optionally substituted group selected from C_{1-8} aliphatic, C_{6-10} aryl, a heteroaryl ring having 5-10 ring atoms, or a heterocyclyl ring having 3-10 ring atoms, or wherein R and R' taken together with the atom(s) to which they are bound, or two occurrences of R' taken together with the atom(s) to which they are bound, form a 5-8 membered cycloalkyl, heterocyclyl, aryl, or heteroaryl ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur; and

each occurrence of R^3, R^6 or R^8 is independently R', -COR', $-CO_2(C_{1-6}$ aliphatic), $-CON(R')_2$, or $-SO_2R'$.

144. The method according to claim 143, wherein said compound is according to claim 1 or 15.

145. The method according to claim 136 or 143, wherein said compound is selected from Table 1.

146. A compound selected from Table 1.