PYRIMIDINES USEFUL AS MODULATORS 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
NaV1.4	Skeletal muscle	25nM	Myotonia
NaV1.5	Heart	2μM	Arrythmia, long QT
NaV1.6	CNS widespread, most abuntant	6nM	Pain, movement disorders
NaV1.7	PNS, DRG, terminals	25nM	Pain, Neuroendocrine disorders

	neuroendocrine		
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 5-10 fold upregulated (See, Dib-Hajj, S. D., J. Fjell, et al. (1999) "Plasticity of sodium channel expression in DRG neurons in the chronic constriction injury model of neuropathic pain." Pain **83**(3): 591-600.) The timecourse of the increase in NaV1.3 parallels the appearance of allodynia in animal models subsequent to nerve injury. The biophysics of the NaV1.3 channel is distinctive in that it shows very fast repriming after inactivation following an action potential. This allows for sustained rates of high firing as is often seen in the injured nerve (See, Cummins, T. R., F. Aglieco, et al. (2001) "Nav1.3 sodium channels: rapid repriming and slow closed-state inactivation display quantitative differences after expression in a mammalian cell line and in spinal sensory neurons" J Neurosci **21**(16): 5952-61.). NaV1.3 is expressed in the central and peripheral systems of man. NaV1.9 is similar to NaV1.8 as it is selectively localized to small sensory neurons of the dorsal root ganglion and trigeminal ganglion (See, Fang, X., L. Djouhri, et al. (2002). "The presence and role of the tetrodotoxin-resistant sodium channel Na(v)1.9 (NaN) in nociceptive primary afferent neurons." J Neurosci **22**(17): 7425-33.). It has a slow rate of inactivation and left-shifted voltage dependence for activation (See, Dib-Hajj, S., J. A. Black, et al. (2002) "NaN/Nav1.9: a sodium channel with unique properties" Trends Neurosci **25**(5): 253-9.). These two biophysical properties allow NaV1.9 to play a role in establishing the resting membrane potential of nociceptive neurons. The resting membrane potential of NaV1.9 expressing cells is in the –55 to –50mV range compared to –65mV for most other peripheral and central neurons. This persistent depolarization is in large part due to the sustained low-level activation of NaV1.9 channels. This depolarization allows the neurons to more easily reach the threshold for firing action potentials in response to nociceptive stimuli. Compounds that block the NaV1.9 channel may play an important role in establishing the set point for detection of painful stimuli. In chronic pain states, nerve and nerve ending can become swollen and hypersensitive exhibiting high frequency action potential firing with mild or even no stimulation. These pathologic nerve swellings are termed neuromas and the primary Na channels expressed in them are NaV1.8 and NaV1.7 (See, Kretschmer, T., L. T. Happel, et al. (2002) "Accumulation of PN1 and PN3

sodium channels in painful human neuroma- evidence from immunocytochemistry" Acta Neurochir (Wien) **144**(8): 803-10; discussion 810.). NaV1.6 and NaV1.7 are also expressed in dorsal root ganglion neurons and contribute to the small TTX sensitive component seen in these cells. NaV1.7 in particular my therefore be a potential pain target in addition to it's role in neuroendocrine excitability (See, Klugbauer, N., L. Lacinova, et al. (1995) "Structure and functional expression of a new member of the tetrodotoxin- sensitive voltage-activated sodium channel family from human neuroendocrine cells" Embo J **14**(6): 1084-90).

[0010] 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)

[0011] 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).

[0012] 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)

[0013] Calcium channels are membrane-spanning, multi-subunit proteins that allow Ca entry from the external milieu and concurrent depolarization of the cell's membrane potential. Traditionally calcium channels have been classified based on their functional characteristics such as low voltage or high voltage activated and their kinetics (L,T,N,P,Q). The ability to clone and express the calcium channel subunits has lead to an increased understanding of the channel composition that produces these functional responses. There are three primary subunit types that make up calcium channels - $\alpha 1$, $\alpha 2\delta$, and β. The $\alpha 1$ is the subunit containing the channel pore and voltage sensor, $\alpha 2$ is primarily extracellular and is disulfide linked to the transmembrane δ subunit, β is nonglycosylated subunit found bound to the cytoplasmic region of the $\alpha 1$ subunit of the Ca channel. Currently the various calcium channel subtypes are believed to made up of the following specific subunits:

- L-type, comprising subunits $\alpha_{1C}\alpha_{1D}\alpha_{1F}$, or α_{1S}, $\alpha 2\delta$ and β_{3a}
- N-Type, comprising subunits α_{1B}, $\alpha 2\delta$, β_{1b}
- P-Type, comprising subunits α_{1A}, $\alpha 2\delta$, β_{4a}
- Q-Type, comprising subunits α_{1A} (splice variant) $\alpha 2\delta$, β_{4a}
- R-Type, comprising subunits α_{1E}, $\alpha 2\delta$, β_{1b}
- T-Type, comprising subunits α_{1G}, α_{1H}, or α_{1I}

[0014] Calcium channels play a central role in neurotransmitter release. Ca influx into the presynaptic terminal of a nerve process binds to and produces a cascade of protein-protein interactions (syntaxin 1A, SNAP-25 and synaptotagmin) that ultimately ends with the fusion of a

synaptic vesical and release of the neurotransmitter packet. Blockade of the presynaptic calcium channels reduces the influx of Ca and produces a cubic X^3 decrease in neurotransmitter release.

[0015] The N type Ca channel (CaV2.2) is highly expressed at the presynaptic nerve terminals of the dorsal root ganglion as it forms a synapse with the dorsal horn neurons in lamina I and II. These neurons in turn have large numbers of N type Ca channels at their presynaptic terminals as they synapse onto second and third order neurons. This pathway is very important in relaying pain information to the brain.

[0016] 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 it's intensity is more graded. Inflammation may occur for many reasons including tissue damage, autoimmune response, and pathogen invasion. Inflammatory pain is mediated by an "inflammatory soup" that consists of substance P, histamines, acid, prostaglandin, bradykinin, CGRP, cytokines, ATP, and neurotransmitter release. The third class of pain is neuropathic and involves nerve damage that results in reorganization of neuronal proteins and circuits yielding a pathologic "sensitized" state that can produce chronic pain lasting for years. This type of pain provides no adaptive benefit and is particularly difficult to treat with existing therapies.

[0017] Pain, particularly neuropathic and intractable pain is a large unmet medical need. Millions of individuals suffer from severe pain that is not well controlled by current therapeutics. The current drugs used to treat pain include NSAIDS, COX2 inhibitors, opioids, tricyclic antidepressants, and anticonvulsants. Neuropathic pain has been particularly difficult to treat as it does not respond well to opiods until high doses are reached. Gabapentin is currently the favored therapeutic for the treatment of neuropathic pain although it works in only 60% of patients where it shows modest efficacy. The drug is however very safe and side effects are generally tolerable although sedation is an issue at higher doses.

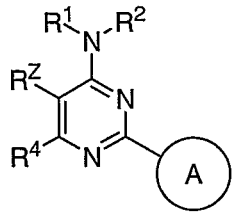
[0018] The N type Ca channel has been validated in man by intrathecal infusion of the toxin Ziconotide for the treatment of intractable pain, cancer pain, opioid resistant pain, and

neuropathic and severe pain. The toxin has an 85% success rate for the treatment of pain in humans with a greater potency than morphine. An orally available N type Ca channel antagonist would garner a much larger share of the pain market. Ziconotide causes mast cell degranulation and produces dose-dependent central side effects. These include dizziness, nystagmus, agitation, and dysmetria. There is also orthostatic hypotension in some patients at high doses. The primary risk for this target involves the CNS side-effects seen with Ziconotide at high dosing. These include dizziness, nystagmus, agitation, and dysmetria. There is also orthostatic hypotension in some patients at high doses. It is believed that this may be due to Ziconotide induced mast cell degranulation and/or its effects on the sympathetic ganglion that like the dorsal root ganglion also expresses the N type Ca channel. Use-dependent compounds that block preferentially in the higher frequency range >10Hz should be helpful in minimizing these potential side-effect issues. The firing rate in man of the sympathetic efferents is in the 0.3 Hz range. CNS neurons can fire at high frequencies but generally only do so in short bursts of action potentials. Even with the selectivity imparted by use-dependence intrinsic selectivity against the L type calcium channel is still necessary as it is involved in cardiac and vascular smooth muscle contraction.

[0019] 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

[0020] 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

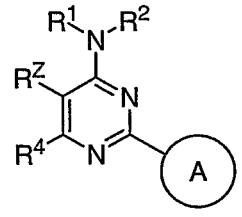
or a pharmaceutically acceptable derivative thereof, wherein R^1, R^2, R^z, R^4, and ring A are as defined herein.

[0021] These compounds and pharmaceutically acceptable compositions are useful for treating or lessening the severity of a variety of diseases, disorders, or conditions, including, but not limited to, acute, chronic, neuropathic, or inflammatory pain, arthritis, migrane, cluster headaches, trigeminal neuralgia, herpetic neuralgia, general neuralgias, epilepsy or epilepsy conditions, neurodegenerative disorders, psychiatric disorders such as anxiety and depression, myotonia, arrythmia, movement disorders, neuroendocrine disorders, ataxia, multiple sclerosis, irritable bowel syndrome, and incontinence.

DETAILED DESCRIPTION OF THE INVENTION

[0022] *I. General Description of Compounds of the Invention:*

[0023] The present invention relates to compounds of formula **I** useful as inhibitors of voltage-gated sodium channels:



I

or a pharmaceutically acceptable salt thereof, wherein:

R^Z is $-C(O)R^3$, $-C(O)OR^3$, or R^{Z1};

R^{Z1} is $-C(O)N(R')_2$, $-SO_2R'$, $-SO_2NHR'$, $-NHSO_2R'$, $-P(O)(OR')_2$, $-C(O)N(CN)R'$, an optionally substituted 5-membered heteroaryl ring having1-4 heteroatoms selected from O, S, or N, or an optionally substituted pyran-4-one-yl;

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 aryl ring 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^3, 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 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; and each occurrence of R^X is independently selected from R', halogen, NO_2, or CN, provided that when R^Z is $-OR^3$, then $Q\text{-}R^X$ is bonded to the oxygen atom through a carbon atom;

wherein each occurrence of R is independently selected from hydrogen or an optionally substituted C_{1-6} aliphatic group; and 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 when R^Z is R^3, then R^3 is bonded to the carbon atom of the carbonyl group through an atom other than oxygen, preferably, through a carbon atom.

[0024] In certain other embodiments[KG1], for compounds of the invention wherein R^Z is $-R^3$ as described generally above and herein:

a) when ring A is unsubstituted phenyl, R^3 is methyl, and R^4 is =S or –SMe, then R^1 and R^2 taken together cannot be N-morpholino, N-pyrrolidinyl, or optionally substituted piperazinyl;

b) when ring A is N-morpholino, R^3 is H, and R^4 is Cl or Me, then R^1 is not Et, when R^2 is 4-Cl-phenyl, or R^1 and R^2, taken together, cannot be N-morpholino;

c) when ring A is N-pyrrolidinyl and R^3 is H, then:

i) when R^4 is $-N(CH_3)COPh$, then R^1 and R^2, taken together, cannot be pyrrolidinyl; and

ii) when R^4 is Cl, then R^1 is not Et, when R^2 is 4-Me-phenyl;

d) when ring A is N-piperidinyl, R^3 is hydrogen, and R^4 is methyl, then R^1 and R^2, taken together, cannot be N-piperidinyl;

e) when ring A is optionally substituted piperazinyl, R^3 is hydrogen, and R^4 is chloro, then when R^1 is Et, then R^2 is not 4-Cl-phenyl, 4-Me-phenyl, or 4-F-phenyl, or R^1 and R^2, taken together, cannot be thiomorpholino;

f) when ring A is 2,5-dimethyl-1H-pyrrol-1-yl, R^3 is hydrogen, and R^4 is OMe, then when R^1 is Me, then R^2 is not benzyl;

g) when ring A is 1-oxido-4-thiomorpholinyl, R^3 is hydrogen, and R^4 is OEt, then R^1 and R^2, taken together, cannot be piperizinyl;

h) when R^3 is CH_3 or optionally substituted phenyl R^1 is hydrogen, R^2 is optionally substituted phenyl, methyl, ethyl, COR', NR', or CONHR', and R^4 is =S, Me ,SMe, or SCH_2CO_2Me, SCH_2CN, then ring A is not unsubstituted phenyl or 4-Cl-phenyl;

i) when R^3 is CH_3, R^1 is hydrogen, R^2 is ethyl, and R^4 is hydrogen, then ring A is not N-pyrrolidinyl, piperazin-1-yl, N-morpholinyl, or 1-piperidinyl;

j) when R^3 is $N(R')_2$, R^1 is hydrogen, R^2 is 3-,5-Cl-phenyl, 4-Cl-phenyl, methyl, optionally substituted cyclohexyl, 3-Cl, 4-OMe-benzyl, 4-Ac-phenyl, ethyl, i-propyl, 4-OEt-phenyl, 4-OMe-phenyl, benzyl, or $(CH_2)_2OR$, and R^4 is CH_3, hydrogen, or SMe, then ring A is not unsubstituted phenyl, piperidinyl, optionally substituted piperazinyl, morpholinyl, optionally

substituted pyrrolidinyl, 5,8-dihydro-1,7-naphthyridin-7(6H)-yl, or 5,6-dihydro-8-imidazo[1,2-a]pyrazin-7-yl;

k) when R^3 is -CH=CHN$(CH_3)_2$, CH_3, -$(CH_2)_2$-N-morpholino, -$(CH_2)_2$-OMe, -$(CH_2)_2$-OH, -CH_2OMe, n-butyl, pyridin-2-ylmethyl, pyridin-2-yl, pyrimidin-5-yl, CH_2SO_2Me, -$(CH_2)_2$-NMe_2, -$(CH_2)_2$-N-(4-methylpiperazyl), -$(CH_2)_2$-NH-pyridin-3-yl, -$(CH_2)_2$-NH-CH_2-pyridin-3-yl, 1-methyl-1H-imidazol-2-yl, 5-amino-1,2-dimethyl-1H-imidazol-4-yl, 4-(dimethylamino)phenyl, 3,4-(methylenedioxy)phenyl, -CH_2=CH_2, -CH=CH_2, or -CH(CN)COOEt, R^1 is hydrogen, R^2 is optionally substituted benzyl or ethyl, R^4 is SMe or hydrogen, then ring A is not unsubstituted phenyl or optionally substituted pyrrolidinyl;

l) when R^1 is hydrogen and R^2 is hydrogen or 4,6-dimethylpyrimidin-2-yl, ring A is optionally substituted phenyl, R^3 is Me or unsubstituted phenyl, then R^4 is not SMe, =S, Me, or unsubstituted phenyl;

m) when R^1 is hydrogen and R^2 is optionally substituted benzyl, then R^3 is not 3,4,5-trimethoxyphenyl;

n) when R^1 and R^2 are both hydrogen, ring A is (2-fluorophenylmethyl)-1H-pyrazolo[3,4-b]pyridin-3-yl, R^3 is ethyl or 2-ethoxyethyl, then R^4 is not hydrogen;

o) when R^1 is hydrogen, R^2 is benzoyl, then R^3, R^4, and ring A are all not simultaneously unsubstituted phenyl;

p) when R^1 and R^2 are both hydrogen, ring A is 4-(4'-morpholinyl)-5-methyl-2-phenylthieno[2,3-d]pyrimidin-6-yl, 4-amino-5-methyl-2-phenylthieno[2,3-d]pyrimidin-6-yl, 4-(4-(4-fluorophenyl)-piperazyl)-5-methyl-2-phenylthieno[2,3-d]pyrimidin-6-yl, 4-(4,6-dimethyl-pyrimidin-2-yl)amino-5-methyl-2-phenylthieno[2,3-d]pyrimidin-6-yl, 4-(N-pyrrolidinyl)-5-methyl-2-phenylthieno[2,3-d]pyrimidin-6-yl,or unsubstituted phenyl, R^3 is methyl, then R^4 is not methyl or SMe;

q) when R^1 and R^2 both are hydrogen, R^3 is methyl, R^4 is =S or unsubstituted phenyl, then ring A is not unsubstituted phenyl; and

r) when R^1 and R^2 taken together form a N-pyrrolidinyl ring, R^3 is –NHCH$_2$(4-trifluoromethylphenyl), R^4 is H, then ring A is not N-pyrrolidinyl, 3,4-dimethoxyphenyl, 2-methoxyphenyl, thiophen-3-yl, or thiophen-2-yl.

[0025] For certain other embodiments[KG2], when R^Z in compound of formula I is C(O)N$(R')_2$, then:

a) when R^1 and R^2 are both hydrogen, then $N(R')_2$ is not NH_2 or NH-C(=NH)NH_2;

b) when R^1 is hydrogen, methyl, or ethyl, and R^2 is $-(CH_2)_2$-OH, $-(CH_2)_2$-OAc, 3,5-dichlorophenyl, or benzyl, R^4 is hydrogen or methyl, ring A is unsubstituted phenyl, then $N(R')_2$ is not NH_2, $NHNH_2$, NHMe, $NH(CH_2)_2$-OH, or NH-benzyl;

c) when R^1 is hydrogen and R^2 is methyl, R^4 is OH, ring A is unsubstituted phenyl, then $N(R')_2$ is not NHMe;

d) when ring A is optionally substituted phenyl, R^1 is hydrogen and R^2 is optionally substituted phenyl, R^4 is optionally substituted phenyl or unsubstituted naphthyl, then $N(R')_2$ is not NH_2;

e) when R^1 and R^2 are both hydrogen, $N(R')_2$ is NH_2, NH-(optionally substituted phenyl), N(optionally substituted C1-6 aliphatic)(optionally substituted phenyl), or NH(6,7,8,9-tetrahydro-5H-benzocyclohepten-6-yl), R^4 is hydrogen, then ring A is not 1-imidazolyl, 1-piperidyl, unsubstituted phenyl, optionally substituted 2-oxo-imidazolidin-1-yl or 1-[(2-fluorophenyl)methyl]-1H-indazol-3-yl;

f) when R^1 is hydrogen, R^2 is optionally substituted phenyl, ring A is unsubstituted phenyl, R4 is methyl or hydrogen, then $N(R')_2$ is not NHEt, $N(Et)_2$, NH(optionally substituted phenyl),

g) when R^1 is hydrogen, R^2 is 2-pyridinyl, ring A is unsubstituted phenyl, R^4 is hydrogen, then $N(R')_2$ is not N-morpholinyl;

h) when R^1 is hydrogen, R^2 is hydrogen or C_{1-4} aliphatic, $N(R')_2$ is NH(C1-4 aliphatic) or N(C1-4 aliphatic)$_2$, R^4 is hydrogen, then ring A is not N-piperidyl or optionally substituted N-piperazyl;

i) when R^1 is hydrogen, R^2 is 4-chlorophenyl, ring A is unsubstituted phenyl, R^4 is methyl, then $N(R')_2$ is not NHCH2-furan-2-yl;

j) ring A is not 2-formyl-pyrrolin-1-yl, optionally substituted hydroxymethyl-pyrrolidin-1-yl, hydroxypiperidinyl, or hydroxymethylpiperidinyl;

k) the following compounds are excluded:

R^1	R^2	$N(R')_2$	R^4	Ring A
H	Optionally substituted cyclohexyl	N-morpholinyl	H	phenyl

H	Optionally substituted cyclohexyl	N-morpholinyl	H	N-pyrrolidinyl
H	Optionally substituted cyclohexyl	N-morpholinyl	H	phenyl
H	Optionally substituted cyclohexyl or benzyl	NMe_2 or NH(optionally substituted cyclohexyl)	H	N-morpholino
H	H	NH(6,7,8,9-tetrahydro-5H-benzocyclohepten-6-yl	H	pyridinyl
H	4-nitrophenyl	4-methylpiperazyl	methyl	phenyl
Methyl	methyl	NH-tetrazolyl	H	phenyl
H	optionally substituted cyclohexyl or benzyl	NH(Optionally substituted benzyl or cyclohexyl)	H	optionally substituted N-piperazyl or imidazol-1-yl or 2-hydroxypyrrolyl
H	optionally substituted benzyl	NH(optionally substituted cyclohexyl)	H	optionally substituted 2,3-dihydro-1H-isoindol-2-yl
H	optionally substituted benzyl	NH-pyridylmethyl	H	2,3-dihydro-1H-isoindol-2-yl
H	optionally substituted benzyl	NHpyridylmethyl or $NHCH_2CH_2$-N-morpholino	H	2-aminocarbonyl-prrolidin-1-yl or N-morpholino or 1H-imidazo[4,5-c]pyridine-(6-CO_2Me)-4,5,6,7-tetrahydro-1-yl or 1,2,3,4,6,7-hexahydro-3-oxo-5H-pyrazolo[4,3-c]pyridin-5-yl
H	(aryl or heteroaryl) substituted C1-4 aliphatic		H	3,4-dihydro-(1H)-isoquinolin-2-yl or 5,6-dihydroimidazo[1,2-a]pyrazin-7(8H)-yl

				or 5,8-dihydro-1,7-napthyridin-7(6H)-yl or 5,7-dihydro-6H-pyrrolo[3,4-b]pyridin-6-yl or 2,3-dihydro-1H-indol-1-yl or 4,5,6,7-tetrahydro-isoxazolo[4,5-c]pyridin-5-yl or 6,7-dihydrothiazolo[5,4-c]pyridin-(4H)-5-yl
H	Optionally substituted benzyl	NH-pyridin-2-ylmethyl	H	1-piperidinyl

l) when R^1 is H or optionally substituted C_{1-4} aliphatic, R^2 is optionally substituted benzyl, R^4 is methoxy, then ring A is not optionally substituted N-piperazyl, 3,4-dihydro-(1H)-isoquinolin-2-yl, 5,6-dihydroimidazo[1,2-a]pyrazin-7(8H)-yl, or 6,7-dihydrothieno[3,2-c]pyridin-5(4H)-2-yl;

m) when R^1 and R^2 are both methyl, R^4 is hydrogen, ring A is 4-[(napth-2-yl)sulfonyl]piperazyl, then $N(R')_2$ is not NHOH or NH-O-(tetrahydro-2H-pyran-2-yl);

n) when R^1 is hydrogen, R^2 is optionally substituted benzyl, R^4 is hydrogen, $N(R')_2$ is $NHCH_2$(pyridin-2-yl), then ring A is not 3-(hydroxymethyl)2(1H)-isoquinolinyl; and

o) when R^1 is hydrogen, R^2 is (aryl or heteroaryl) substituted C_{1-4} aliphatic, R^4 is hydrogen, then ring A is not 3,4-dihydro-(1H)-isoquinolin-2-yl, 5,6-dihydroimidazo[1,2-a]pyrazin-7(8H)-yl, 5,8-dihydro-1,7-napthyridin-7(6H)-yl, 5,7-dihydro-6H-pyrrolo[3,4-b]pyridin-6-yl, 2,3-dihydro-1H-indol-1-yl, 4,5,6,7-tetrahydro-isoxazolo[4,5-c]pyridin-5-yl, or 6,7-dihydrothiazolo[5,4-c]pyridin-(4H)-5-yl; and

o) when R^1 and R^2 taken together is 4-(2-naphthalenylsulfonyl)-1-piperazinyl, ring A is 4-(2-naphthalenylsulfonyl)-1-piperazinyl or 4-(2-naphthalenylsulfonyl)amino-piperidinyl and R^4 is hydrogen, then R^3 is not NH-O-(tetrahydro-2H-pyran-2-yl) or NHOH.

[0026] In certain other embodiments, when R^Z is R^{Z1} as generally described above and herein:

a) when R^{Z1} is tetrazolyl, R^1 is hydrogen, R^2 is hydrogen or optionally substituted phenyl, R^4 is hydrogen, then ring A is not unsubstituted 1-pyrrolidinyl, 1-piperidyl, N-morpholinyl, 1-azepanyl, or phenyl.

[0027] In certain other embodiments, when R^Z is R^{Z1} as generally described above and herein:

a) when R^{Z1} is $-P(O)(OR')_2$ and R' is C_{1-4} aliphatic, R^1 and R^2 are both hydrogen, and R^4 is hydrogen, methyl, anino, $-OCH_2OH$, then ring A is not 1-[(2-fluorophenyl)methyl]-1H-pyrazolo[3,4-b]pyridin-3-yl or unsubstituted phenyl.

[0028] In certain other embodiments, when R^Z is R^{Z1} as generally described above and herein:

a) when R^{Z1} is $-SO_2NHR'$and R' is hydrogen, R^1 and R^2 are both hydrogen, R^4 is amino, then ring A is not N-morpholino.

[0029] In certain other embodiments[KG3], for compounds of the invention wherein R^Z is $-OR^3$ as described generally above and herein:

a) when R^3 is ethyl; R^4 is hydrogen; ring A is unsubstituted phenyl, and R^1 is hydrogen, then R^2 is not optionally substituted 2-pyridinyl, optionally substituted phenyl, optionally substituted benzyl, $-CH_2CO_2H$, $-CH_2CN$, n-propyl, methyl, ethyl, $-CH_2$(4-OMe-phenyl), $-CH_2CON(Me)CH_2Ph$, $-CH_2C{\equiv}CH$, $-CH_2CH_2OMe$, $-CH_2CH{=}CH_2$, or $-(CH_2)_3OH$;

b) when R^3 is ethyl; R^4 is hydrogen; ring A is thienyl; and R^1 is hydrogen; then R^2 is not optionally substituted phenyl;

c) when R^3 is ethyl; R^4 is hydrogen; ring A is unsubstituted phenyl; then when R^1 is methyl, ethyl, CH_2CH_2Ph, $-CH_2CH_2$morpholino, $-CH_2CH_2NEt_2$, $-CH_2CH_2OMe$, n- butyl, or optionally substituted phenyl, then R^2 is not $-CH_2CH_2CN$, $-CH_2CN$, or $-CH_2CH_2OAc$, or R^1 and R^2 taken together are not optionally substituted piperidinyl, morpholino, or thiomorpholino;

d) when R^3 is ethyl; R^4 is NH_2, Cl, Me, or Br, ring A is unsubstituted phenyl or morpholino, and R^1 is hydrogen, then R^2 is not optionally substituted phenyl, or COR';

e) when R^3 is ethyl, R^4 is hydrogen; and ring A is unsubstituted phenyl, then R^1 and R^2 are not simultaneously methyl;

f) when R^3 is methyl, then ring A, R^4, and R^1 and R^2 taken together, are not simultaneously piperidinyl;

g) when R^3 is ethyl, R^1 is hydrogen, R^2 is unsubstituted phenyl, and R^4 is methyl or thiomorpholino, then ring A is not unsubstituted phenyl, 4-OMe-phenyl, 2-pyridinyl, 4-Cl-phenyl, 2-Cl-phenyl, 3,4-dichlorophenyl, 4-Me-phenyl, 3,5-dichlorophenyl, 4-OH-phenyl, or $3CF_3$-,4-Cl-phenyl;

h) when R^3 is ethyl, methyl, or isopropyl, R^1 is hydrogen or ethyl, and R^2 is ethyl, $COCH_3$, isopropyl, $-CH_2CH_2CN$, benzyl, $-CH_2CH_2NEt_2$, $-CH_2CH_2COOEt$, or R^1 and R^2, taken together are piperazinyl, and R^4 is hydrogen, then ring A is not optionally substituted piperazinyl, pyrrolidinyl, morpholino, or piperidinyl;

i) when R^3 is ethyl, and R^1 is hydrogen, then R^2 is not optionally substituted cyclohexyl;

j) when R^3 is methyl, and R^4 is N(Me)COPh, then ring A and R^1 and R^2, taken together, are not simultaneously N-pyrrolidinyl;

k) when R^3 is ethyl, R^4 is optionally substituted phenyl, ring A is optionally substituted phenyl, and R^1 is hydrogen, then R^2 is not optionally substituted naphthyl, methyl, optionally substituted phenyl, or R^1 and R^2, taken together are not morpholino;

l) when R^3 is ethyl, then when one of R^1 and R^2, taken together or ring A is optionally substituted piperazinyl, then the other of R^1 and R^2, taken together or ring A is not thiomorpholino or morpholino;

m) R^1 and R^2, taken together and ring A are not simultaneously morpholino or thiomorpholino;

o) when R^3 is methyl, R^4 is hydrogen or OMe, ring A is unsubstituted phenyl, and R^1 is hydrogen, then R^2 is not methyl, 2,3-dimethylphenyl, or 3-CF_3phenyl;

p) when R^3 is ethyl, R^4 is hydrogen, and ring A is unsubstituted phenyl, then:

i) R^1 and R^2 taken together do not form a 1-pyrrolidinyl, 4-methylpiperazinyl, or 1-piperidyl;

ii) R^1 and R^2 both are not hydrogen, methyl, or ethyl;

iii) when R^1 is hydrogen then R^2 is not 2-hydroxyethyl.

[0030] In still other embodiments, for compounds of the invention wherein R^Z is $-C(O)R^3$, as described generally above and in subsets herein, R^3 is bonded to the carbon atom of the carbonyl group through an atom other than oxygen or nitrogen.

[0031] In yet other embodiments, for compounds of the invention wherein R^Z is $-C(O)R^3$, as described generally above and in subsets herein, for R^4, Q is not O or S, when R^X is optionally substituted furyl, or thiophene.

[0032] In still other embodiments, for compounds of the invention wherein R^Z is $-C(O)R^3$, as described generally above and in subsets herein, when R^1 is hydrogen, R^2 is a group other than NR'.

[0033] *2. Compounds and Definitions:*

[0034] 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.

[0035] 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.

[0036] 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.

[0037] 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.

[0038] 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.

[0039] 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)).

[0040] The term "unsaturated", as used herein, means that a moiety has one or more units of unsaturation.

[0041] 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.

[0042] 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.

[0043] 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.

[0044] 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".

[0045] 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)$N(R°)_2$; -$S(O)_2$R°; -$SO_2N(R°)_2$; -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.

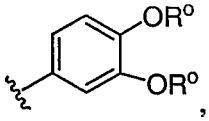
[0046] An aliphatic or heteroaliphatic group, or a non-aromatic heterocyclic ring may contain one or more substituents. Suitable substituents on the saturated carbon of an aliphatic or heteroaliphatic group, or of a non-aromatic heterocyclic ring are selected from those listed above for the unsaturated 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.

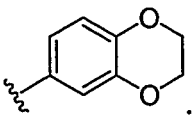
[0047] Optional substituents on the nitrogen of a non-aromatic heterocyclic ring are selected from –R+, -N(R+)$_2$, -C(O)R+, -CO_2R+, -C(O)C(O)R+, -C(O)CH_2C(O)R+, -SO_2R+, -$SO_2N(R^+)_2$, -C(=S)$N(R^+)_2$, -C(=NH)-$N(R^+)_2$, or -NR+SO_2R+; wherein R+ is hydrogen, an optionally substituted C_{1-6} 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.

[0048] 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.

[0049] As detailed above, in some embodiments, two independent occurrences of R° (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° (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° (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, $N(R^\circ)_2$, where both occurrences of R° 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° (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°



, these two occurrences of R° 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°

(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.

[0050] 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.

[0051] *3. Description of Exemplary Compounds:*

[0052] In certain embodiments of the present invention, R' is hydrogen.

[0053] In certain embodiments of the present invention, R' is independently selected from 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.

[0054] In certain embodiments of the present invention, R' is an optionally substituted C_{1-8} aliphatic group. In certain such embodiments, R' is C_{1-4} aliphatic group optionally substituted with halo, OH, COOH, CN, $-OC_{1-4}$alkyl. Or, R' is C_{1-4} aliphatic group optionally substituted with a 5-6 membered heterocyclic ring containing optional substituents. Examples of such heterocyclic ring includes, e.g., tetrahydrofuranyl, pyranyl, piperidinyl, and piperazinyl. Or, R' is C_{1-4} aliphatic group optionally substituted with an aryl group containing optional substituents.

[0055] In other embodiments of the present invention, R' is an optionally substituted C_{6-10} aryl group. Suitable aryl gruops include phenyl and napthyl.

[0056] In certain other embodiments of the compounds of the present invention, R' is an optionally substituted heteroaryl ring having 5-10 ring atoms. Suitable heteroaryl rings include 5-membered heteroaryl rings such as, e.g., pyrrolyl, thienyl, and thiazolyl.

[0057] Or, R' is an optionally substituted heterocyclyl ring having 3-10 ring atoms. Such rings include, e.g., tetrahydrofuranyl, pyranyl, piperidinyl, and piperazinyl.

[0058] In other embodiments of the present invention, 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. In certain embodiments, two occurrences of R' taken together with the atom(s) to which they are bound, form a 5-8 membered cycloalkyl ring. In certain other embodiments, two occurrences of R' taken together with the atom(s) to which they are bound, form a 5-8 membered heterocyclyl ring. In certain other embodiments, two occurrences of R' taken together with the atom(s) to which they are bound, form a 5-8 membered heterocyclyl ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur. In certain other embodiments, two occurrences of R' taken together with the atom(s) to which they are bound, form an aryl ring or they form a 5-8 membered having 0-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

[0059] In some embodiments of the present invention, 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 $-R^6$.

[0060] In certain embodiments of the present invention, neither R^1 nor R^2 is hydrogen. Or, R^1 and R^2 are each independently an optionally substituted C_{1-6}aliphatic group.

[0061] In certain other embodiments of the present invention, 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 or an optionally substituted C_{1-4}aliphatic group, wherein one or more methylene units in the C_{1-4}aliphatic group are optionally replaced with NR, O, (CO)O, O(CO), NR(CO), (CO)NR, SO_2(NR), or (NR)SO_2.

[0062] In other embodiments of the present invention, 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 replaced with NR, O, (CO)O, O(CO), NR(CO), (CO)NR, SO_2(NR), or (NR)SO_2. In yet other preferred embodiments, one of R^1 and 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 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. More preferred R^1 and R^2 groups include those shown below in Table 2.

[0063] In other embodiments of the present invention, R^1 and R^2 are both C_{1-4} aliphatic or R^1 and R^2 taken together form a 5-6 membered heterocyclic ring. Preferred R^1 and R^2 include methyl, ethyl, or propyl; or R^1 and R^2, taken together form an optionally substiuted 1-pyrrolidinyl or 1-piperidinyl. In another embodiment, R^1 and R^2 both are simultaneously methyl or ethyl.

[0064] In other embodiments of the compounds of the present invention, R^1 and R^2 are both C_{1-4} alphatic or R^1 and R^2 taken together form a 3-6 membered heterocyclic ring having up to 2 heteroatoms. Preferred R^1 and R^2 include methyl, ethyl, propyl; or R^1 and R^2, taken together form an optionally substituted 1-azetidinyl, 1-pyrrolidinyl, 1-piperidinyl, or 1-piperazinyl. : In one embodiment, R^1 and R^2 both are methyl or ethyl, or R^1 and R^2, taken together form a 1-pyrrolidinyl ring. In one embodiment, R^1 and R^2 both simultaneously are methyl or ethyl.

[0065] In other embodiments of the compounds of the present invention, R^1 and R^2 are both simultaneously C_{1-4} alphatic. Preferred R^1 and R^2 include methyl, ethyl, or propyl.

[0066] In other embodiments of the compounds of the present invention, R^1 and R^2 are both C_{1-4} alphatic or R^1 and R^2 taken together form a 4-6 membered heterocyclic ring having up to 2

nitrogen heteroatoms. Preferred R^1 and R^2 include methyl, ethyl, propyl; or R^1 and R^2, taken together form an optionally substituted 1-pyrrolidinyl or 1-piperazinyl. In one embodiment, R^1 and R^2 both are methyl or ethyl, or R^1 and R^2, taken together form a 1-pyrrolidinyl ring, R^3 is ethyl or propyl. In another embodiment, R^1 and R^2 both are methyl or ethyl,

[0067] In one embodiment of the present invention, R^1 and R^2 are both C_{1-4} alphatic or R^1 and R^2 taken together form a 4-6 membered heterocyclic ring having up to 2 nitrogen heteroatoms. Preferred R^1 and R^2 include methyl, ethyl, propyl; or R^1 and R^2, taken together form 1-azetidinyl, 1-pyrrolidinyl, or 2,5-dihydropyrrolyl. Preferably, R^1 and R^2 are both methyl or ethyl.

[0068] In one embodiment of the present invention, R^1 and R^2 are both C_{1-4} alphatic or R^1 and R^2 taken together form a 4-6 membered heterocyclic ring having up to 2 nitrogen heteroatoms. Preferred R^1 and R^2 include methyl, ethyl, propyl; or R^1 and R^2, taken together form an optionally substituted 1-azetidinyl, 1-pyrrolidinyl, 2,5-dihydro-1H-pyrrolyl, 1-piperidinyl, or 1-piperazinyl. In one embodiment, R^1 and R^2 are both C_{1-4} alphatic. Preferably, R^1 and R^2 are both methyl or ethyl.

[0069] In one embodiment of the present invention, R^1 and R^2 are both C_{1-4} alphatic Preferably, R^1 and R^2 are both methyl or ethyl. In other embodiments of the present invention, 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 replaced with NR, O, (CO)O, O(CO), NR(CO), (CO)NR, SO_2(NR), or (NR)SO_2.

[0070] In one embodiment of the present invention, R^1 is hydrogen or C_{1-6} aliphatic and R^2 is optionally substituted C_{1-6} aliphatic, or R^1 and R^2 taken together form an optionally substituted 4-7 membered saturated ring, wherein said ring optionally contains a second heteroatom selected from O or N. In a preferred embodiment, R^1 is hydrogen or C_{1-6} aliphatic and R^2 is optionally substituted C_{1-6} aliphatic, furanylmethyl, allyl, or benzyl, or R^1 and R^2 taken together is 4-carboethoxy-1-piperidinyl, 2-methylpiperidinyl, 2-hydroxymethylpiperidinyl, 3-hydroxypiperidinyl, 4-isobutylcarbamate-1-piperidinyl, 3-diethylaminocarbonyl-1-piperidinyl, 1-piperidyl, 1-pyrrolidinyl, 2-carboethoxypyrrolidinyl, N-morpholino, 3,5-dimethyl-N-morpholino, 4-methylpiperazinyl, 4-hydroxyethyl piperazinyl, 1-pyrrolyl, 2,4-dihydro-1-pyrrolyl, 1-azetidinyl, or 1-azepanyl. Preferably, R^1 is hydrogen or C_{1-4} aliphatic and R^2 is C_{1-4} aliphatic, furanylmethyl, allyl, or benzyl, or R^1 and R^2 taken together is 4-carboethoxy-1-piperidinyl, 2-

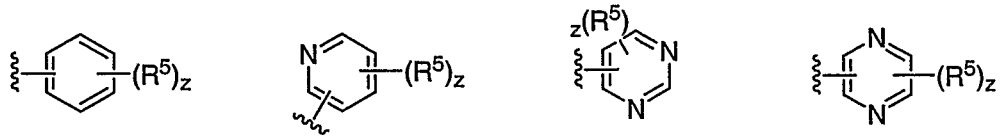
methylpiperidinyl, 4-isobutylcarbamate-1-piperidinyl, 3-diethylaminocarbonyl-1-piperidinyl, 1-piperidyl, 1-pyrrolidinyl, 2-carboethoxypyrrolidinyl, 4-methylpiperazyl, 2,4-dihydro-1-pyrrolyl, 1-azetidinyl, or 1-azepanyl. Or, R^1 is hydrogen or C_{1-4} aliphatic and R^2 C_{1-4} aliphatic, furanylmethyl, allyl, or benzyl, or R^1 and R^2 taken together is 4-carboethoxy-1-piperidinyl, 2-methylpiperidinyl, 1-piperidinyl, 1-pyrrolidinyl, 4-methylpiperazyl, 2,4-dihydro-1-pyrrolyl, or 1-azetidinyl;

[0071] In another embodiment of the present invention, R^1 and R^2 are both methyl, or R^1 and R^2 taken together form 1-pyrrolidinyl, N-morpholinyl, 1-piperidyl, or 4-methyl piperidyl. Preferably, R^1 and R^2 are both methyl, or R^1 and R^2 taken together form 1-pyrrolidinyl, N-morpholinyl, 1-piperidyl, or 4-methyl piperidyl. Or, R^1 and R^2 are both methyl. Or, R^1 and R^2 taken together form 1-pyrrolidinyl, N-morpholinyl, 1-piperidyl, or 4-methyl piperidyl, preferably, 4-methyl piperidyl.

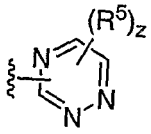
[0072] In another embodiment of the present invention, one of R^1 and R^2 is hydrogen, C_{1-4} aliphatic, and the other of R^1 and R^2 is C_{1-4} aliphatic, or benzyl, or R^1 and R^2 taken together form 1-pyrrolidinyl, 1-piperidinyl, or N-morpholinyl ring. Preferably, one of R^1 and R^2 is hydrogen, methyl, or ethyl, and the other of R^1 and R^2 is methyl, ethyl, or benzyl.

[0073] In other embodiments of the present invention, 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 replaced with NR, O, (CO)O, O(CO), NR(CO), (CO)NR, SO_2(NR), or (NR)SO_2.

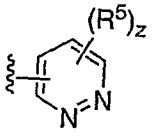
[0074] In embodiments of the present invention, wherein R^1 or R^2 is a 5- or 6-membered aryl ring having 0-5 heteroatoms independently selected from N, O, or S, or a 3-7-membered saturated or partially unsaturated ring having 0-3 heteroatoms independently selected from N, O, or S, preferred R^1 and R^2 groups are selected from:



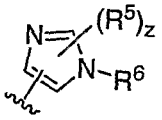
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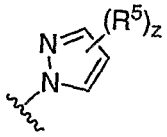
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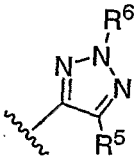
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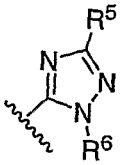
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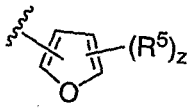
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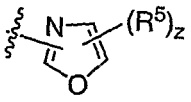
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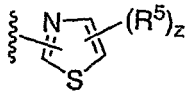
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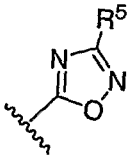
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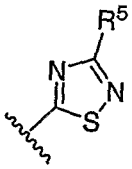
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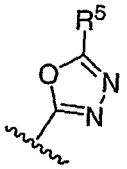
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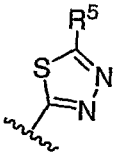
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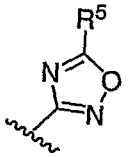
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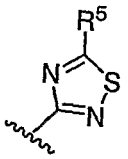
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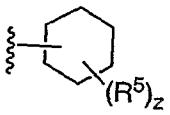
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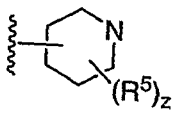
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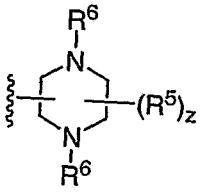
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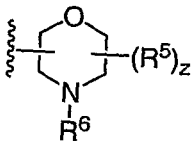
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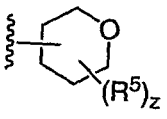
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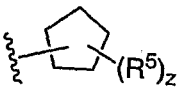
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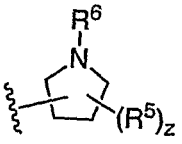
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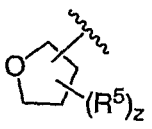
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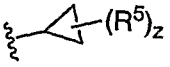
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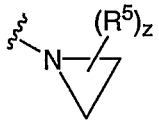
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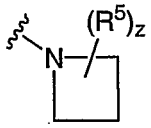
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wherein R^5 and R^6 are as previously defined and z is 0-4. Most preferred rings include those shown below in Table 2.

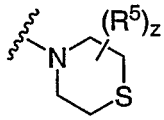
[0075] In still other embodiments of the present invention, R^1 and R^2, taken together with the nitrogen atom to which they are bound, form an optionally substituted 3-8 membered heterocyclyl ring having 1-3 heteroatoms independently selected from nitrogen, sulfur, or oxygen. In certain preferred embodiments, 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:



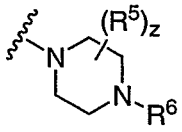
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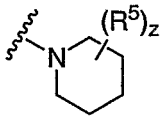
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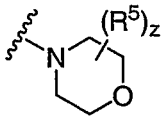
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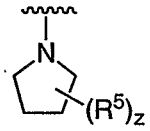
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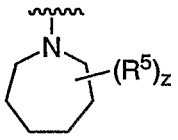
ee



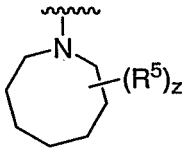
ff



gg



hh



jj

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

[0076] In certain preferred embodiments of the present invention, R^1 and R^2 are taken together are an optionally substituted azetidinyl ring (**bb**). Or, R^1 and R^2 are taken together are an optionally substituted piperidinyl ring (**ee**). Or, R^1 and R^2 are taken together are an optionally substituted piperazinyl ring (**dd**). Or, R^1 and R^2 are taken together are an optionally substituted pyrrolidinyl ring (**gg**).

[0077] In other preferred of the present invention, R^1 and R^2 taken together are optionally substituted pyrrolidin-1-yl (**ff**), piperidin1-yl (**ee**), piperazin-1-yl (**dd**), or morpholin-4-yl (**ee**).

[0078] In certain other embodiments of the compounds of the present invention, R^1 and R^2 are each independently an optionally substituted C_{1-6}aliphatic group, or R^1 and R^2 taken together form an optionally substituted pyrrolidinyl ring.

[0079] In certain other embodiments of the compounds of the present invention, R^1 and R^2 are each independently an optionally substituted C_{1-6}aliphatic group, or R^1 and R^2 taken together form an optionally substituted piperidinyl ring.

[0080] In certain other embodiments of the compounds of the present invention, R^1 and R^2 are each independently an optionally substituted C_{1-6}aliphatic group, or R^1 and R^2 taken together form an optionally substituted piperazinyl ring.

[0081] In certain other embodiments of the compounds of the present invention, R^1 and R^2 are each independently an optionally substituted C_{1-6}aliphatic group, or R^1 and R^2 taken together form an optionally substituted azetidinyl ring

[0082] In certain other embodiments of the compounds of the present invention, R^1 and R^2 are each independently an optionally substituted C_{1-6}aliphatic group, R^1 and R^2 taken together form an optionally substituted pyrrolidinyl ring, optionally substituted piperidyl ring, optionally substituted dihydropyrrolidinyl ring, or optionally substituted azetidinyl ring.

[0083] In the present invention, 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, each ring is 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 $-R^6$.

[0084] In preferred embodiments of the present invention, z is 0-3. In other preferred embodiments, z is 0 and the ring is unsubstituted.

[0085] Preferred R^5 groups, when present, are 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', -NRC(O)OR', -(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^5 groups are each independently Cl, Br, F, CF_3, CHF_2, Me, Et, propyl, CN, NO_2, -COOH, NH_2, $-N(C_{1-4}$ alkyl)$_2$, -O(C_{1-4}

alkyl)OCH_3, -$CONH_2$, -NHC(O)C_{1-4} alkyl, -NHC(O)(C_{5-6} heterocyclyl), -NHC(O)OC_{1-4} alkyl, -NHC(O)O(C_{5-6} heterocyclyl), -C(O)OC_{1-4} alkyl, -C(O)O(C_{5-6} heterocyclyl), OH, -CH_2OH, -NHCO C_{1-4} alkyl, -NHC(O)(C_{5-6} heterocyclyl), -SO_2NH_2, or $SO_2N(C_{1-4}$ alkyl$)_2$. In certain embodiments, 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, -$NHCOCH_3$, -NHC(O)O(iPr), -NHC(O)O-tetrahydrofuranyl, -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. In preferred embodiments, R^6 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', -$(CH_2)_2N(R')_2$, -$(CH_2)_2OR'$, -$(CH_2)_2SR'$, -COR', -C(O)OR', $CON(R')_2$, or -$S(O)_2N(R')_2$. In more preferred embodiments, R^6 groups are each independently H, Me, CF_3, ethyl, propyl, butyl, pentyl, CO(C_1-C_4alkyl), -$CONH_2$, -C(O)(C_1-C_4alkyl), -C(O)(C_{5-6} heterocyclyl), -C(O)O(C_1-C_4alkyl), -C(O)O(C_{5-6}heterocyclyl), -CH_2OH, -SO_2NH_2, $SO_2N(CH_3)_2$, or optionally substituted phenyl. Most preferred R^6 groups include those shown below in Table 2.

[0086] In certain embodiments of the present invention, R^1 and R^2 identical.

[0087] In certain embodiments of the present invention, R^Z is –$C(O)R^3$. In other embodiments, R^Z is –$C(O)OR^3$. In certain other embodiments, R^Z is -SO_2R', -SO_2NHR', -$NHSO_2R'$, -$P(O)(OR')_2$, or -C(O)N(CN)R'. In yet other embodiments, R^Z is an optionally substituted 5-membered heteroaryl ring having1-4 heteroatoms selected from O, S, or N, or an optionally substituted pyran-4-one-yl.

[0088] In still other embodiments of the present invention, R^z is an optionally substituted oxazolyl ring. In other embodiments, R^Z is –$C(O)R^3$, wherein R^3 is an optionally substituted C_1-C_6 alkyl group. In other embodiments, R^Z is –$C(O)R^3$, wherin R^3 is an optionally substituted C_1-C_6 alkyl group or an aryl ring optionally substituted with 0-5 occurances of Q-R^x.

[0089] In yet other embodiments of the present invention, R^z is an aryl ring optionally substituted with 0-5 occurrences of Q-R^x. Or R^z is R'.

[0090] In other embodiments of the present invention, R^z is $C(O)R^3$ where R^3 is an optionally substituted C_1-C_6 alkyl group, an aryl ring optionally substituted with 0-5 occurrences of Q-R^x, an optionally substituted pyran-4-one-yl, or an optionally substituted 5-membered heteroaryl ring having 1-4 heteroatoms selected from O, S, or N.

[0091] In other embodiments of the present invention, R^z is R', -C(O)R^3 where R^3 is an optionally substituted C_1-C_6 alkyl group, an aryl ring optionally substituted with 0-5 occurances of Q-R^x, an optionally substituted pyran-4-one-yl, or an optionally substituted 5-membered heteroaryl ring having 1-4 heteroatoms selected from O, S, or N.

[0092] In other embodiments of the present invention, R^z is R', C(O)R^3 where R^3 is –N(R')$_2$, C(O)R^3 where R^3 is an optionally substituted C_1-C_6 alkyl group, an aryl ring optionally substituted with 0-5 occurances of Q-R^x, an optionally substituted pyran-4-one-yl, or an optionally substituted 5-membered heteroaryl ring having 1-4 heteroatoms selected from O, S, or N.

[0093] In other embodiments, R^Z is –C(O)R^3, C(O)OR^3, CN, or an optionally substituted C_1-C_6 alkyl group where 0-5 carbon atoms have been optionally replaced with O, N, S, or carbonyl. Preferred R^Z groups are as shown below in Table 2.

[0094] Preferred R^Z groups are as shown below in Table 2.

[0095] In still other embodiments of the present invention R^3 is bonded to the carbon atom of the carbonyl group through an atom other than oxygen or nitrogen.

[0096] In yet other embodiments of the present invention, R^3 is further defined as -CF_2H, -CF_3, -$CHCl_2$, -$CHBr_2$, CH_2CN, -CH_2OR', -CH_2SR', -$CH_2N(R')_2$, or as Q-R^X; wherein Q is an optionally substituted C_2-C_6 alkylidene chain wherein up to two non-adjacent methylene units of Q are optionally 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; and each occurrence of R^X is independently selected from R', halogen, NO_2, or CN, provided that Q is bonded to the carbon atom of the carbonyl group through a carbon atom.

[0097] In still other embodiments of the present invention, R^3 is further defined as -CF_2H, -CF_3, -$CHCl_2$, -$CHBr_2$, CH_2CN, -CH_2OR', -CH_2SR', -$CH_2N(R')_2$, or as Q-R^X; wherein Q is a bond, and R^X is an optionally substituted group selected from C_{2-8} aliphatic, C_{6-10} aryl, a heteroaryl ring having 5-10 ring atoms, or a heterocyclyl ring having 3-10 ring atoms.

[0098] In other embodiments, R^3 is 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 -$S(O)_2N(R')_2$.

[0099] In still other preferred embodiments, R^3 is H, Me, CF_3, ethyl, propyl, butyl, pentyl, $CO(C_1\text{-}C_4alkyl)$, $-CONH_2$, $-COO(C_1\text{-}C_4alkyl)$, $-CH_2OH$, $-SO_2NH_2$, $SO_2N(CH_3)_2$, or optionally substituted phenyl. Most preferred R^3 groups include those shown below in Table 2.

[00100] In some embodiments of the present invention, R^4 is hydrogen. In other embodiments R^4 is an optionally substituted C_1-C_6 alkyl group. In yet other embodiments, R^4 is an optionally substituted aryl group. In other embodiments, R^4 is hydrogen or an optionally substituted C_1-C_6 alkyl group.

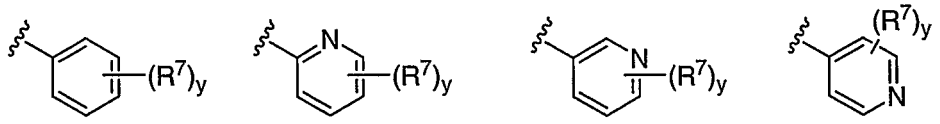
[00101] In preferred embodiments, R^4 is hydrogen, halogen, CN, NO_2, or an optionally substituted group selected from $C_{1\text{-}6}alkyl$, aryl, $aryl(C_{1\text{-}6})alkyl$, $-N(R')_2$, $-CH_2N(R')_2$, OR', $-CH_2OR'$, SR', $-CH_2SR'$, COOR', -NRCOR', $-(CH_2)_2N(R')_2$, $-(CH_2)_2OR'$, $-(CH_2)_2SR'$, -COR', $-CON(R')_2$, or $-S(O)_2N(R')_2$. In more preferred embodiments, R^4 is 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. Most preferred R^4 groups include those shown below in Table 2.

[00102] As described generally above for the present invention, ring A is a 5-6 membered aryl ring having 0-5 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 $-R^8$.

[00103] In other embodiments of the present invention, ring A is 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 $-R^8$.

[00104] In certain embodiments of the present invention, 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, ring A is optionally substituted phenyl, 2-pyridyl, 3-pyridyl, or 4-pyridyl:

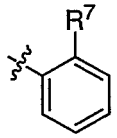


a **b** **c** **d**

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

[00105] In preferred embodiments, y is 0-3. In other preferred embodiments, y is 0 and ring A is unsubstituted.

[00106] In another embodiment of the present invention, ring A is:



aa.

[00107] In yet other embodiments of the present invention, ring A is an optionally substituted piperidyl ring or an optionally substituted pyrrolyl ring.

[00108] In certain embodiments of the present invention, ring A is a phenyl ring optionally substituted with one or more halogens, an optionally substituted piperidyl ring, or an optionally substituted pyrrolyl ring.

[00109] In other embodiments of the present invention, ring A is a phenyl ring optionally substituted with 1-5 occurrences of $Q\text{-}R^x$, wherein Q is selected from a bond, O, N, and R^x is R'.

[00110] In yet other embodiments of the present invention, ring A is a phenyl ring optionally substituted with 1-5 occurrences of $Q\text{-}R^x$, an optionally substituted imidazolyl ring, an optionally substituted pyrazolyl ring, an optionally substituted piperidyl ring, an optionally substituted pyrrolyl ring, or an optionally substituted indolyl ring.

[00111] In yet other embodiments of the present invention, ring A is a phenyl ring optionally substituted with one or more halogens, an optionally substituted piperidyl ring, an optionally substituted pyrrolyl ring. Or, ring A is a phenyl ring optionally substituted with 1-5 occurrences of $Q\text{-}R^x$ where Q is selected from a bond, O, N and R^x is R'.

[00112] In certain embodiments of the present invention, ring A is a phenyl ring optionally substituted with one or more halogens, an optionally substituted piperidyl ring, an optionally substituted pyrrolyl ring, an optionally substituted thienyl ring, or ring A is a phenyl ring

optionally substituted with 1-5 occurances of Q-R^x where Q is selected from a bond, O, N and R^x is selected from R'.

[00113] In preferred embodiments, R^7 groups are hydrogen, halogen, CN, NO_2, or an optionally substituted group selected from C_{1-6}alkyl, haloalkyl, 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, -CHF_2, -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 any one of those shown below in Table 2. In preferred embodiments, R^8 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')$_2$, or -S(O)$_2$N(R')$_2$. In more preferred embodiments, 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_2NH_2, SO_2N(CH_3)$_2$, or optionally substituted phenyl. Most preferred R^8 groups include those shown below in Table 2.

[00114] In one embodiment of the present invention, ring A is phenyl having up to one Q-R^X substituent, 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 replaced by CO, CO_2, COCO, CONR, OCONR, NRNR, NRNRCO, NRCO, $NRCO_2$, NRCONR, SO, SO_2, $NRSO_2$, SO_2NR, $NRSO_2$NR, O, S, or NR; and each occurrence of R^X is independently selected from R', halogen, NO_2, or CN. Preferably, ring A is a 2-substituted phenyl, wherein said substituent is Q-R^X, wherein Q is a bond.

[00115] In another embodiment of the present invention, ring A is optionally substituted phenyl, 5 membered heteroaryl, or 6-membered heterocyclyl ring. Preferred ring A includes Preferred ring A includes phenyl or a 5-membered heteroaryl having 1 heteroatom, wherein said ring A has up to two Q- R^X substituents, 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 replaced by CO, CO_2, COCO, CONR, OCONR, NRNR, NRNRCO, NRCO, $NRCO_2$, NRCONR, SO, SO_2, $NRSO_2$, SO_2NR, $NRSO_2$NR, O, S, or NR; and each occurrence of R^X is independently selected from R', halogen, NO_2, or CN. Or, and ring A is optionally substituted phenyl, piperidyl, or pyrrolyl.

Preferred embodiments are those wherein ring A has up to two substituents selected from halo, OH, OCF_3, or C_{1-4} aliphatic. Or, ring A is phenyl, 1-piperidyl, or 1-pyrrolyl, wherein ring A has up to two substituents selected from halo or OH.

[00116] In another embodiment of the present invention, ring A is optionally substituted phenyl, 5-membered heteroaryl, or six-membered heterocyclyl. Preferred ring A include phenyl having up to one Q-R^X substituent, 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 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; and each occurrence of R^X is independently selected from R', halogen, NO_2, or CN. Or, ring A is phenyl optionally substituted with halo, or OH.

[00117] In another embodiment of the present invention, ring A is optionally subsituted phenyl, 5-6 membered heterocyclic or heteroaryl ring. Preferred ring A includes phenyl or a 5-membered heteroaryl having 1 heteroatom, wherein said ring A has up to two Q- R^X substituents, 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 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; and each occurrence of R^X is independently selected from R', halogen, NO_2, or CN. Or, ring A is phenyl, 1-pyrrolidyl, or 1-pyrrolyl, having up to two substituents selected from halo, OH, OCF_3, or C_{1-4} aliphatic.

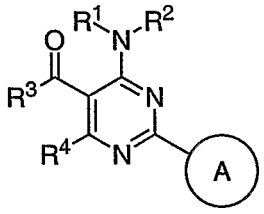
[00118] In another embodiment, ring A is phenyl having up to two Q- R^X substituents, wherein Q is a bond or is a C_1-C_6 alkylidene chain wherein up to two non-adjacent methylene units of Q are optionally replaced by CO, CO_2, COCO, CONR, OCONR, NRNR, NRNRCO, NRCO, $NRCO_2$, NRCONR, SO, SO_2, $NRSO_2$, SO_2NR, $NRSO_2NR$, O, S, or NR; and each occurrence of R^X is independently selected from R', halogen, NO_2, or CN. Preferably, ring A is phenyl having up to two substituents selected from halo, OH, OMe, OCF_3, or C_{1-4} aliphatic.

[00119] In another embodiment, ring A is aryl or 5-10 membered heteroaromatic or heterocyclyl, having up to four Q- R^X substituents, 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 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; and each occurrence of R^X is independently selected from R', halogen, NO_2, or CN. Preferably, ring A is phenyl, indolyl, or pyrrolyl having up to two

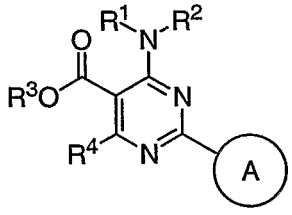
substituents selected from halo, OH, OMe, OCF_3, or C_{1-4} aliphatic. Or, ring A is phenyl or pyrrolyl having up to two substituents selected from halo, OH, OMe, OCF_3, or C_{1-4} aliphatic. Or, ring A is phenyl or pyrrolyl having up to two substituents selected from halo, OH, OMe, OCF_3, or C_{1-4} aliphatic.

[00120] In another embodiment, ring A ring A is phenyl, 1-piperidinyl, 1-pyrrolyl, thienyl, 2-methyl-indol-1-yl, 3,4,-methyldioxyphenyl, having up to two R^7 substituents selected from H, Cl, Br, F, CF_3, CN, Me, -SMe, Et, -OH, $-OCH_3$, $-OCF_3$, $-C(O)CH_3$, or phenyloxy. Preferably, ring A is phenyl, 1-piperidinyl, 1-pyrrolyl, thienyl, 2-methyl-indol-1-yl, 3,4,-methyldioxyphenyl, having up to two R^7 substituents selected from H, Cl, Br, F, CF_3, CN, Me, -SMe, Et, -OH, $-OCH_3$, $-OCF_3$, $-C(O)CH_3$, or phenyloxy. Or, ring A is phenyl, 1-piperidinyl, 1-pyrrolyl, thienyl, 2-methyl-indol-1-yl, 3,4,-methyldioxyphenyl, having up to two R^7 substituents selected from H, Cl, Br, F, CF_3, Me, Et, -OH, $-OCH_3$, $-OCF_3$, or phenyloxy. Or, ring A is phenyl, 1-piperidyl or 1-pyrrolyl, having up to two R^7 substituents selected from H, Cl, Br, F, CF_3, Me, -OH, $-OCF_3$, OR phenyloxy.

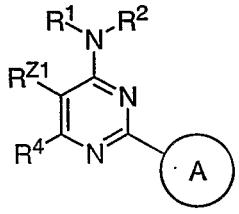
[00121] In another embodiment, the present invention provides compounds of formula **IA**, formula **IB**, or formula **IC**:



IA



IB



IC

wherein R^{Z1} is $-SO_2R'$, $-SO_2NHR'$, $-NHSO_2R'$, $-P(O)(OR')_2$, $-C(O)N(CN)R'$, an optionally substituted 5-membered heteroaryl ring having1-4 heteroatoms selected from O, S, or N, or an optionally substituted pyran-4-one-yl.

[00122] In one embodiment of compounds of formula **IA**, R^1 and R^2 both are optionally substituted C_{1-4} aliphatic, R^3 is C_{1-4} aliphatic, R^4 is hydrogen, and ring A is optionally substituted phenyl. Preferred R^1 and R^2 include methyl, ethyl, or propyl. Preferred R^3 include ethyl, propyl or butyl. Preferred ring A includes phenyl having up to one Q- R^X substituent, 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 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; and each occurrence of R^X is independently selected from R', halogen, NO_2, or CN.

[00123] In one embodiment of compounds of formula **IB**, R^1 and R^2 both are optionally substituted C_{1-4} aliphatic, R^3 is C_{1-4} aliphatic, R^4 is hydrogen, and ring A is optionally substituted 5-6 membered aryl, heteroaryl, or heterocyclic ring. Preferred R^1 and R^2 include methyl, ethyl, or propyl. Preferred R^3 include ethy, propyl or butyl. Preferred ring A includes phenyl or a 5-6 membered heteroaryl or heterocyclyl ring having one nitrogen ring atom, wherein ring A has up to one Q- R^X substituent, 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 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; and each occurrence of R^X is independently selected from R', halogen, NO_2, or CN.

[00124] In one embodiment of compounds of formula **IC**, R^1 and R^2 both are optionally substituted C_{1-4} aliphatic, R^{Z1} is an optionally substituted 5-membered heteroaryl ring having up to 2 heteroatoms selected from O and N, R^4 is hydrogen, and ring A is an optionally substituted phenyl. Preferred R^1 and R^2 include methyl, ethyl, or propyl. Preferred ring A includes phenyl having up to one Q- R^X substituent, 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 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; and each occurrence of R^X is independently selected from R', halogen, NO_2, or CN.

[00125] In one embodiment of compounds of formula **IA**, R^1 and R^2 are both C_{1-4} aliphatic or R^1 and R^2 taken together form a 5-6 membered heterocyclic ring, R^3 is optionally substituted C_{1-4} aliphatic or aryl, R^4 is hydrogen, and ring A is optionally substituted phenyl. Preferred R^1 and R^2 include methyl, ethyl, or propyl; or R^1 and R^2, taken together form an optionally substiuted 1-pyrrolidinyl or 1-piperidinyl. Preferred R^3 includes optionally substituted ethyl, propyl, butyl, or phenyl. Preferred ring A include phenyl having up to one Q-R^X substituent, 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 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; and each occurrence of R^X is independently selected from R', halogen, NO_2, or CN.

[00126] In another embodiment, R^1 and R^2 both are methyl or ethyl, R^3 is ethyl or propyl, R^4 is hydrogen, and ring A is a 2-substituted phenyl, wherein said substituent is Q-R^X, wherein Q is a bond.

[00127] In one embodiment of formula **IB**, R^1 and R^2 are both C_{1-4} alphatic or R^1 and R^2 taken together form a 3-6 membered heterocyclic ring having up to 2 heteroatoms, R^3 is optionally C_{1-4} aliphatic, R^4 is hydrogen, and ring A is optionally substituted phenyl, 5 membered heteroaryl, or 6-membered heterocyclyl. Preferred R^1 and R^2 include methyl, ethyl, propyl; or R^1 and R^2, taken together form an optionally substituted 1-azetidinyl, 1-pyrrolidinyl, 1-piperidinyl, or 1-piperazinyl. Preferred R^3 includes optionally substituted ethyl, propyl, or butyl. Preferred ring A includes phenyl or a 5-membered heteroaryl having 1 heteroatom, wherein said ring A has up to two Q- R^X substituents, 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 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; and each occurrence of R^X is independently selected from R', halogen, NO_2, or CN.

[00128] In one embodiment, R^1 and R^2 both are methyl or ethyl, or R^1 and R^2, taken together form a 1-pyrrolidinyl ring, R^3 is ethyl or propyl, R^4 is hydrogen, and ring A is optionally substituted phenyl, piperidyl, or pyrrolyl. Preferred embodiments are those wherein ring A has up to two substituents selected from halo, OH, OCF_3, or C_{1-4} aliphatic.

[00129] In one embodiment, R^1 and R^2 both are methyl or ethyl, R^3 is ethyl, R^4 is hydrogen, and ring A is phenyl, 1-piperidyl, or 1-pyrrolyl, wherein ring A has up to two substituents selected from halo or OH.

[00130] In one embodiment of formula **IC**, R^1 and R^2 are both C_{1-4} alphatic, R^{Z1} is a 5-membered heteraryl having up to two heteroatoms, R^4 is hydrogen, and and ring A is an optionally substituted phenyl. Preferred R^1 and R^2 include methyl, ethyl, or propyl. Preferred R^{Z1} includes optionally substituted oxazolyl. Preferred ring A includes phenyl having up to one Q- R^X substituent, 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 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; and each occurrence of R^X is independently selected from R', halogen, NO_2, or CN.

[00131] In one embodiment of compounds of formula **IA**, R^1 and R^2 are both C_{1-4} alphatic, R^3 is optionally substituted C_{1-4} aliphatic, R^4 is hydrogen, and ring A is optionally substituted phenyl. Preferred R^1 and R^2 include methyl or ethyl. Preferred R^3 includes optionally substituted ethyl, or propyl. Preferred ring A include phenyl having up to one Q-R^X substituent, 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 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; and each occurrence of R^X is independently selected from R', halogen, NO_2, or CN.

[00132] In one embodiment of compounds of formula **IA**, R^1 and R^2 are both methyl or ethyl, R^3 is ethyl or propyl, R^4 is hydrogen, and ring A is phenyl optionally substituted with halo, or OH.

[00133] In one embodiment of formula **IB**, R^1 and R^2 are both C_{1-4} alphatic or R^1 and R^2 taken together form a 4-6 membered heterocyclic ring having up to 2 nitrogen heteroatoms, R^3 is optionally substituted C_{1-4} aliphatic, R^4 is hydrogen, and ring A is optionally substituted phenyl or 5-membered heteroaryl. Preferred R^1 and R^2 include methyl, ethyl, propyl; or R^1 and R^2, taken together form an optionally substituted 1-pyrrolidinyl or 1-piperazinyl. Preferred R^3 includes optionally substituted ethyl, propyl, or butyl. Preferred ring A includes phenyl or a 5-membered heteroaryl having 1 heteroatom, wherein said ring A has up to two Q- R^X substituents, 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 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; and each occurrence of R^X is independently selected from R', halogen, NO_2, or CN.

[00134] In one embodiment, R^1 and R^2 both are methyl or ethyl, or R^1 and R^2, taken together form a 1-pyrrolidinyl ring, R^3 is ethyl or propyl, R^4 is hydrogen, and ring A is optionally substituted phenyl, piperidyl, or pyrrolyl. Preferred embodiments are those wherein ring A has up to two substituents selected from halo, OH, OCF_3, or C_{1-4} aliphatic.

[00135] In one embodiment, R^1 and R^2 both are methyl or ethyl, R^3 is ethyl, R^4 is hydrogen, and ring A is phenyl, 1-piperidyl, or 1-pyrrolyl, wherein ring A has up to two substituents selected from halo or OH.

[00136] In one embodiment of compounds of formula **IA**, R^1 and R^2 are both C_{1-4} alphatic or R^1 and R^2 taken together form a 4-6 membered heterocyclic ring, R^3 is optionally substituted C_{1-4} aliphatic or aryl, R^4 is hydrogen, and ring A is optionally substituted phenyl, 5-membered heteroaryl, or six-membered heterocyclyl. Preferred R^1 and R^2 include methyl, ethyl, or propyl; or R^1 and R^2, taken together form a 4-6 membered heterocyclic ring having up to 2 nitrogen heteroatoms, including 1-azetidinyl, 1-pyrrolidinyl, or or 2,5-dihydropyrrolyl. Preferred R^3 includes optionally substituted ethyl, propyl, butyl, or phenyl. Preferred ring A include phenyl having up to one $Q\text{-}R^X$ substituent, 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 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; and each occurrence of R^X is independently selected from R', halogen, NO_2, or CN.

[00137] In one embodiment of compounds of formula **IA**, R^1 and R^2 are both methyl or ethyl, R^3 is ethyl or propyl, R^4 is hydrogen, and ring A is phenyl optionally substituted with halo, or OH.

[00138] In one embodiment of formula **IB**, R^1 and R^2 are both C_{1-4} alphatic or R^1 and R^2 taken together form a 4-6 membered heterocyclic ring having up to 2 nitrogen heteroatoms, R^3 is optionally substituted C_{1-4} aliphatic, R^4 is hydrogen, and ring A is optionally subsituted phenyl, 5-6 membered heterocyclic or heteroaryl ring. Preferred R^1 and R^2 include methyl, ethyl, propyl; or R^1 and R^2, taken together form an optionally substituted 1-azetidinyl, 1-pyrrolidinyl, 2,5-dihydro-1H-pyrrolyl, 1-piperidinyl, or 1-piperazinyl. Preferred R^3 includes optionally substituted ethyl, propyl, or butyl. Preferred ring A includes phenyl or a 5-membered heteroaryl

having 1 heteroatom, wherein said ring A has up to two Q- R^X substituents, 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 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; and each occurrence of R^X is independently selected from R', halogen, NO_2, or CN.

[00139] In one embodiment of formula **IB**, R^1 and R^2 are both C_{1-4} alphatic, R^3 is ethyl, propyl, or butyl, R^4 is hydrogen, ring A is phenyl, 1-pyrrolidyl, or 1-pyrrolyl, having up to two substituents selected from halo, OH, OCF_3, or C_{1-4} aliphatic.

[00140] In one embodiment of formula **IB**, R^1 and R^2 are both methyl or ethyl, R^3 is ethyl, R^4 is hydrogen, ring A is phenyl, 1-pyrrolidyl, or 1-pyrrolyl, having up to two substituents selected from halo, OH, OCF_3, or C_{1-4} aliphatic. Preferred ring A in this embodiment includes optionally substituted 1-piperidyl or 1-pyrrolyl.

[00141] In one embodiment of formula **IC**, R^1 and R^2 are both C_{1-4} alphatic, R^{Z1} is a 5-membered heteraryl having up to two heteroatoms, R^4 is hydrogen, and and ring A is an optionally substituted phenyl. Preferred R^1 and R^2 include methyl, ethyl, or propyl. Preferred R^{Z1} includes optionally substituted oxazolyl, cyano, or aliphatic-oxymethyl. Preferred ring A includes phenyl having up to one Q- R^X substituent, 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 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; and each occurrence of R^X is independently selected from R', halogen, NO_2, or CN.

[00142] In one embodiment, R^1 and R^2 are both C_{1-4} aliphatic, R^3 is R^3 is C_{1-4} aliphatic, R^4 is hydrogen, and ring A is phenyl having up to two Q- R^X substituents, 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 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; and each occurrence of R^X is independently selected from R', halogen, NO_2, or CN.

[00143] In one embodiment, R^1 and R^2 are both methyl or ethyl, R^3 is propyl, n-butyl, or isobutyl, R^4 is hydrogen, and ring A is phenyl having up to two substituents selected from halo, OH, OMe, OCF_3, or C_{1-4} aliphatic.

[00144] In one embodiment, R^1 and R^2 are both C_{1-4} aliphatic, or R^1 and R^2 together form an optionally substituted 5-6 membered heterocyclic ring having up to 2 heteroatoms, R^3 is C_{1-4} aliphatic, R^4 is hydrogen, and ring A is aryl or 5-10 membered heteroaromatic or heterocyclyl, having up to four Q- R^X substituents, 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 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; and each occurrence of R^X is independently selected from R', halogen, NO_2, or CN.

[00145] In one embodiment, R^1 and R^2 are both C_{1-4} aliphatic, or R^1 and R^2 together form an optionally substituted 5-6 membered heterocyclic ring having up to 2 heteroatoms, R^3 is C_{1-4} aliphatic, R^4 is hydrogen, and ring A is phenyl, indolyl, or pyrrolyl having up to two substituents selected from halo, OH, OMe, OCF_3, or C_{1-4} aliphatic.

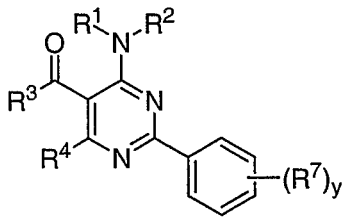
[00146] In one embodiment, R^1 and R^2 are both methyl or ethyl, or R^1 and R^2 together form an optionally substituted pyrrolidinyl or piperidinyl ring, R^3 is methyl or ethyl, R^4 is hydrogen, and ring A is phenyl or pyrrolyl having up to two substituents selected from halo, OH, OMe, OCF_3, or C_{1-4} aliphatic.

[00147] In one embodiment, R^1 and R^2 are both methyl or ethyl, or R^1 and R^2 together form a pyrrolidinyl or 3-hydroxy-piperidinyl ring, R^3 is methyl or ethyl, R^4 is hydrogen, and ring A is phenyl or pyrrolyl having up to two substituents selected from halo, OH, OMe, OCF_3, or C_{1-4} aliphatic.

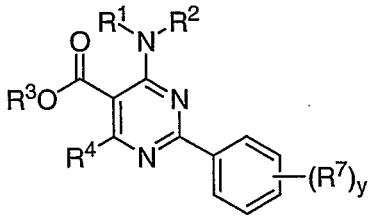
[00148] In one embodiment of formula **IC**, R^1 and R^2 are both C_{1-4} aliphatic, R^{Z1} is optionally substituted phenyl or 5-membered heteroaromatic having up to 3 heteroatoms, R^4 is hydrogen, and ring A is phenyl having up to two substituents selected from halo, OH, OMe, OCF_3, or C_{1-4} aliphatic. Or, R^{Z1} in this embodiment is -C(O)NH(C_{1-4} aliphatic).

[00149] In one embodiment of formula I, R^1 and R^2 are both methyl or ethyl, R^{Z1} is optionally substituted phenyl or oxadiazolyl, R^4 is hydrogen, and ring A is phenyl having up to two substituents selected from halo, OH, OMe, OCF_3, or C_{1-4} aliphatic.

[00150] In another embodiment, ring A is optionally substituted phenyl, and compounds of formula **IIA** or formula **IIB** are provided:



IIA



IIB

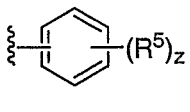
wherein R^1, R^2, R^3, R^7, and y are defined generally above and in subsets herein.

[00151] In certain preferred embodiments, neither R^1 nor R^2 is hydrogen. In certain other embodiments, 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 or an optionally substituted C_{1-4}aliphatic group, wherein one or more methylene units in the C_{1-4}aliphatic group are optionally replaced with NR, O, (CO)O, O(CO), NR(CO), (CO)NR, SO_2(NR), or (NR)SO_2. In more preferred embodiments, 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 replaced with NR, O, (CO)O, O(CO), NR(CO), (CO)NR, SO_2(NR), or (NR)SO_2. In yet other preferred embodiments, 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 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 include those shown below in Table 2.

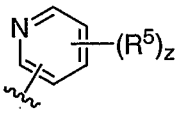
[00152] In other preferred embodiments, one of R^1 or R^2 is hydrogen and the other of R^1 or R^2 is a 5-6 membered aryl ring having 0-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or a 3-7-membered saturated or partially unsaturated ring having 0-3 heteroatoms independently 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 replaced with NR, O, (CO)O, O(CO), NR(CO), (CO)NR, SO_2(NR), or (NR)SO_2.

[00153] 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-

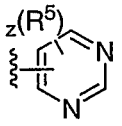
membered saturated or partially unsaturated ring having 0-3 heteroatoms independently selected from N, O, or S, preferred R^1 and R^2 groups are selected from:



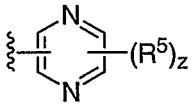
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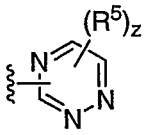
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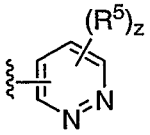
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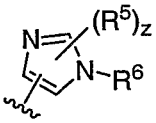
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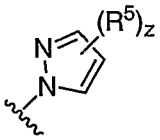
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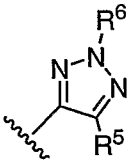
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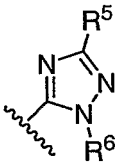
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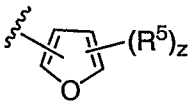
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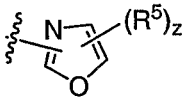
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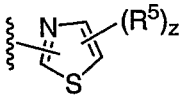
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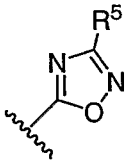
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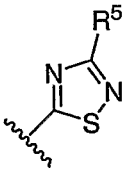
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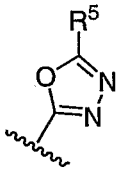
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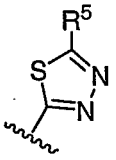
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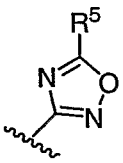
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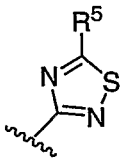
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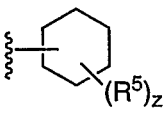
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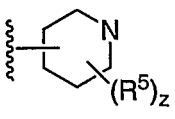
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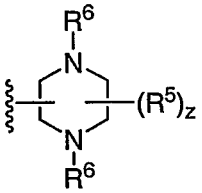
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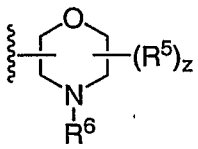
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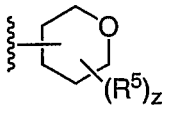
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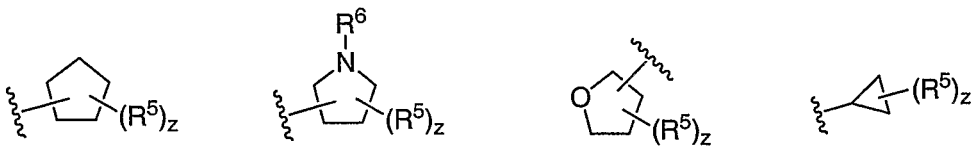
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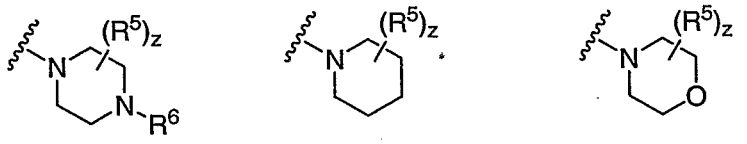
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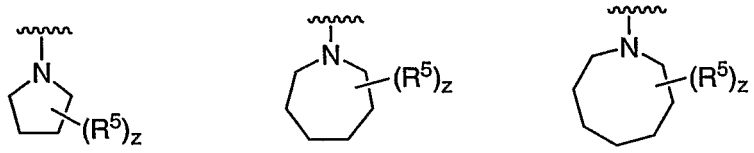
y **z** **aa** **bb**

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

[00154] In still other embodiments, for compounds of formula **IIA** or formula **IIB**, 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, sulfur, 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 R^5 and R^6 are as previously defined and z is 0-4.

[00155] In other preferred embodiments, for compounds of formula **IIA** or formula **IIB**, 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**).

[00156] As described generally above, 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. In preferred embodiments, z is 0-2. In other preferred embodiments, z is 0 and the ring is unsubstituted. Preferred R^5 groups, when present, are 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', NRC(O)OR', -(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^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. In preferred embodiments, R^6 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', -C(O)OR', -CON(R')$_2$, or -S(O)$_2$N(R')$_2$. In more preferred embodiments, 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 include those shown below in Table 2.

[00157] In still other embodiments, for compounds of formula **IIA** as described generally above and in subsets herein R^3 is bonded to the carbon atom of the carbonyl group through an atom other than oxygen or nitrogen.

[00158] In yet other embodiments, for compounds of general formula **IIA** or formula **IIB**, R^3 is further defined as -CF_2H, -CF_3, -$CHCl_2$, -$CHBr_2$, CH_2CN, -CH_2OR', -CH_2SR', -CH_2N(R')$_2$, or as Q-R^X; wherein Q is an optionally substituted C_2-C_6 alkylidene chain wherein up to two non-adjacent methylene units of Q are optionally replaced by CO, CO_2, COCO, CONR, OCONR, NRNR, NRNRCO, NRCO, $NRCO_2$, NRCONR, SO, SO_2, $NRSO_2$, SO_2NR, $NRSO_2$NR, O, S, or NR; and each occurrence of R^X is independently selected from R', halogen, NO_2, or CN, provided that Q is bonded to the carbon atom of the carbonyl group through a carbon atom.

[00159] In still other preferred embodiments, for compounds of general formula **IIA** or formula **IIB**, R^3 is further defined as Q-R^X; wherein Q is a bond, and R^X is an optionally substituted group selected from C_{2-8} aliphatic, C_{6-10} aryl, a heteroaryl ring having 5-10 ring atoms, or a heterocyclyl ring having 3-10 ring atoms.

[00160] In other preferred embodiments, R^3 is an optionally substituted group selected from C_{1-6}alkyl, aryl, aryl(C_{1-6})alkyl, -$CH_2N(R')_2$, -CH_2OR', -CH_2SR', -$(CH_2)_2N(R')_2$, -$(CH_2)_2OR'$, or -$(CH_2)_2SR'$.

[00161] In still other preferred embodiments, for compounds of general formula **IIA** or formula **IIB**, R^3 is further defined as -CF_2H, -CF_3, -$CHCl_2$, -$CHBr_2$, CH_2CN, -CH_2OR', -CH_2SR', -$CH_2N(R')_2$, or as Q-R^X; wherein Q is a bond, and R^X is an optionally substituted group selected from C_{2-8} aliphatic, C_{6-10} aryl, a heteroaryl ring having 5-10 ring atoms, or a heterocyclyl ring having 3-10 ring atoms.

[00162] In other preferred embodiments, R^3 is 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 -$S(O)_2N(R')_2$.

[00163] In still other preferred embodiments, R^3 is 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^3 groups include those shown below in Table 2.

[00164] In preferred embodiments, 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 -$S(O)_2N(R')_2$. In more preferred embodiments, R^4 is 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^4 groups include those shown below in Table 2.

[00165] 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 hydrogen, halogen, CN, NO_2, or an optionally substituted group selected from C_{1-6}alkyl, haloalkyl, 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, R^7 groups are

each independently H, Cl, Br, F, CF_3, -CHF_2, 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, -OCF_3, -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.

[00166] In another embodiment, compounds of formula **IIB** have at least one, and preferably all, of the following features:

a. R^1 is hydrogen or C_{1-6} aliphatic and R^2 is optionally substituted C_{1-6} aliphatic, or R^1 and R^2 taken together form an optionally substituted 4-7 membered saturated ring, wherein said ring optionally contains a second heteroatom selected from O or N;

b. R^3 is methyl, ethyl, propyl, isopropyl, butyl, -CH_2CCH, -$CH_2C(O)CH_3$, pyran-2-ylmethyl, optionally substituted phenyl, cyclopentyl, cyclohexyl, 3-chlorophenyl, or 3-tolyl;

c. ring A is phenyl, 1-piperidinyl, 1-pyrrolyl, thienyl, 2-methyl-indol-1-yl, 3,4,-methyldioxyphenyl, having up to two R^7 substituents selected from H, Cl, Br, F, CF_3, CN, Me, -SMe, Et, -OH, -OCH_3, -OCF_3, -$C(O)CH_3$, or phenyloxy.

[00167] In another embodiment, compounds of formula **IIB** have at least one, and preferably all, of the following features:

a. R^1 is hydrogen or C_{1-6} aliphatic and R^2 is optionally substituted C_{1-6} aliphatic, furanylmethyl, allyl, or benzyl, or R^1 and R^2 taken together is 4-carboethoxy-1-piperidinyl, 2-methylpiperidinyl, 2-hydroxymethylpiperidinyl, 3-hydroxypiperidinyl, 4-isobutylcarbamate-1-piperidinyl, 3-diethylaminocarbonyl-1-piperidinyl, 1-piperidyl, 1-pyrrolidinyl, 2-carboethoxypyrrolidinyl, N-morpholino, 3,5-dimethyl-N-morpholino, 4-methylpiperazinyl, 4-hydroxyethyl piperazinyl, 1-pyrrolyl, 2,4-dihydro-1-pyrrolyl, 1-azetidinyl, or 1-azepanyl;

b. R^3 is methyl, ethyl, propyl, isopropyl, butyl, -CH_2CCH, -$CH_2C(O)CH_3$, pyran-2-ylmethyl, optionally substituted phenyl, cyclopentyl, cyclohexyl, 3-chlorophenyl, or 3-tolyl;

c. ring A is phenyl, 1-piperidinyl, 1-pyrrolyl, thienyl, 2-methyl-indol-1-yl, 3,4,-methyldioxyphenyl, having up to two R^7 substituents selected from H, Cl, Br, F, CF_3, -CHF_2, CN, Me, -SMe, Et, -OH, -OCH_3, -OCF_3, -$C(O)CH_3$, or phenyloxy.

[00168] In another embodiment, compounds of formula **IIB** have at least one, and preferably all, of the following features:

a. R^1 is hydrogen or C_{1-4} aliphatic and R^2 is C_{1-4} aliphatic, furanylmethyl, allyl, or benzyl, or R^1 and R^2 taken together is 4-carboethoxy-1-piperidinyl, 2-methylpiperidinyl, 4-isobutylcarbamate-1-piperidinyl, 3-diethylaminocarbonyl-1-piperidinyl, 1-piperidyl, 1-pyrrolidinyl, 2-carboethoxypyrrolidinyl, 4-methylpiperazyl, 2,4-dihydro-1-pyrrolyl, 1-azetidinyl, or 1-azepanyl;

b. R^3 is methyl, ethyl, propyl, butyl, optionally substituted phenyl, cyclopentyl, or 3-tolylmethyl;

c. R^4 is hydrogen;

d. ring A is phenyl, 1-piperidinyl, 1-pyrrolyl, thienyl, 2-methyl-indol-1-yl, 3,4,-methyldioxyphenyl, having up to two R^7 substituents selected from H, Cl, Br, F, CF_3, -CHF_2, Me, Et, -OH, -OCH_3, -OCF_3, or phenyloxy.

[00169] In another embodiment, compounds of formula **IIB** have at least one, and preferably all, of the following features:

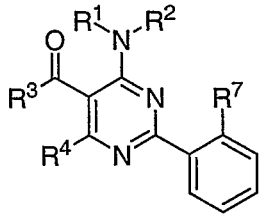
a. R^1 is hydrogen or C_{1-4} aliphatic and R^2 C_{1-4} aliphatic, furanylmethyl, allyl, or benzyl, or R^1 and R^2 taken together is 4-carboethoxy-1-piperidinyl, 2-methylpiperidinyl, 1-piperidinyl, 1-pyrrolidinyl, 4-methylpiperazyl, 2,4-dihydro-1-pyrrolyl, or 1-azetidinyl;

b. R^3 is methyl, ethyl, or propyl;

c. R^4 is hydrogen;

d. ring A is phenyl, 1-piperidyl or 1-pyrrolyl, having up to two R^7 substituents selected from H, Cl, Br, F, CF_3, -CHF_2, Me, -OH, -OCF_3, phenyloxy,

[00170] In yet other preferred embodiments y is 1 and compounds have the general formula **IIIA**:



IIIA

wherein R^1, R^2, R^3 and R^4 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 $-S(O)_2N(R')_2$.

[00171] In another embodiment, compounds have the general formula IIIA, wherein R^7 is hydrogen.

[00172] In still other preferred embodiments compounds of the invention are defined according to formula **IIIA** 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 replaced with NR, O, (CO)O, O(CO), NR(CO), (CO)NR, SO_2(NR), or (NR)SO_2;

b. R^3 is bonded to the carbon atom of the carbonyl group through an atom other than oxygen or nitrogen; or

c. 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 $-S(O)_2N(R')_2$.

[00173] In still other preferred embodiments compounds of the invention are defined according to formula **IIIA** 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 replaced with NR, O, (CO)O, O(CO), NR(CO), (CO)NR, SO_2(NR), or (NR)SO_2;

b. R^3 is $-CF_2H$, $-CF_3$, $-CHCl_2$, $-CHBr_2$, CH_2CN, $-CH_2OR'$, $-CH_2SR'$, $-CH_2N(R')_2$, or as Q-R^X; wherein Q is an optionally substituted C_2-C_6 alkylidene chain wherein up to two non-adjacent methylene units of Q are optionally 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; and each occurrence of R^X is independently selected from R', halogen, NO_2, or CN, provided that Q is bonded to the carbon atom of the carbonyl group through a carbon atom; or

c. 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 $-S(O)_2N(R')_2$.

[00174] In still other preferred embodiments compounds of the invention are defined according to formula **IIIA** 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 replaced with NR, O, (CO)O, O(CO), NR(CO), (CO)NR, SO_2(NR), or (NR)SO_2;

b. R^3 is $-CF_2H$, $-CF_3$, $-CHCl_2$, $-CHBr_2$, CH_2CN, $-CH_2OR'$, $-CH_2SR'$, $-CH_2N(R')_2$, or as Q-R^X; wherein Q is a bond, and R^X is an optionally substituted group selected from C_{2-8} aliphatic, C_{6-10} aryl, a heteroaryl ring having 5-10 ring atoms, or a heterocyclyl ring having 3-10 ring atoms; or

c. 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 $-S(O)_2N(R')_2$.

[00175] In still other preferred embodiments compounds of the invention are defined according to formula **IIIA** 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 replaced with NR, O, (CO)O, O(CO), NR(CO), (CO)NR, SO_2(NR), or (NR)SO_2;

b. R^3 is 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')$_2$; or

c. 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')$_2$.

[00176] In still other preferred embodiments compounds of the invention are defined according to formula **IIIA** 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)$_2$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. R^3 is 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;

c. R^4 is 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; or

d. R^7 is Cl, Br, F, CF_3, -CHF_2, 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.

[00177] In still other preferred embodiments compounds of the invention are defined according to formula **IIIA** 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. R^3 is 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;

c. R^4 is 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; or

d. R^7 is hydrogen.

[00178] In another embodiment, compounds of formula **IIIA** have at least one, and preferably all, of the following features:

a. R^1 and R^2 are both methyl, or R^1 and R^2 taken together form 1-pyrrolidinyl, N-morpholinyl, 1-piperidyl, or 4-methyl piperidyl;

b. R^7 is hydroxy, methoxy, or hydrogen;

c. R^4 is hydrogen; and

d. R^3 is ethyl, propyl, isopropyl, butyl, isobutyl, pentyl, but-1-en-4-yl, cyclopentylethyl, or phenyl.

[00179] In another embodiment, compounds of formula **IIIA** have at least one, and preferably all, of the following features:

a. R^1 and R^2 are both methyl, or R^1 and R^2 taken together form 1-pyrrolidinyl, N-morpholinyl, 1-piperidyl, or 4-methyl piperidyl;

b. R^7 is hydroxy or hydrogen;

c. R^4 is hydrogen; and

d. R^3 is ethyl, propyl, isopropyl, butyl, isobutyl, pentyl, but-1-en-4-yl, cyclopentylethyl, or phenyl.

[00180] In another embodiment, compounds of formula **IIIA** have at least one, and preferably all, of the following features:

a. R^1 and R^2 are both methyl;

b. R^7 is hydroxy;

c. R^4 is hydrogen; and

d. R^3 is ethyl, propyl, isopropyl, butyl, isobutyl, pentyl, or but-1-en-4-yl .

[00181] In another embodiment, compounds of formula **IIIA** have at least one, and preferably all, of the following features:

a. R^1 and R^2 are both methyl;

b. R^7 is hydroxy;

c. R^4 is hydrogen; and

d. R^3 is optionally substituted phenyl, preferably, unsubstituted phenyl.

[00182] In another embodiment, compounds of formula **IIIA** have at least one, and preferably all, of the following features:

a. R^1 and R^2 taken together form 1-pyrrolidinyl, N-morpholinyl, 1-piperidyl, or 4-methyl piperidyl;

b. R^7 is hydroxy;

c. R^4 is hydrogen; and

d. R^3 is ethyl or propyl.

[00183] In another embodiment, compounds of formula **IIIA** have at least one, and preferably all, of the following features:

a. R^1 and R^2 are both methyl, or R^1 and R^2 taken together form 4-methyl piperidinyl;

b. R^7 is hydroxy;

c. R^4 is hydrogen; and

d. R^3 is ethyl, propyl, butyl, isobutyl, or but-1-en-4-yl.

[00184] In another embodiment, compounds of formula **IIIA** have at least one, and preferably all, of the following features:

a. one of R^1 and R^2 is hydrogen, C_{1-4} aliphatic, and the other of R^1 and R^2 is C_{1-4} aliphatic, or benzyl, or R^1 and R^2 taken together form 1-pyrrolidinyl, 1-piperidinyl, or N-morpholinyl ring;

b. R^3 is C_{1-4} aliphatic;

c. R^7 is hydrogen; and

d. R^4 is C_{1-4} aliphatic, phenyl, pyridyl, or thienyl.

[00185] In another embodiment, compounds of formula **IIIA** have at least one, and preferably all, of the following features:

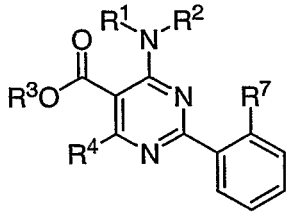
a. one of R^1 and R^2 is hydrogen, methyl, or ethyl, and the other of R^1 and R^2 is methyl, ethyl, or benzyl;

b. R^3 is ethyl or propyl;

c. R^7 is hydrogen; and

d. R^4 is methyl, phenyl, pyridyl, or thienyl.

[00186] In yet other preferred embodiments y is 1 and compounds have the general formula **IIIB**:



IIIB

wherein R^1, R^2, R^3 and R^4 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, $-N(R')_2$, $-CH_2N(R')_2$, $-OR'$, $-CH_2OR'$, $-SR'$, $-CH_2SR'$, $-COOR'$, $-NRCOR'$, $-CON(R')_2$, SO_2R', or $-SO_2N(R')_2$.

[00187] In still other preferred embodiments compounds of the invention are defined according to formula **IIIB**, 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 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 an optionally substituted group selected from C_{1-6}alkyl, aryl, aryl(C_{1-6})alkyl, CH_2OR', $-CH_2SR'$, $-(CH_2)_2N(R')_2$, $-(CH_2)_2OR'$, $-(CH_2)_2SR'$, -COR', or $-CON(R')_2$; 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 $-SO_2N(R')_2$.

[00188] In still other preferred embodiments compounds of the invention are defined according to formula **IIIB**, 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 Me, CF_3, ethyl, propyl, butyl, pentyl, $CO(C_1$-C_4alkyl), $-CONH_2$, $-COO(C_1$-C_4alkyl), $-CH_2OH$, or optionally substituted phenyl or benzyl; and

c. each occurrence of R^4 is 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.

[00189] In still other preferred embodiments compounds of the invention are defined according to formula **IIIB,** 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 Me, CF_3, ethyl, propyl, butyl, pentyl, $CO(C_1\text{-}C_4alkyl)$, $-CONH_2$, $-COO(C_1\text{-}C_4alkyl)$, $-CH_2OH$, or optionally substituted phenyl or benzyl;

c. each occurrence of R^4 is 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, OCF_3, Me, Et, propyl, n-butyl, t-butyl, CN, NO_2, -COOH, NH_2, $-N(CH_3)_2$, $-N(Et)_2$, $-N(iPr)_2$, $-O(CH_2)_2OCH_3$, $-CO(C_1\text{-}C_4alkyl)$, $-CONH_2$, $CON(CH_3)_2$, $-COOCH_3$, -OH, $-SCH_3$, $-CH_2OH$, $-NHCOCH_3$, $-SO_2(C_1\text{-}C_4alkyl)$, $-SO_2NH_2$, $-SO_2N(CH_3)_2$, piperidinyl, piperizinyl, morpholino, or an optionally substituted group selected from $C_{1\text{-}4}$alkoxy, phenyl, phenyloxy, benzyl, or benzyloxy.

[00190] In another embodiment, compounds of formula **IIIB** have at least one, and preferably all, of the following features:

a. one of R^1 and R^2 is hydrogen, $C_{1\text{-}4}$ aliphatic, and the other of R^1 and R^2 is $C_{1\text{-}4}$ aliphatic, or benzyl, or R^1 and R^2 taken together form 1-pyrrolidinyl, 1-piperidinyl, or N-morpholinyl ring;

b. R^3 is $C_{1\text{-}4}$ aliphatic;

c. R^7 is hydrogen; and

d. R^4 is $C_{1\text{-}4}$ aliphatic, phenyl, pyridyl, or thienyl.

[00191] In another embodiment, compounds of formula **IIIB** have at least one, and preferably all, of the following features:

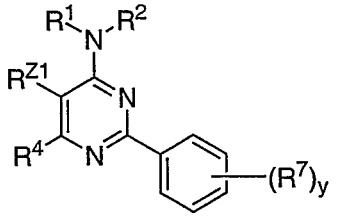
a. one of R^1 and R^2 is hydrogen, methyl, or ethyl, and the other of R^1 and R^2 is methyl, ethyl, or benzyl;

b. R^3 is ethyl or propyl;

c. R^7 is hydrogen; and

d. R^4 is methyl, phenyl, pyridyl, or thienyl.

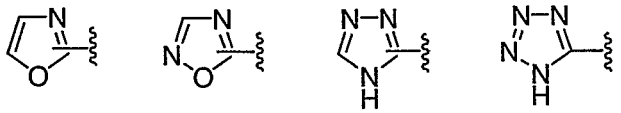
[00192] In another embodiment, ring A is optionally substituted phenyl, and compounds of formula **IIC** are provided:



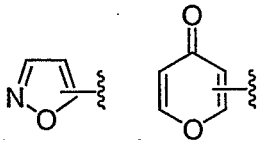
IIC

wherein R^1, R^2, R^3, R^7, and y are defined generally above and in subsets herein; and

wherein R^{Z1} is $-SO_2R'$, $-SO_2NHR'$, $-NHSO_2R'$, $-P(O)(OR')_2$, $-C(O)N(CN)R'$, or an optionally substituted ring selected from:



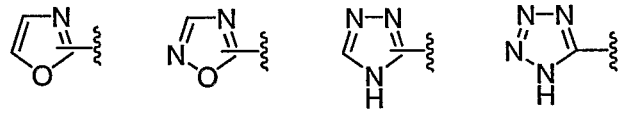
z-a **z-b** **z-c** **z-d**



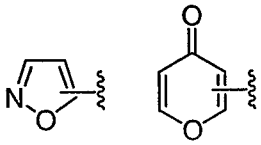
z-e **z-f.**

[00193] In certain embodiments, R^{Z1} is $-SO_2R'$, $-SO_2NHR'$, $-NHSO_2R'$, $-P(O)(OR')_2$, $-C(O)N(CN)R'$. Preferred R^{Z1} include $-SO_2NHR'$, $-NHSO_2R'$, or $-C(O)N(CN)R'$. In certain preferred embodiments, R^{Z1} is $-SO_2R'$, $-NHSO_2R'$, or $-C(O)N(CN)R'$.

In certain other embodiments, R^{Z1} is a ring selected from:



z-a **z-b** **z-c** **z-d**



z-e **z-f;**

wherein said ring is optionally substituted with R' or OR'.

[00194] In still other preferred embodiments compounds of the invention are defined according to formula **IIC**, and one or more of, or all of, R^1, R^2, 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 replaced with NR, O, (CO)O, O(CO), NR(CO), (CO)NR, SO_2(NR), or (NR)SO_2; and

b. 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')$_2$.

[00195] In still other preferred embodiments compounds of the invention are defined according to formula **IIC**, and one or more of, or all of, R^1, R^2, 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)$_2$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. each occurrence of R^4 is 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.

[00196] In still other preferred embodiments compounds of the invention are defined according to formula **IIC**, and one or more of, or all of, R^1, R^2, R^4 or R^7 are further defined according to one or more of, or all of, the following groups:

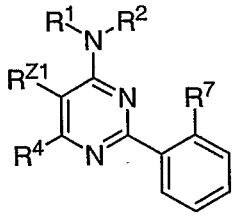
a. R^1 and R^2 are each independently optionally substituted methyl, ethyl, cyclopropyl, n-propyl, propenyl, cyclobutyl, (CO)OCH_2CH_3, (CH_2)$_2$OCH_3, CH_2(CO)OCH_2CH_3, CH_2(CO)OCH_3, CH(CH_3)CH_2CH_3, or t-butyl, or n-butyl;

b. each occurrence of R^4 is 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, $-CH_2OH$, $-NHCOCH_3$, $-SO_2(C_1\text{-}C_4alkyl)$, $-SO_2NH_2$, $-SO_2N(CH_3)_2$, piperidinyl, piperizinyl, morpholino, or an optionally substituted group selected from $C_{1\text{-}4}$alkoxy, phenyl, phenyloxy, benzyl, or benzyloxy; and

c. R^7 is Cl, Br, F, CF_3, OCF_3, Me, Et, propyl, n-butyl, t-butyl, CN, NO_2, -COOH, NH_2, $-N(CH_3)_2$, $-N(Et)_2$, $-N(iPr)_2$, $-O(CH_2)_2OCH_3$, $-CO(C_1\text{-}C_4alkyl)$, $-CONH_2$, $CON(CH_3)_2$, $-COOCH_3$, -OH, $-SCH_3$, $-CH_2OH$, $-NHCOCH_3$, $-SO_2(C_1\text{-}C_4alkyl)$, $-SO_2NH_2$, $-SO_2N(CH_3)_2$, piperidinyl, piperizinyl, morpholino, or an optionally substituted group selected from $C_{1\text{-}4}$alkoxy, phenyl, phenyloxy, benzyl, or benzyloxy.

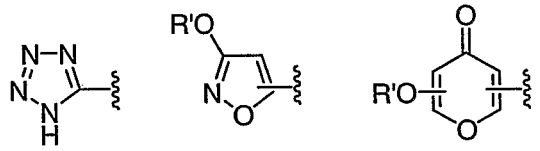
[00197] In another embodiment, ring A is optionally substituted phenyl, and compounds of formula **IIIC** are provided:



IIIC

wherein R^1, R^2, R^3, and R^7 are defined generally above and in subsets herein; and

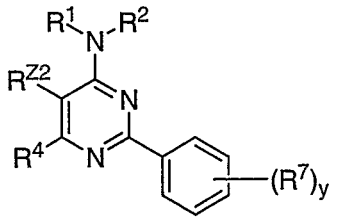
wherein R^{Z1} is $-SO_2R'$, $-NHSO_2R'$, $-C(O)N(CN)R'$, or an optionally substituted ring selected from:



z-dd **z-ee** **z-ff** .

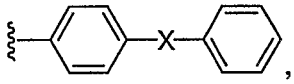
[00198] In certain embodiments of formula **IIIC**, R^1 and R^2 are identical, and they both are methyl or ethyl. Or, R^1 and R^2 are taken together to form a 1-piperidyl, 1-piperazyl, or 1-pyrrolidinyl.

[00199] In certain embodiments, ring A is optionally substituted phenyl, and compounds of **IVC** are provided:



IVC

R^{Z2} is cyano or halo, R^7, y, R^1, R^2, and R^4 are as defined above.

[00200] In certain embodiments of compounds of formula **IVC**, when R^1 and R^2 both are simultaneously hydrogen, then ring A is not , wherein X is O, NH, S, or CH_2, and each of the two phenyl ring is optionally substituted.

[00201] In certain embodiments of formula **IVC**, the following compounds are excluded:

R^1	R^2	R^{Z1}	R^4	Ring A
H	4-pyridyl	F	H	2-F-4-Cl-phenyl
H	3-methyl-pyridin-4-yl	I	H	2-F-4-Cl-phenyl
H	quinolin-6-yl	F	H	3-formylphenyl
H	Quinolin-6-yl	Br	H	3-cyanophenyl
H	1H-indazol-3-yl	Cl	H	2-CF_3-phenyl
H	-CH2-CCH	Br	H	phenyl
H	H	Br	H	phenyl
H	H	F	H	phenyl
H	phenyl	CN	H	Phenyl
H	phenyl	CN	H	4-Cl-phenyl
H	4-tolyl	CN	H	4-Cl-phenyl
H	Ph	CN	H	4-OMe-phenyl
H	4-tolyl	CN	H	phenyl
H	3-tolyl	CN	H	phenyl
H	3-Cl-phenyl	CN	H	phenyl
H	H	CN	H	phenyl
H	methoxyethyl	CN	H	phenyl
H	allyl	CN	H	phenyl

H	cyclopropyl	CN	H	phenyl
H	1-naphthyl	CN	H	phenyl
H	-CH2-C(O)NH2	CN	H	phenyl
H	-CH2C(O)OEt	CN	H	phenyl
Me	cyanomethyl	CN	H	phenyl
H	3-CF3-phenyl	CN	H	phenyl
H	isobutyl	Cl	H	phenyl
H	H	Cl	H	phenyl
H	Ph	Cl	H	phenyl
H	acyl	Br	H	phenyl
H	acyl	CN	H	phenyl
H	6-quinolinyl	Br	H	4-OMe-phenyl
H	6-quinolinyl	Br	H	3-Cl-phenyl
H	6-quinolinyl	Br	H	3-Br-phenyl
H	6-quinolinyl	Br	H	3-OMe-phenyl
H	6-quinolinyl	Br	H	3-CF_3-4-Cl-phenyl
H	6-quinolinyl	Br	H	3-CF3-4-CN-phenyl
H	6-quinolinyl	Br	H	4-cyanophenyl
H	6-quinolinyl	F	H	4-NO_2-phenyl
H	6-quinolinyl	F	H	3-NO_2-phenyl
H	6-quinolinyl	F	H	4-N(Me_2)-phenyl
H	6-quinolinyl	F	H	4-(N-morpholino)-phenyl

[00202] In certain other embodiments of formula **IVC**, the following compounds are excluded:

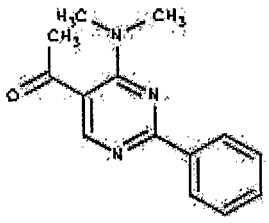
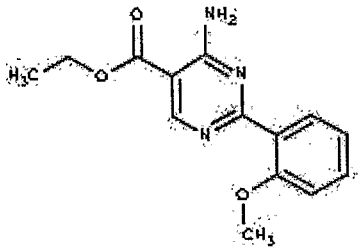
R^1 and R^2 taken together form:	R^{Z1}	R^4	Ring A
N-morpholino	F	H	phenyl
2H-pyridazin-3-one-1-yl	Cl	H	phenyl
N-piperidyl	Cl	H	phenyl

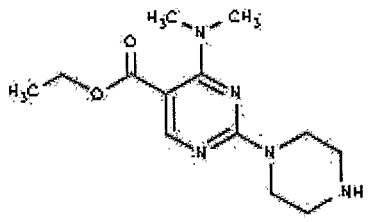
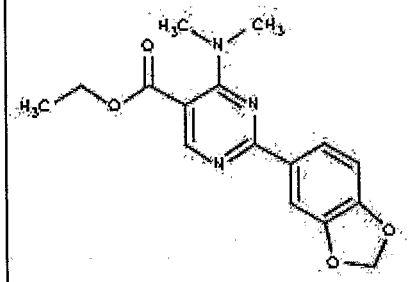
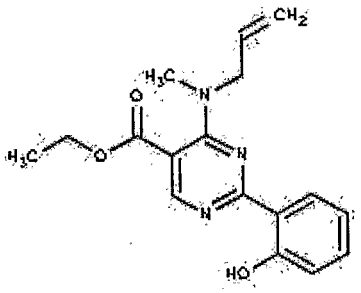
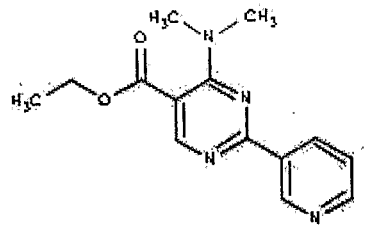
N-morpholino	Cl	H	phenyl
N-piperidyl	Cl	H	4-NO_2-phenyl
N-morpholino	CN	H	2-OH-phenyl

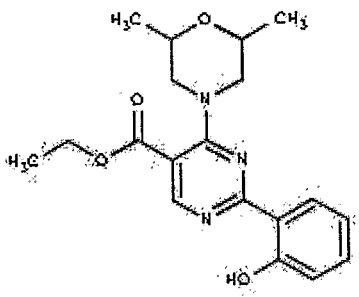
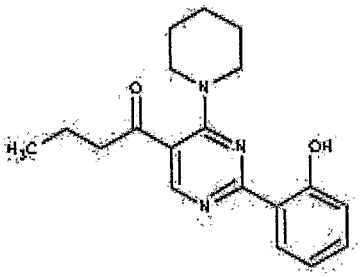
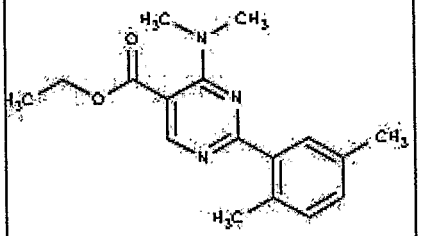
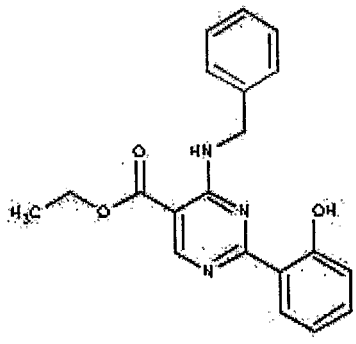
[00203] Representative examples of compounds as described above and herein are set forth below in Table 2.

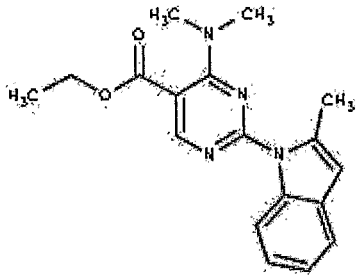
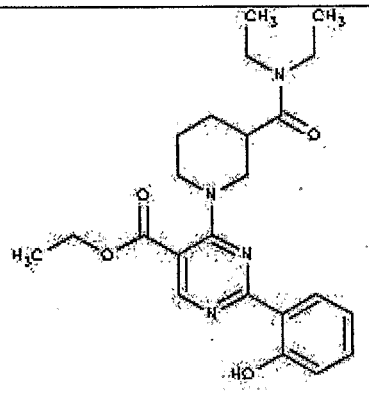
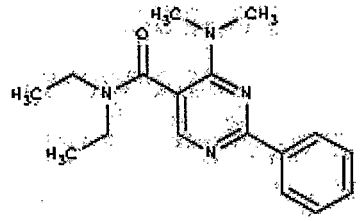
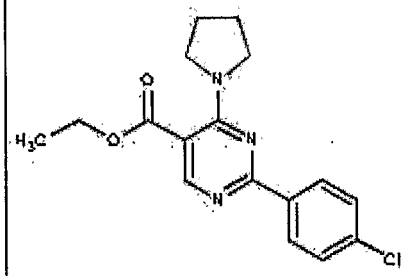
[00204] The compounds described in this invention are useful as inhibitors of ion channels, preferably, voltage gated sodium channels and N-type calcium channels. In certain exemplary embodiments, compounds of the invention are useful as inhibitors of NaV1.2. In certain exemplary embodiments, compounds of the invention are useful as inhibitors of NaV1.5. 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 NaV 1.8 and CaV2.2. In yet other embodiments, compounds of this invention are useful as inhibitors of CaV2.2. In yet other embodiments, comopunds of this invention are useful as dual inhibitors of NaV1.8 and a TTX-sensitive ion channel such as NaV1.3 or NaV1.7.

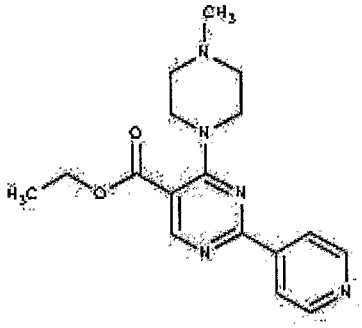
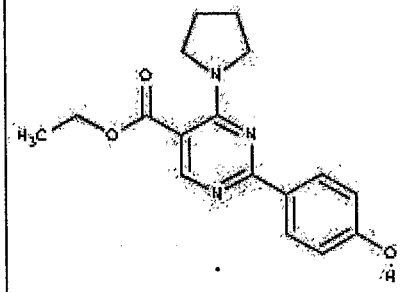
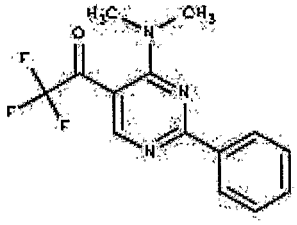
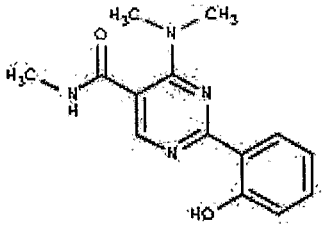
[00205] **Table 2**

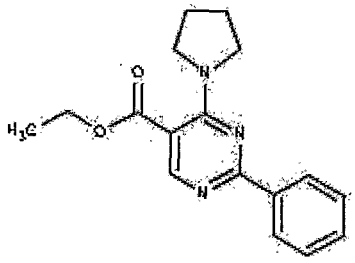
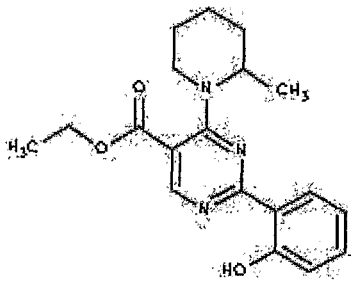
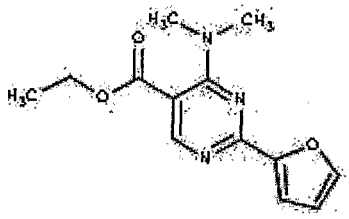
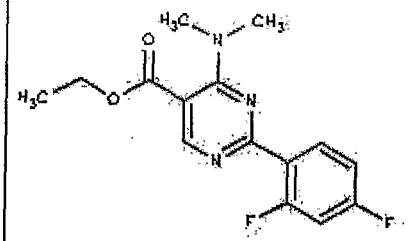
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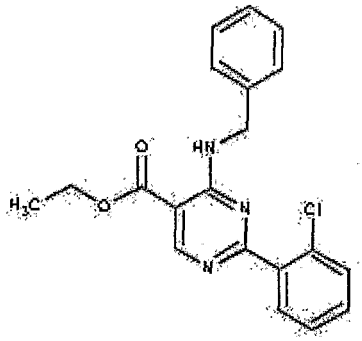
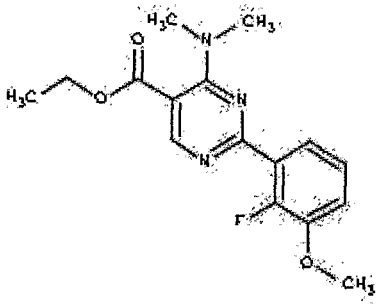
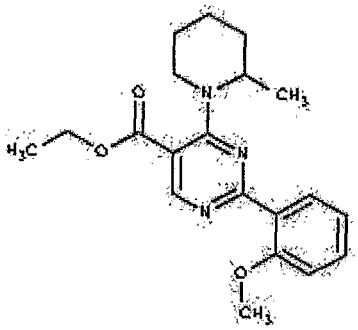
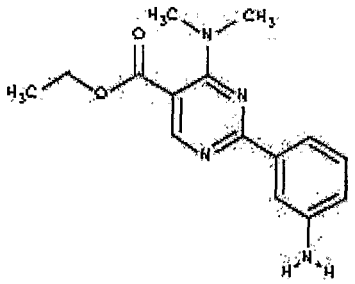
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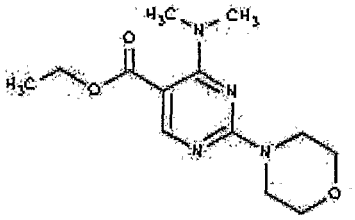
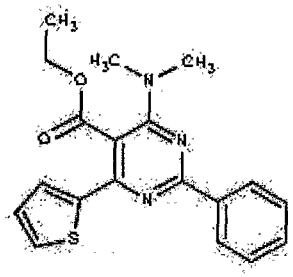
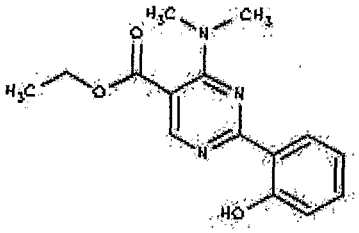
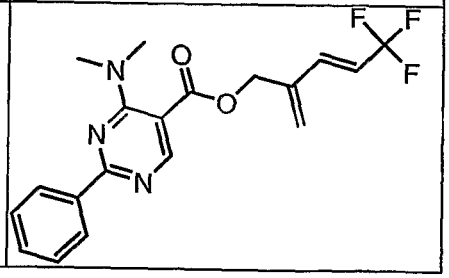
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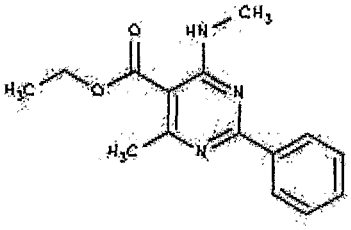
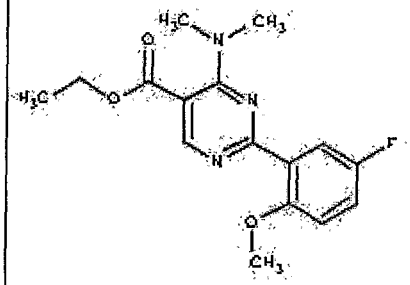
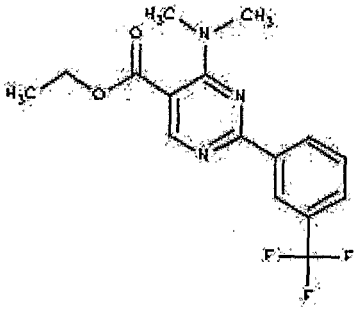
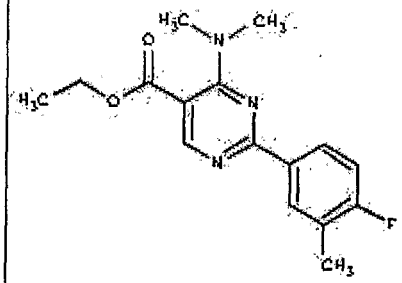
Cmpd No.	Compound
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14	

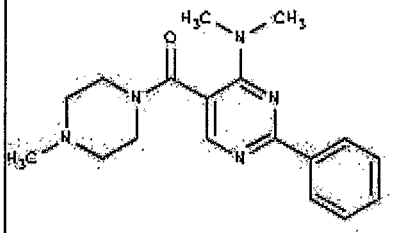
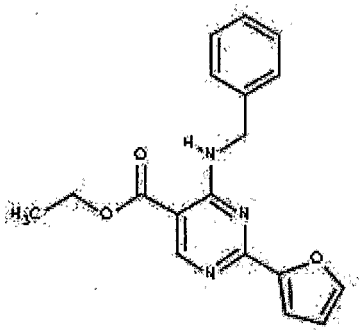
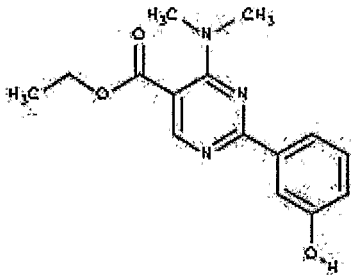
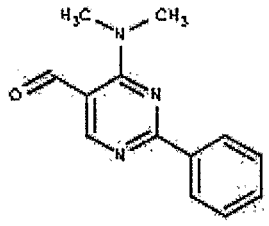
Cmpd No.	Compound
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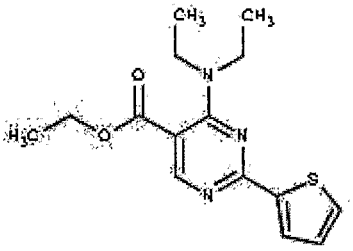
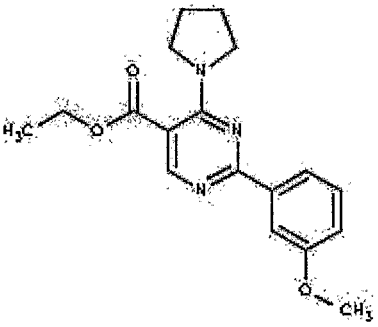
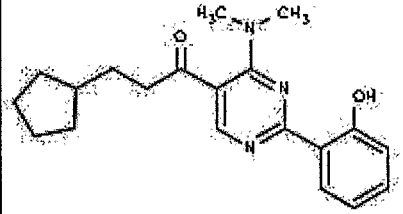
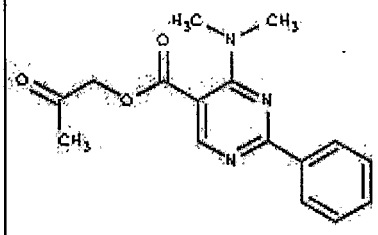
Cmpd No.	Compound
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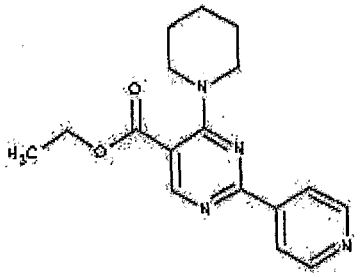
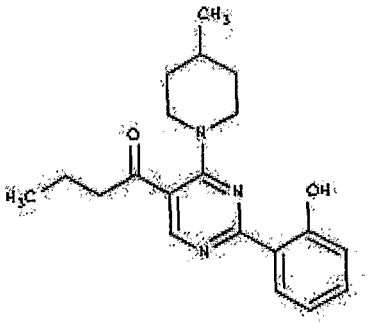
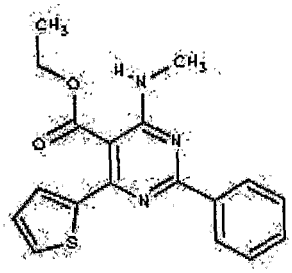
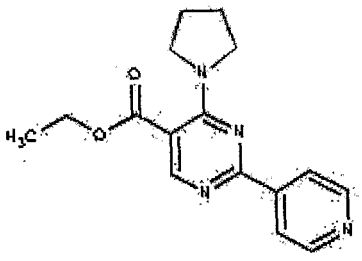
Cmpd No.	Compound
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25	
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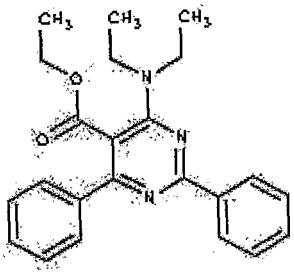
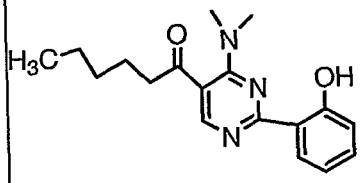
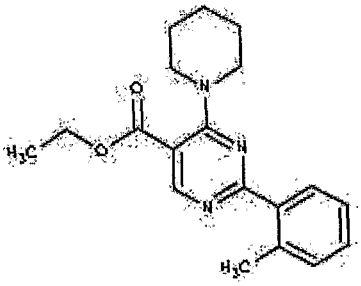
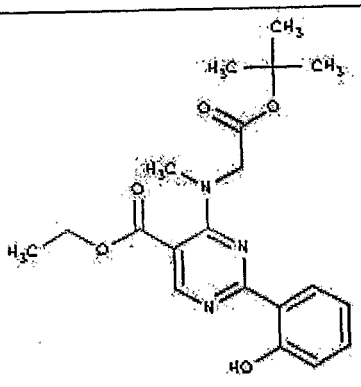
Cmpd #	Compound
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28	
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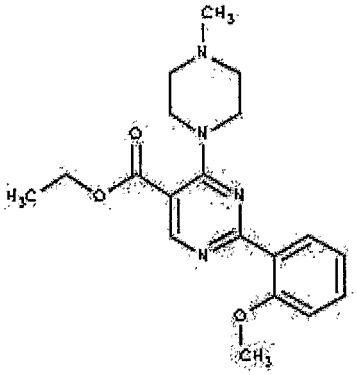
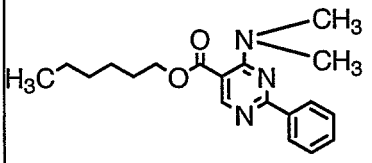
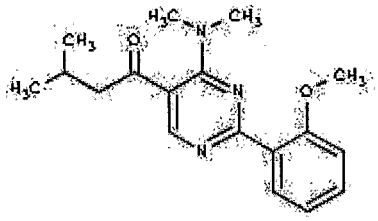
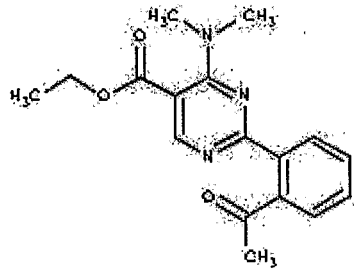
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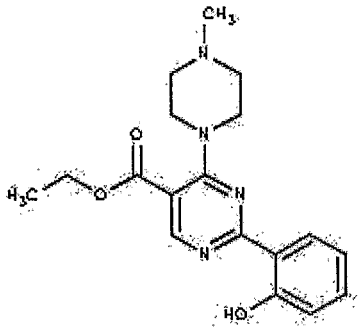
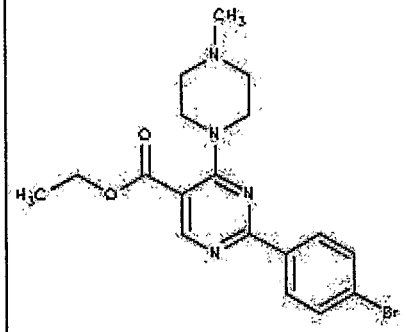
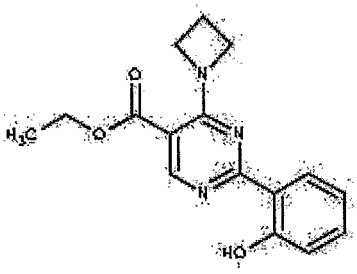
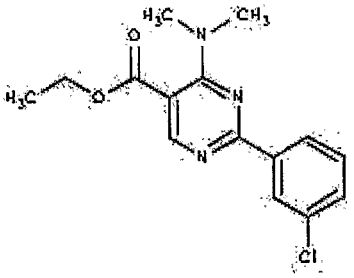
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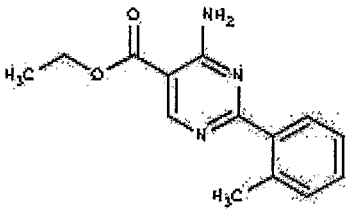
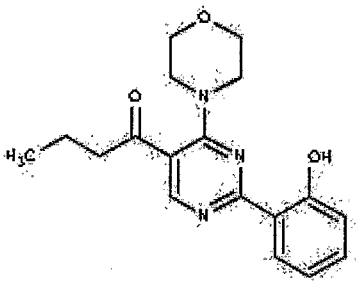
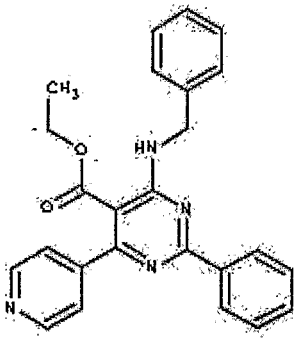
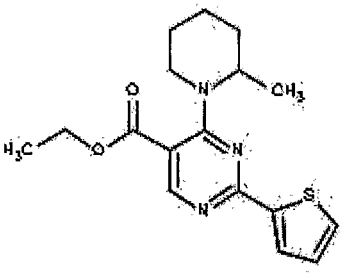
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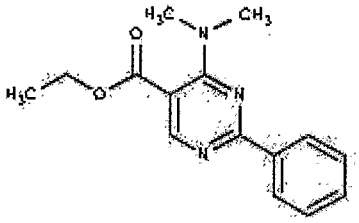
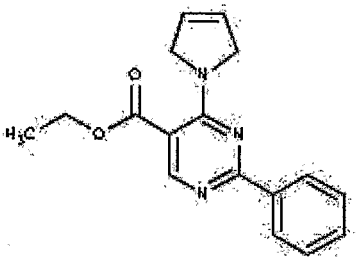
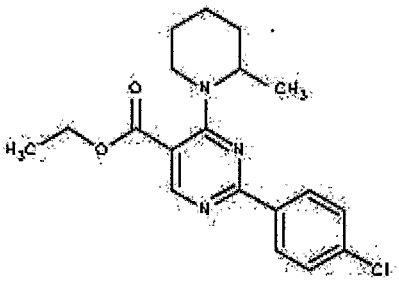
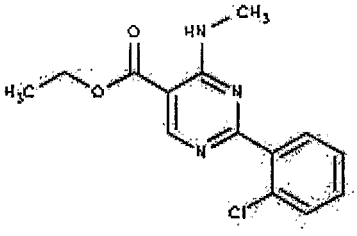
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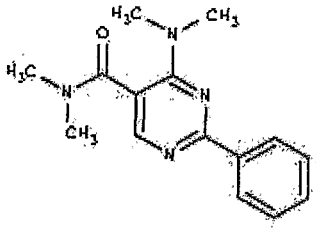
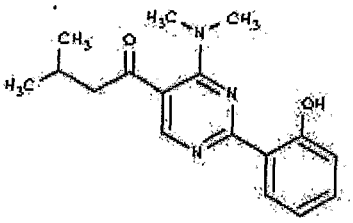
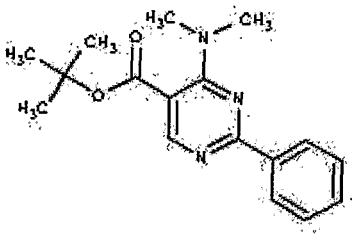
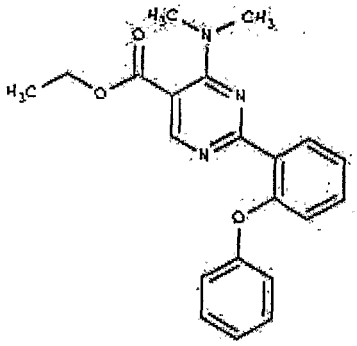
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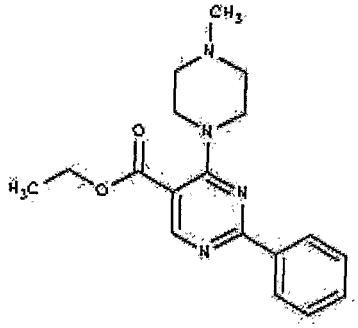
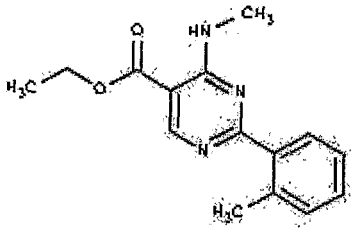
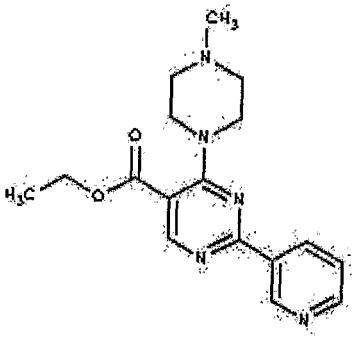
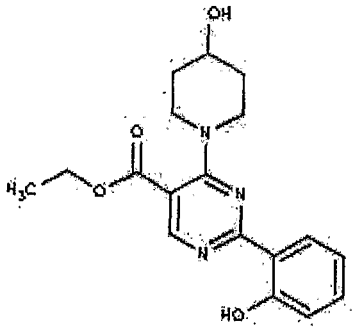
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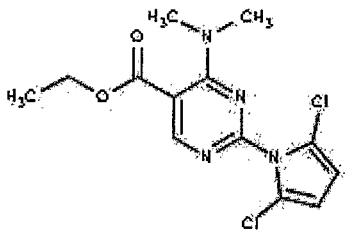
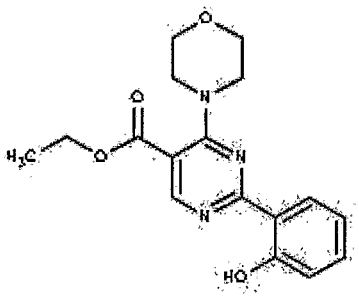
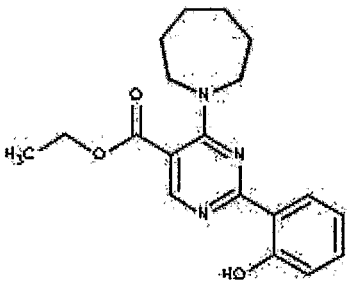
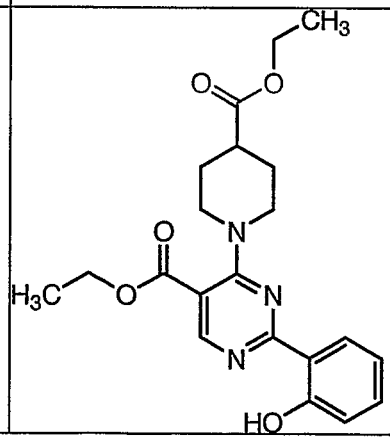
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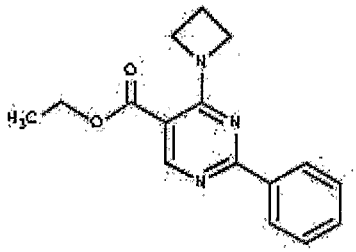
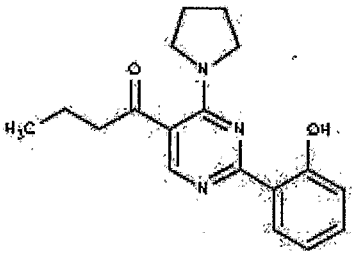
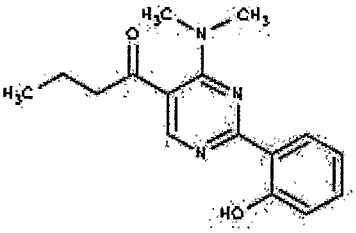
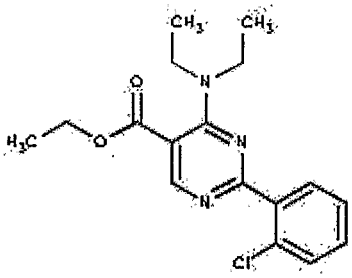
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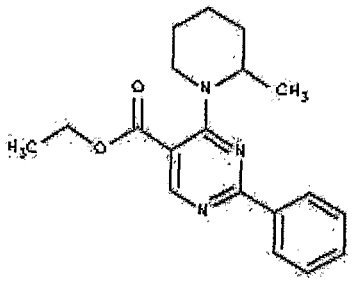
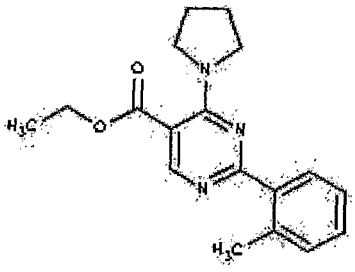
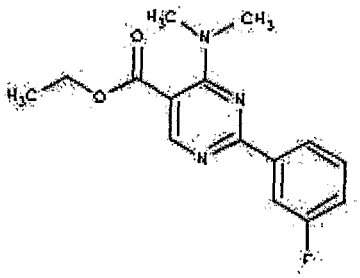
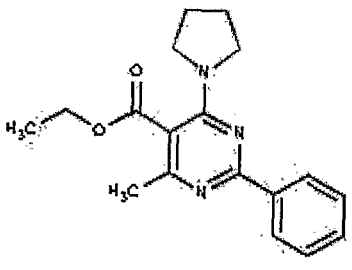
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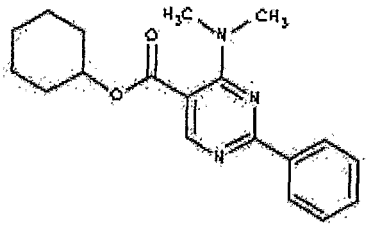
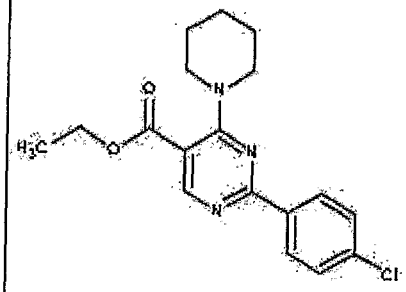
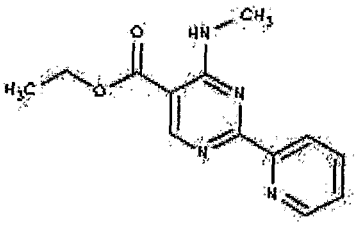
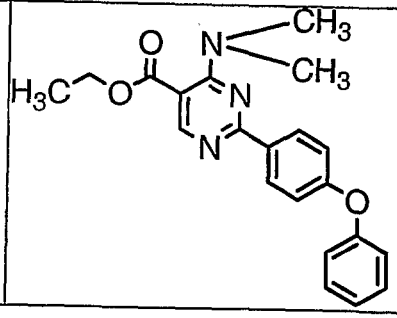
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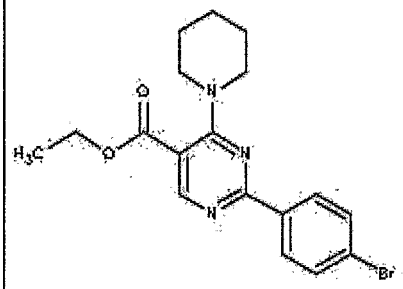
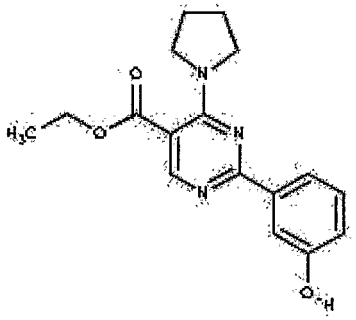
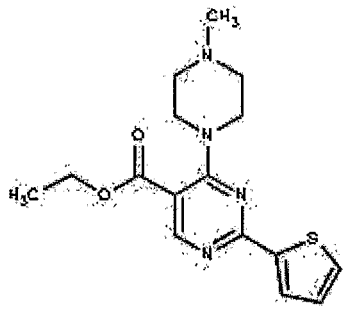
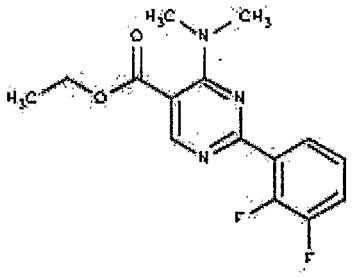
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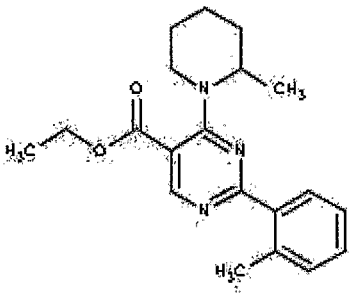
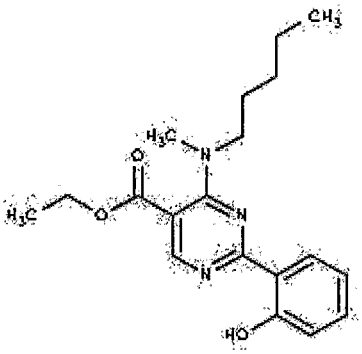
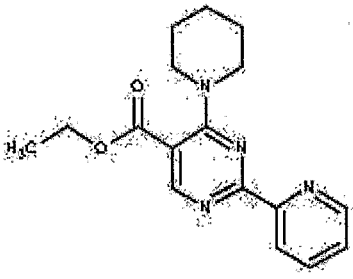
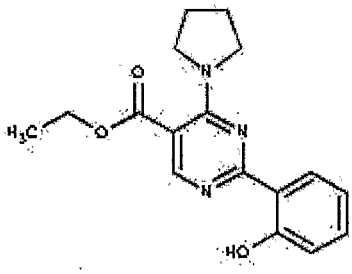
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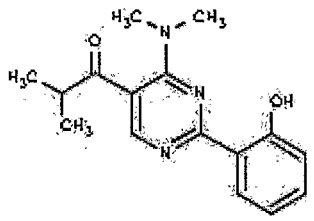
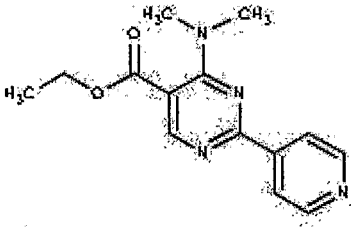
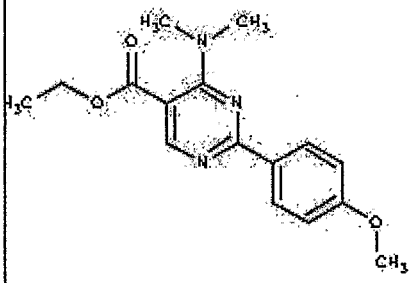
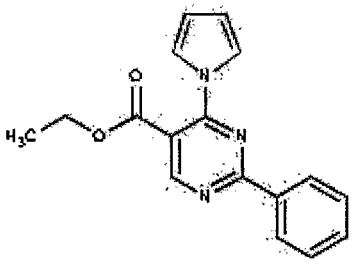
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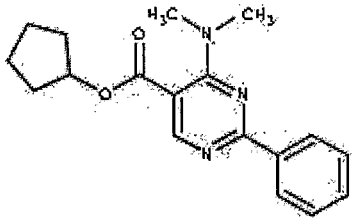
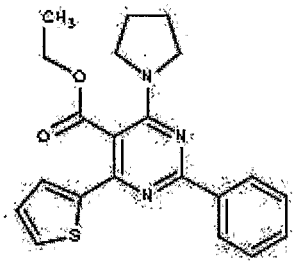
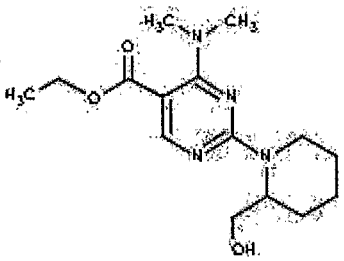
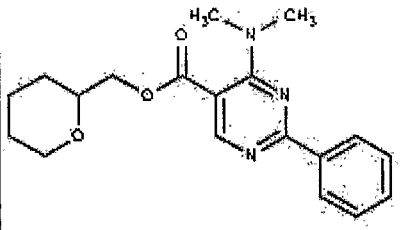
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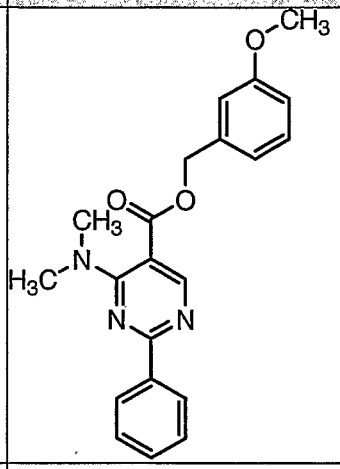
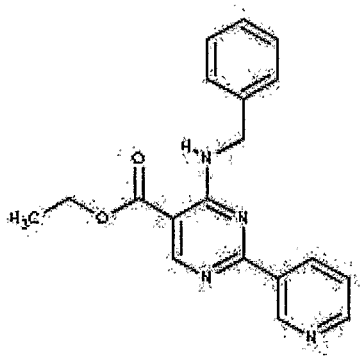
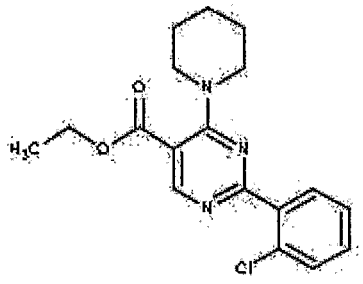
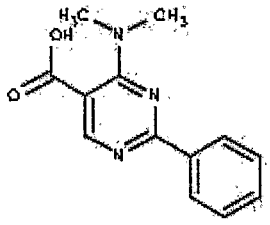
Cmpd #	Compound
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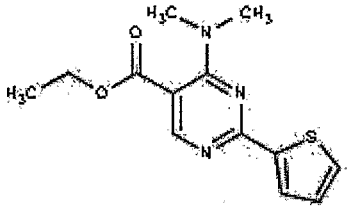
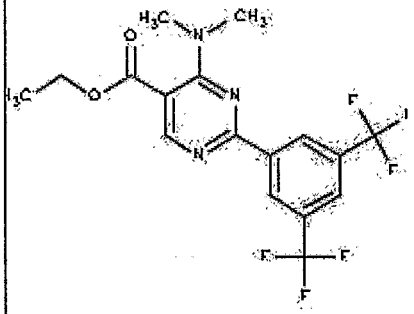
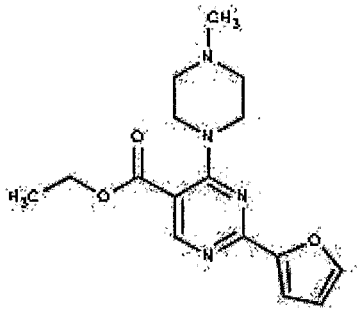
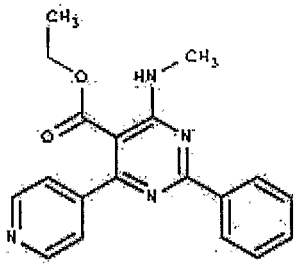
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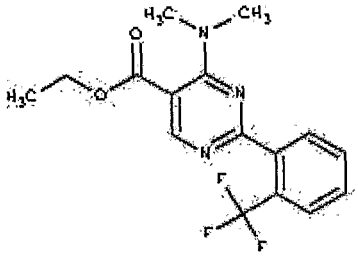
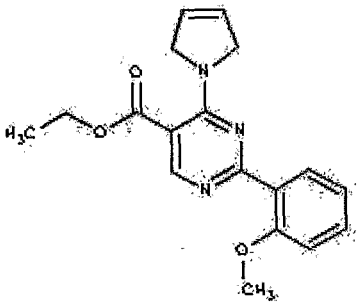
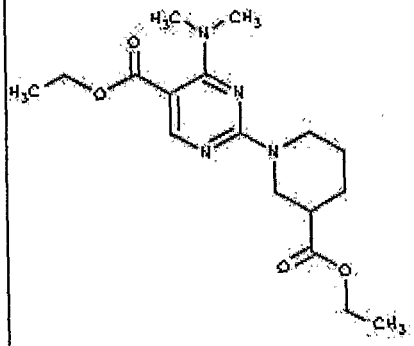
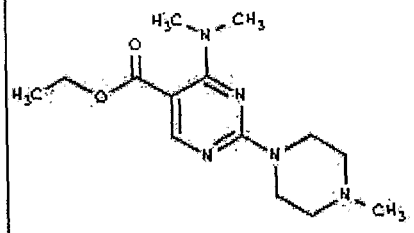
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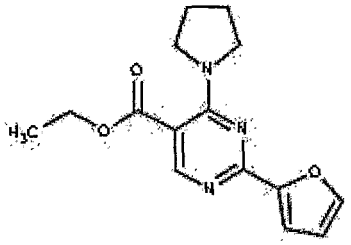
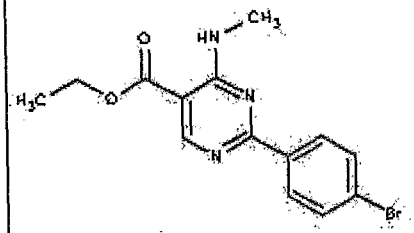
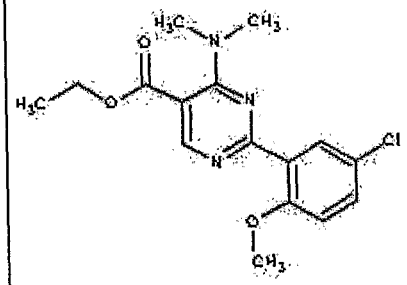
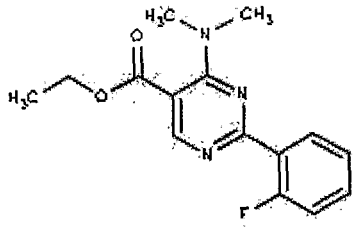
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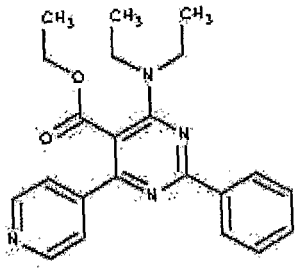
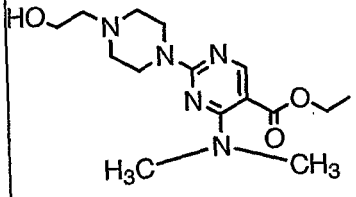
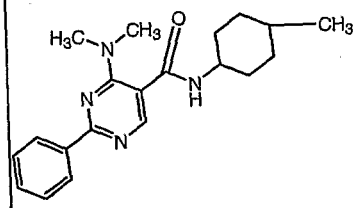
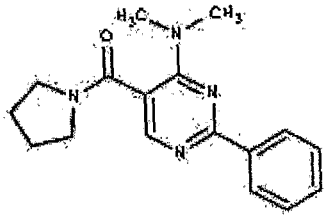
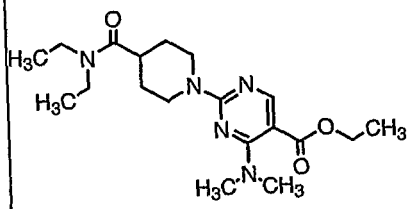
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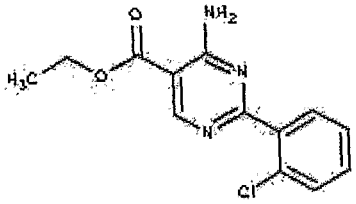
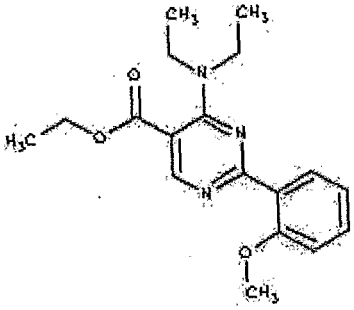
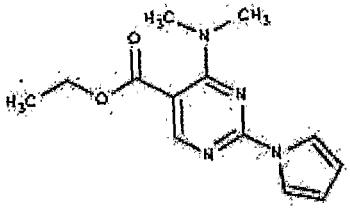
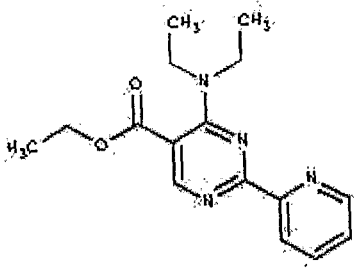
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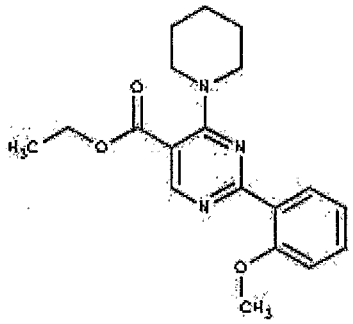
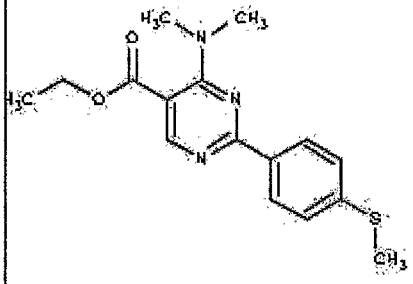
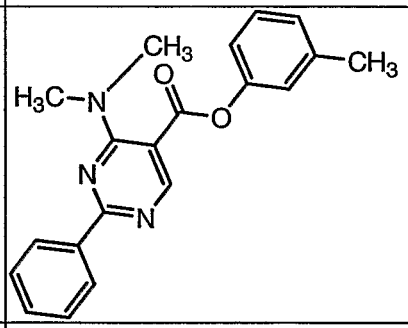
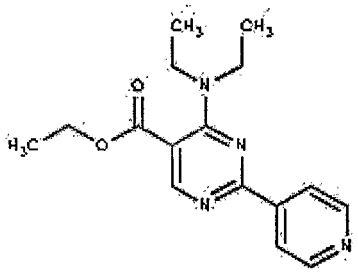
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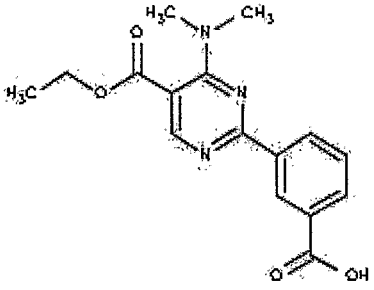
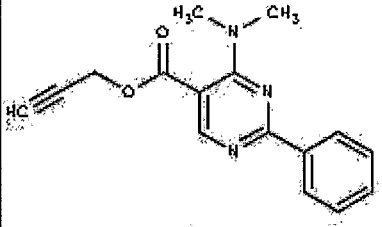
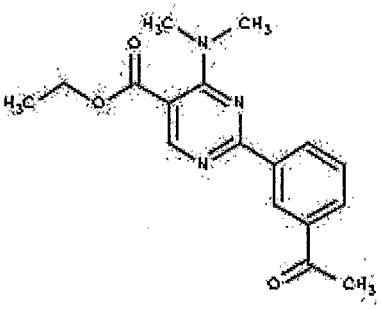
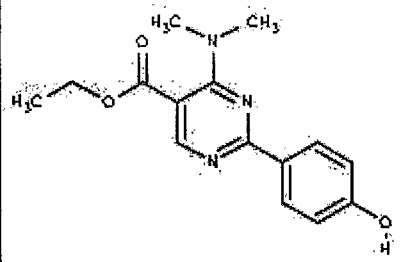
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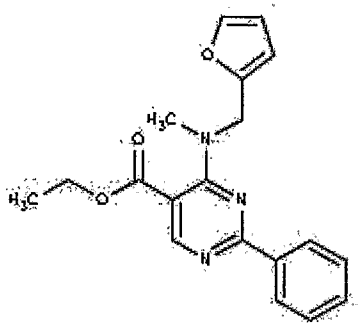
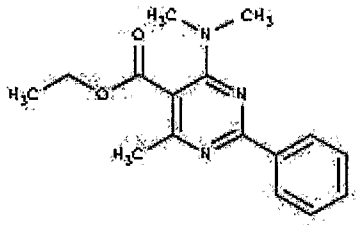
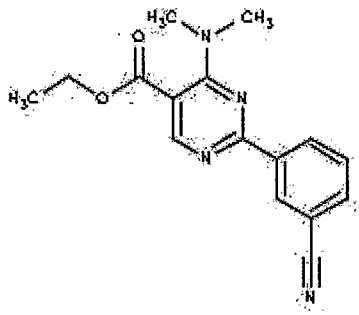
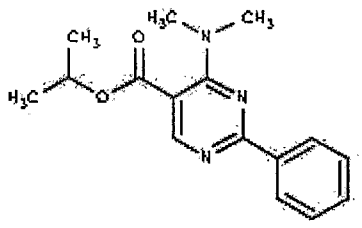
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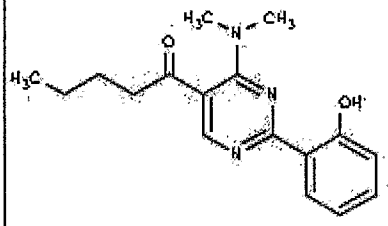
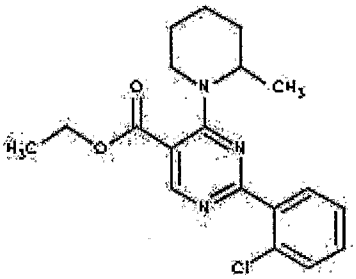
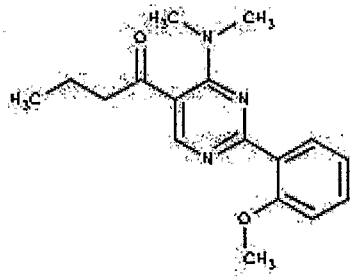
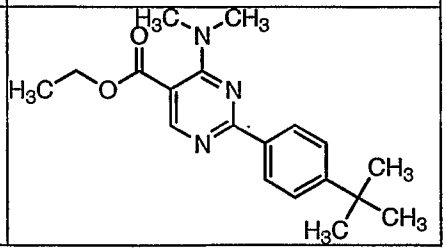
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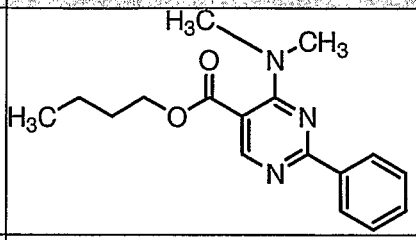
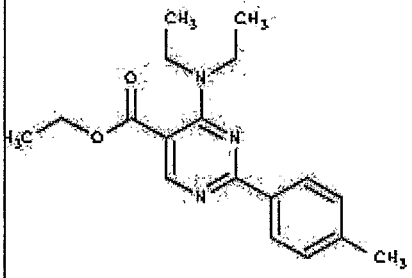
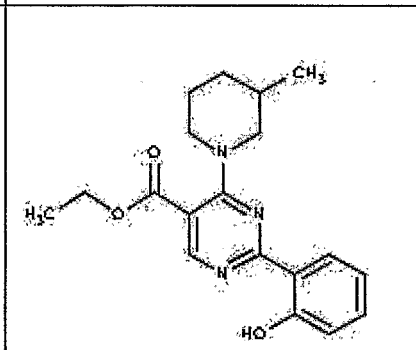
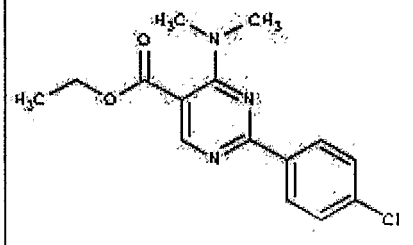
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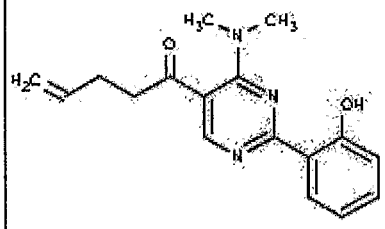
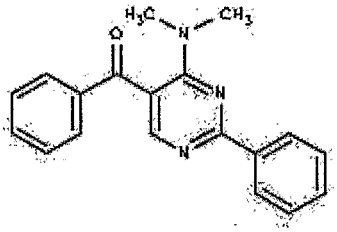
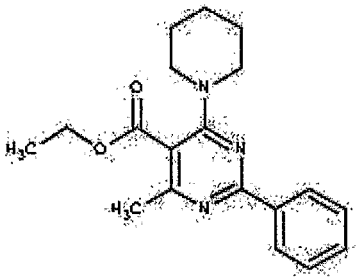
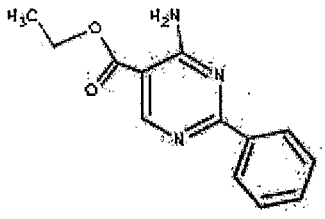
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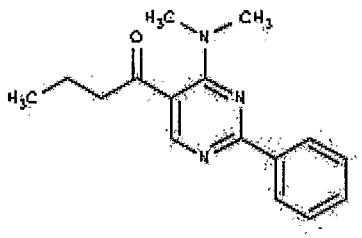
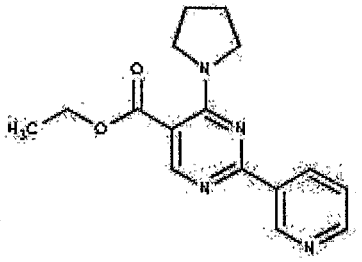
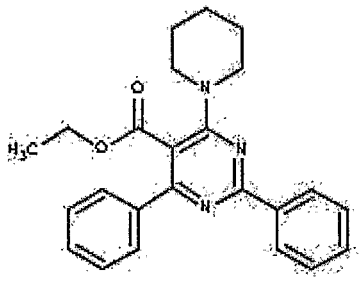
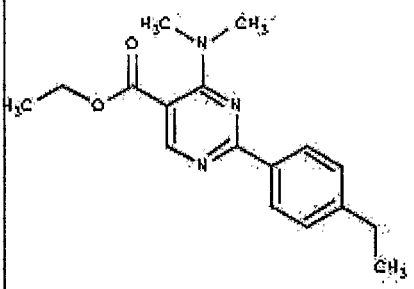
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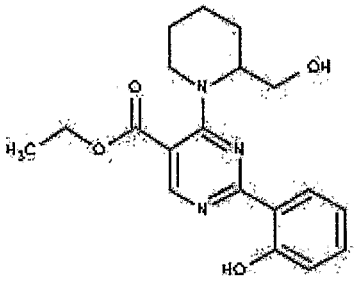
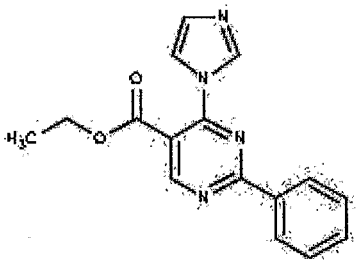
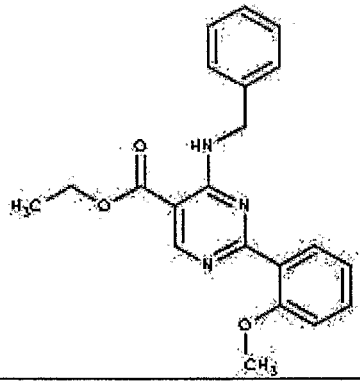
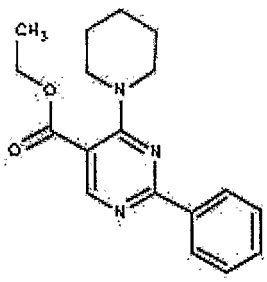
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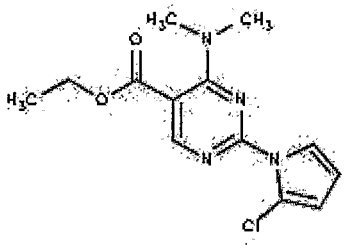
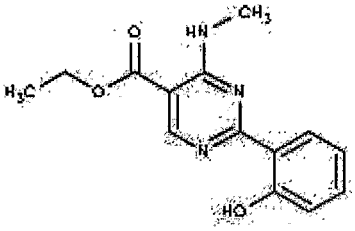
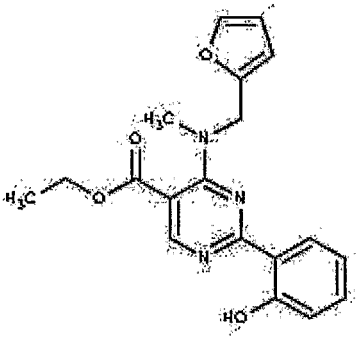
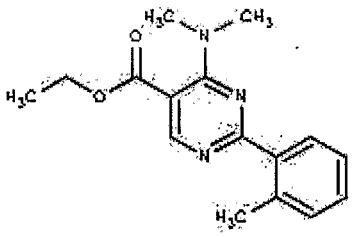
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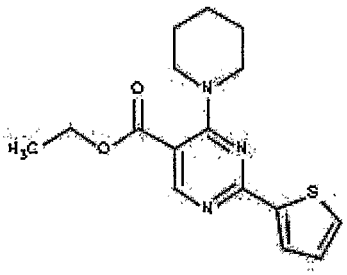
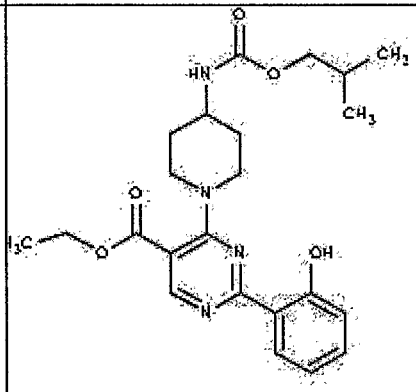
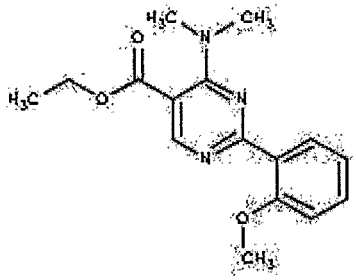
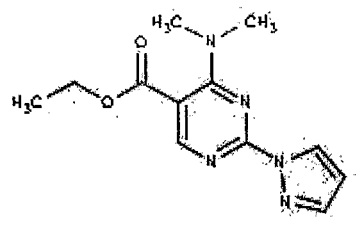
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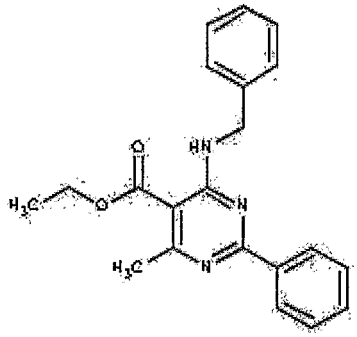
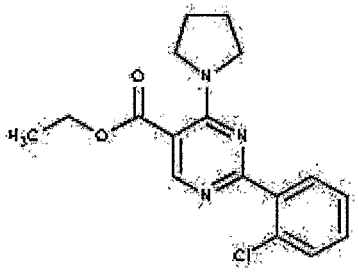
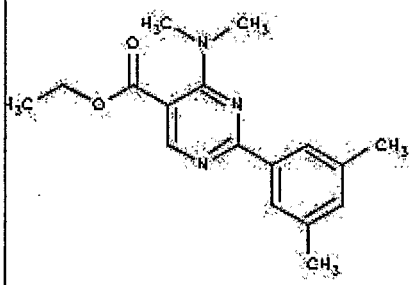
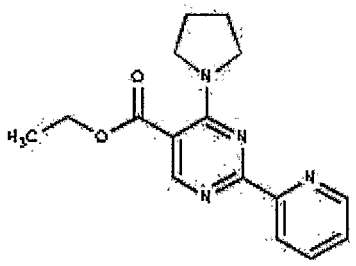
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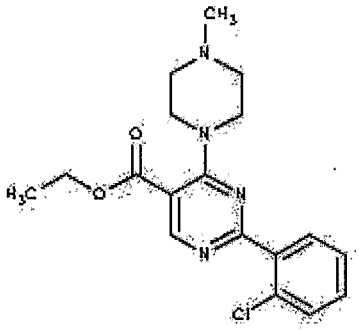
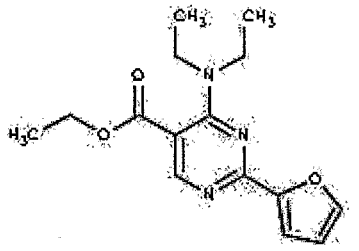
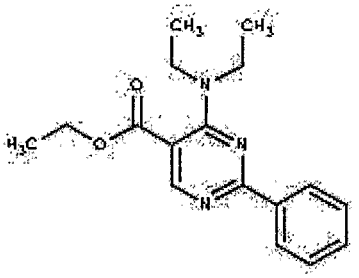
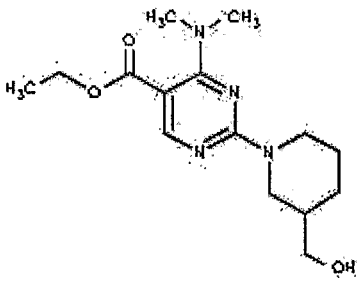
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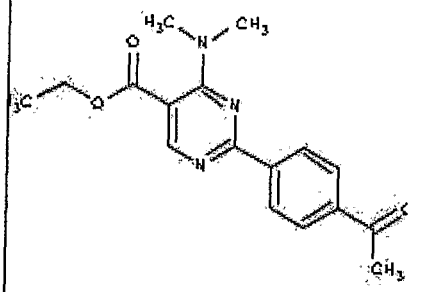
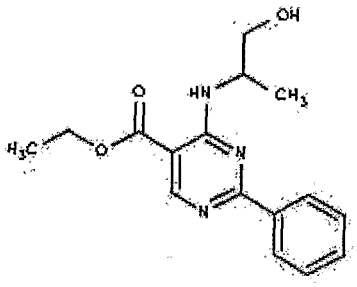
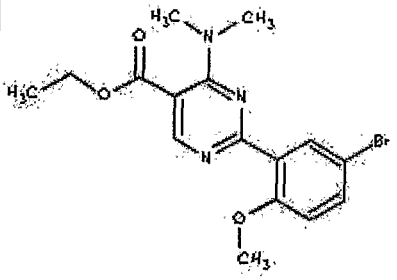
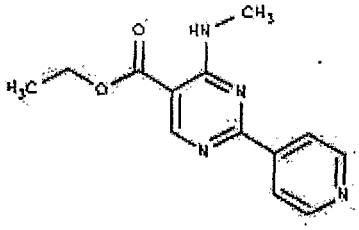
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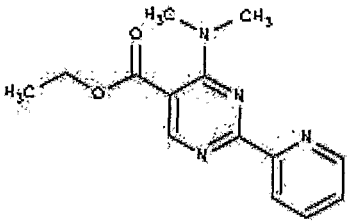
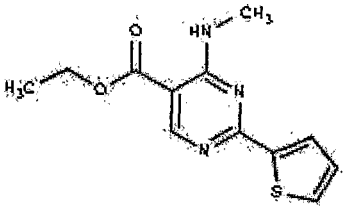
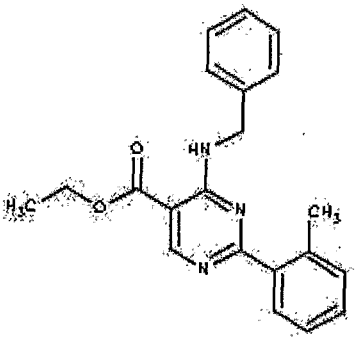
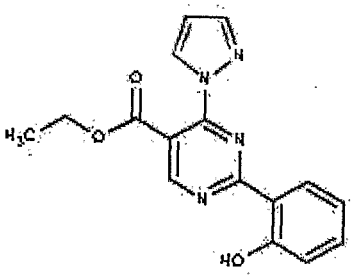
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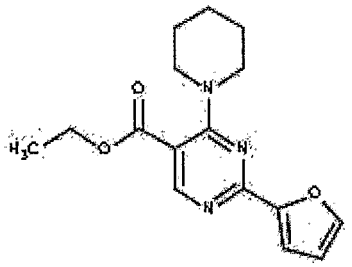
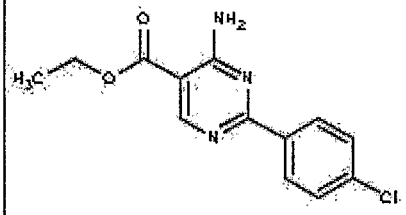
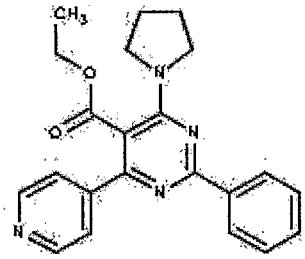
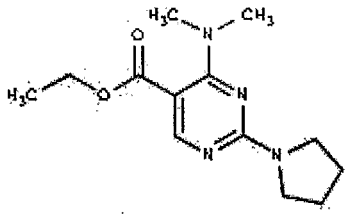
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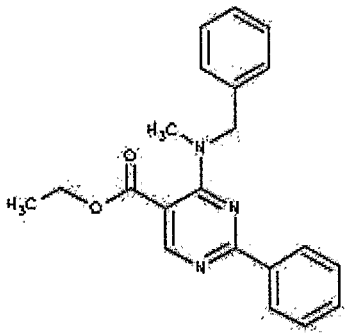
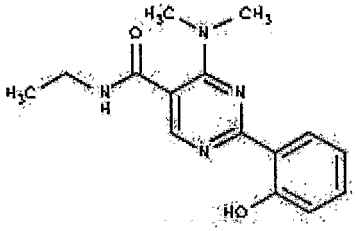
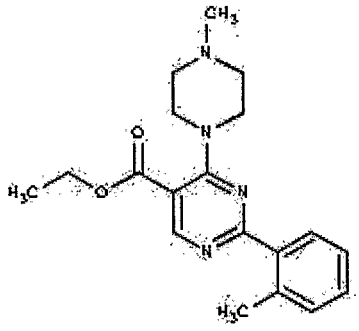
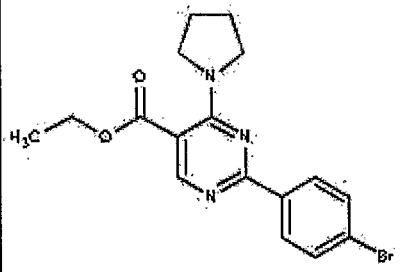
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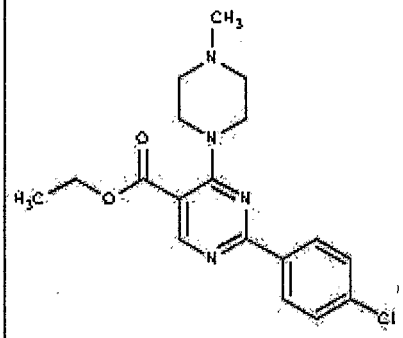
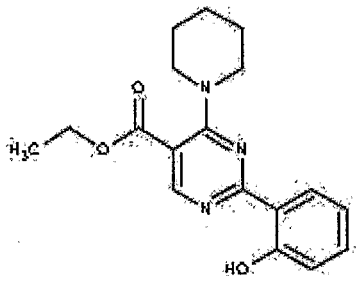
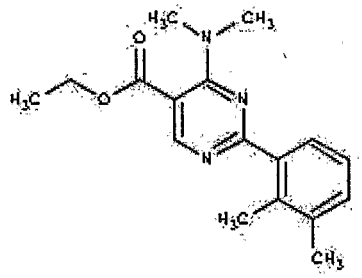
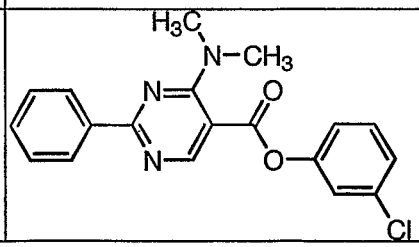
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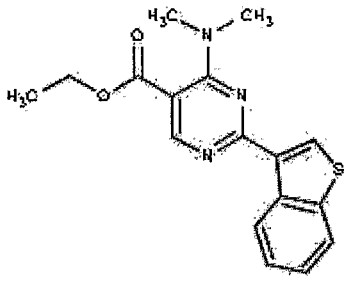
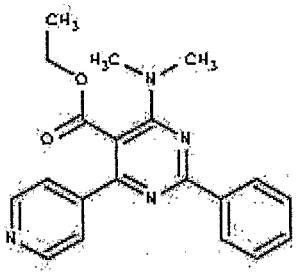
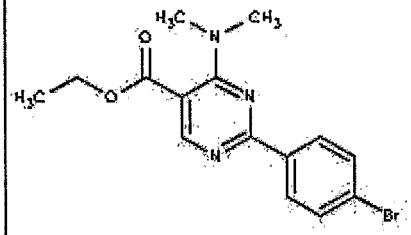
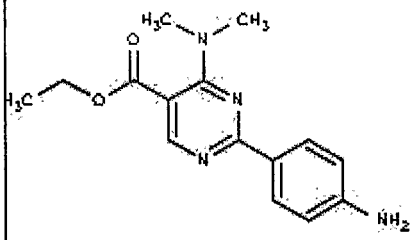
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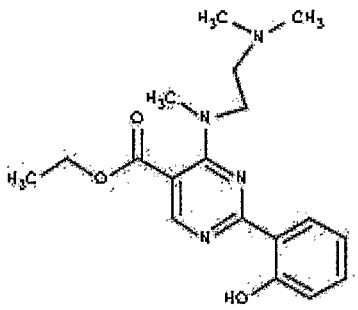
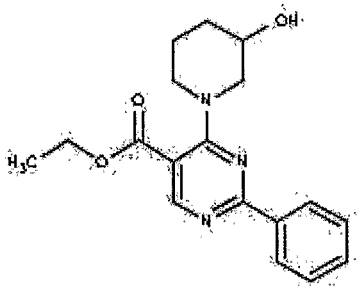
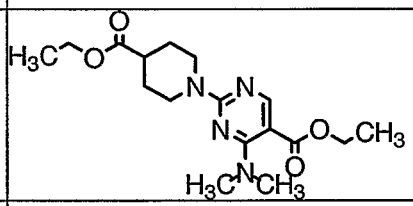
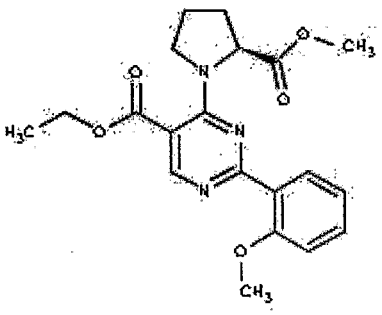
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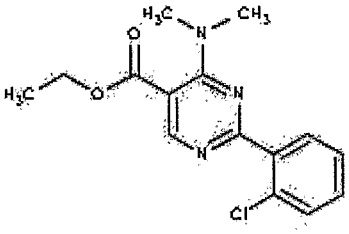
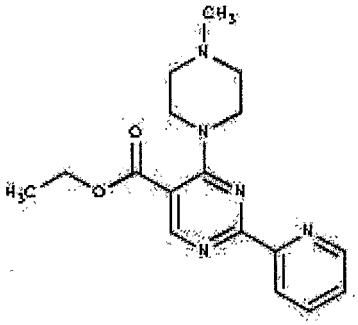
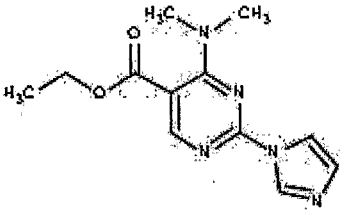
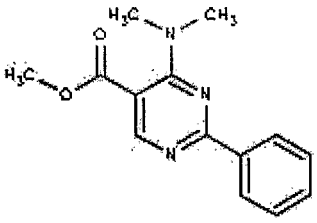
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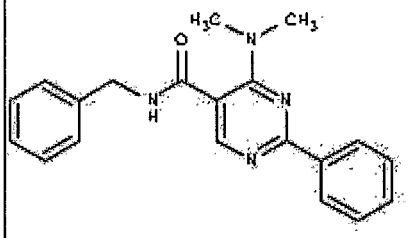
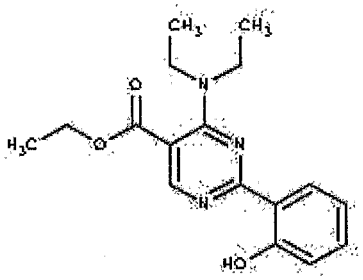
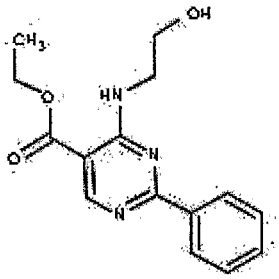
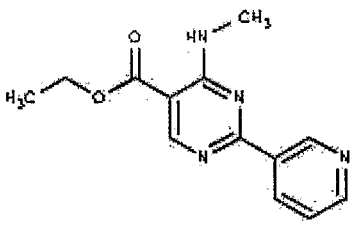
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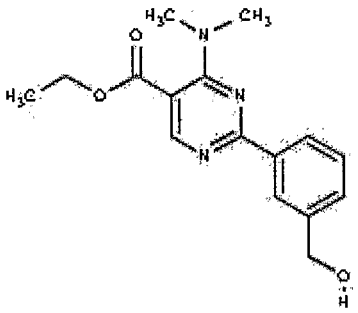
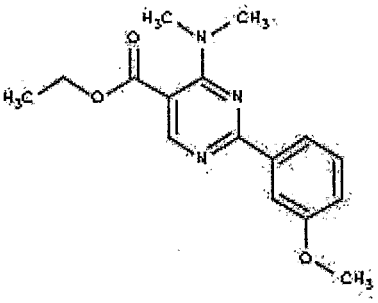
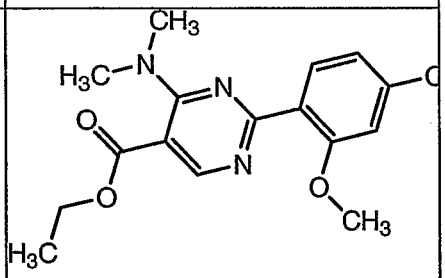
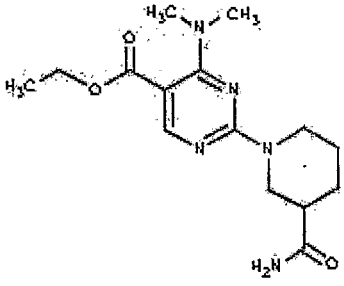
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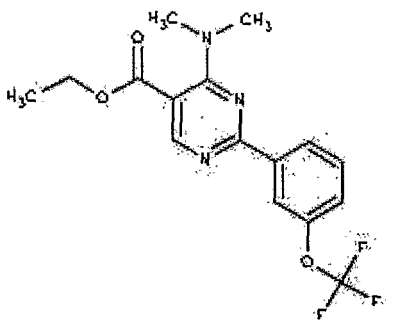
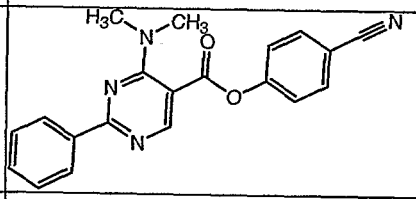
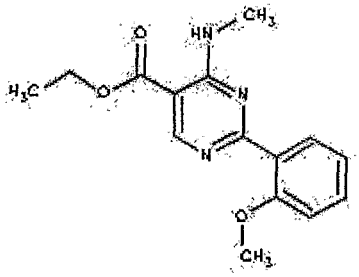
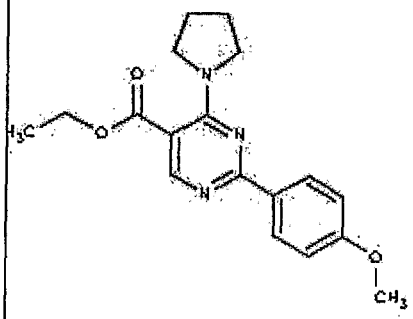
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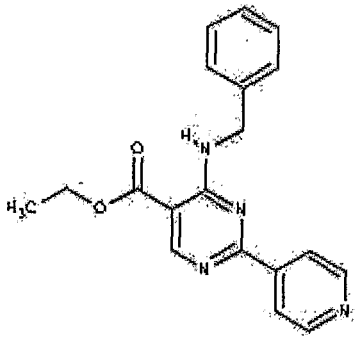
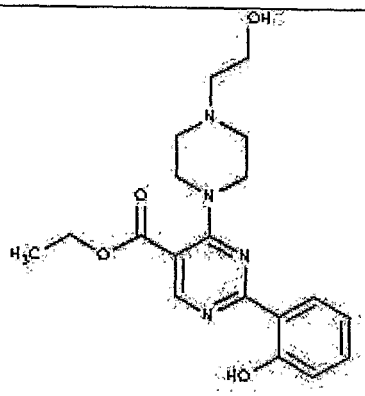
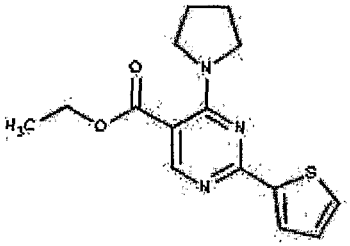
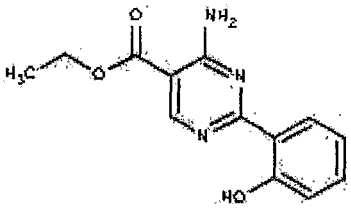
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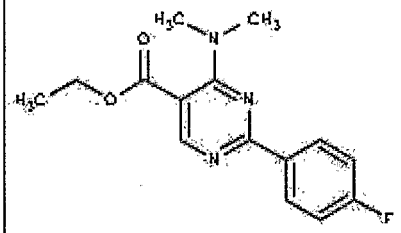
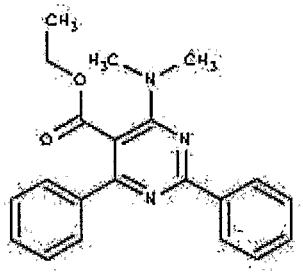
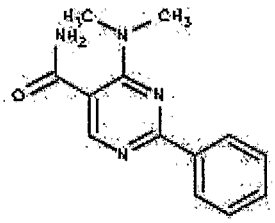
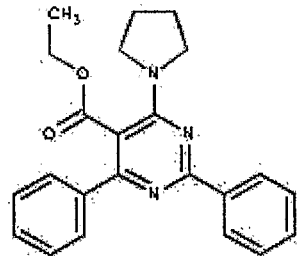
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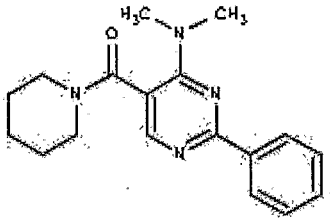
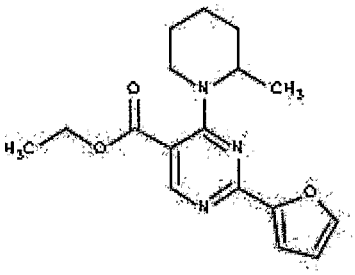
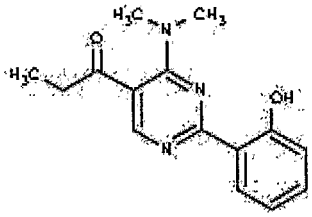
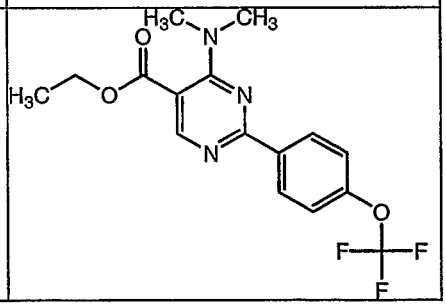
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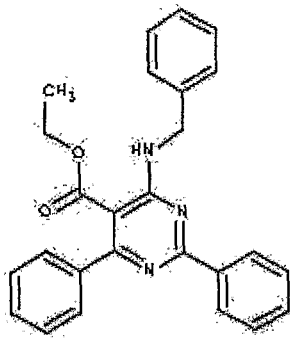
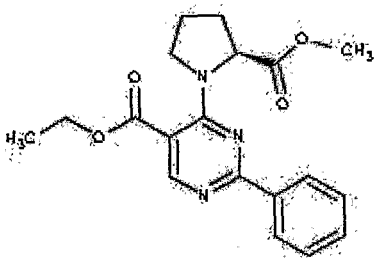
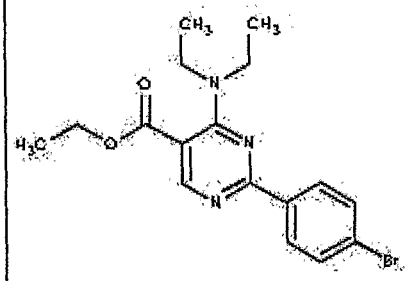
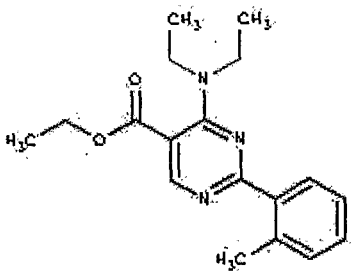
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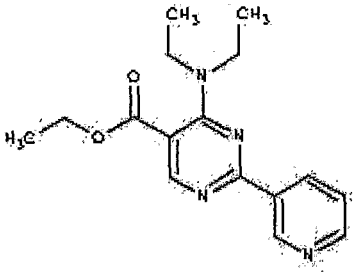
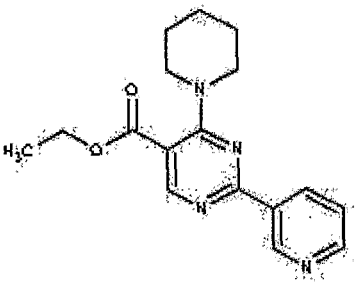
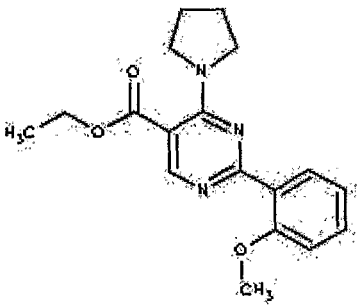
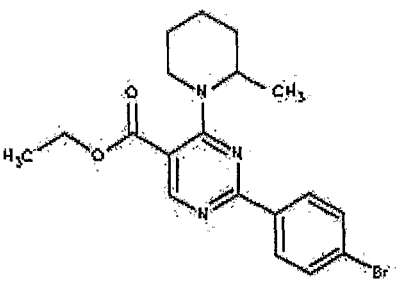
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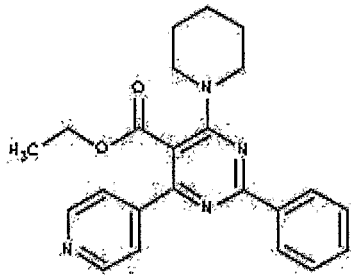
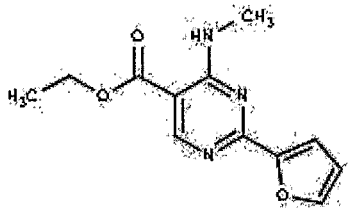
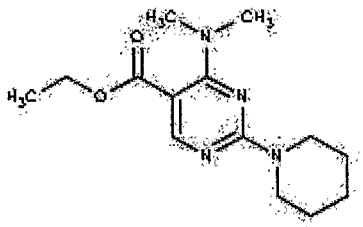
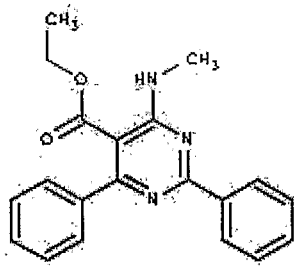
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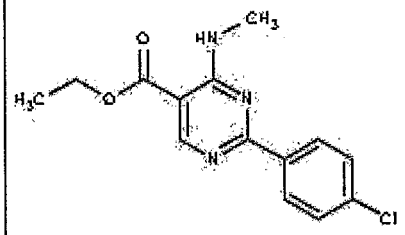
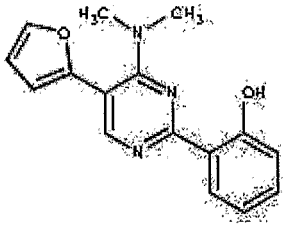
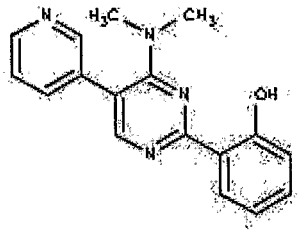
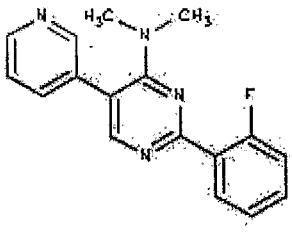
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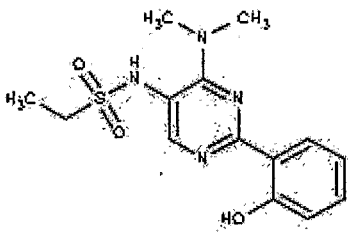
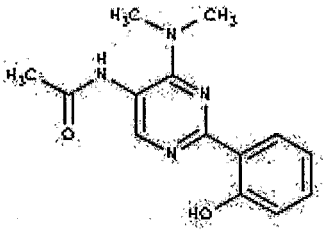
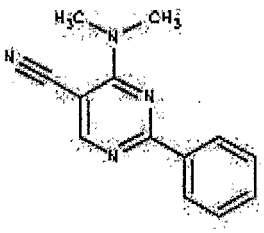
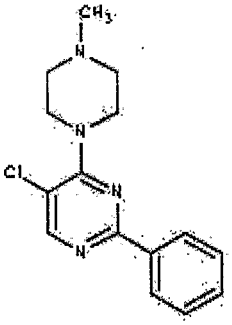
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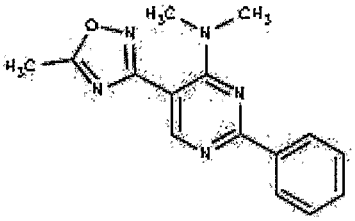
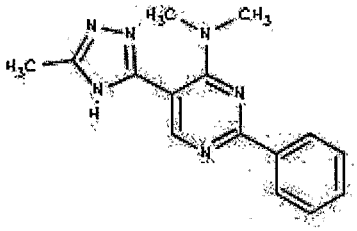
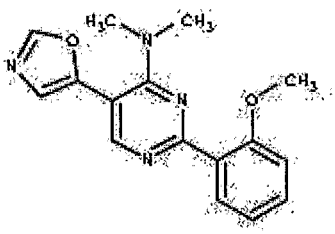
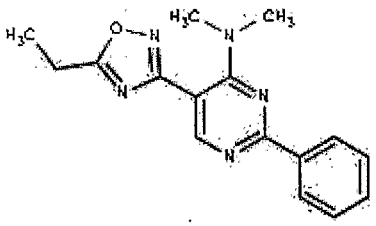
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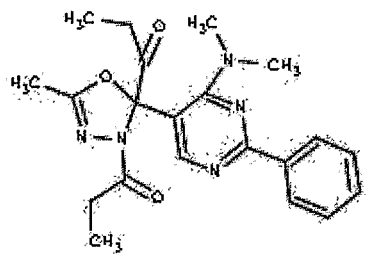
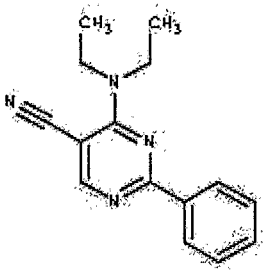
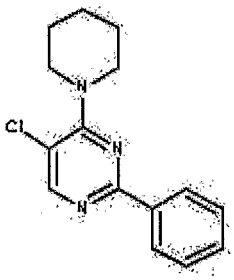
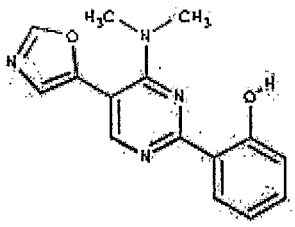
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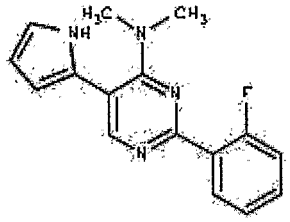
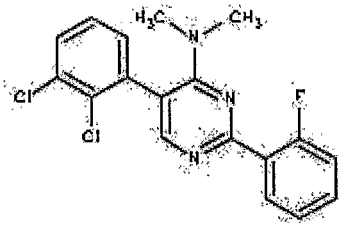
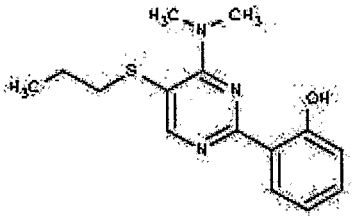
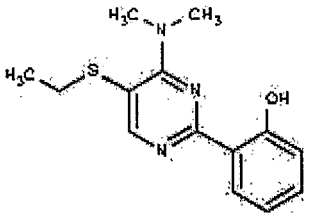
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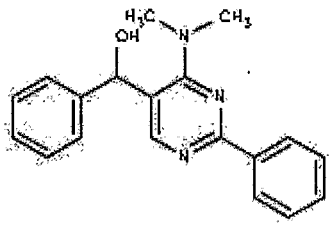
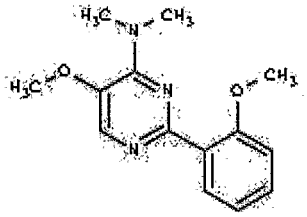
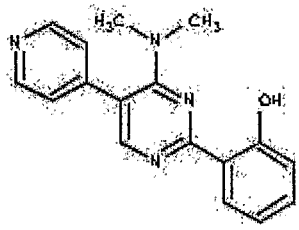
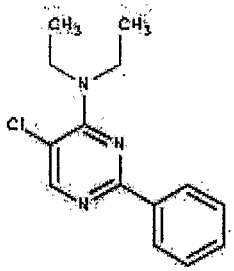
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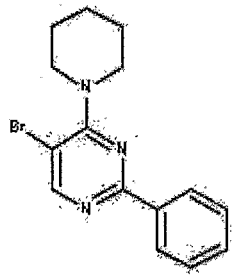
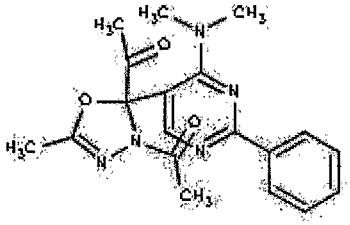
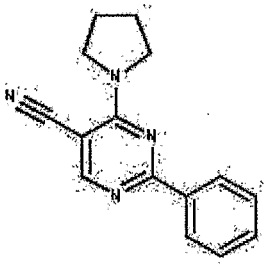
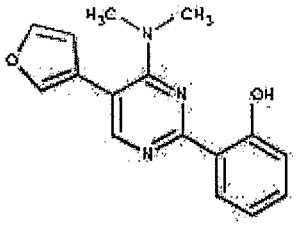
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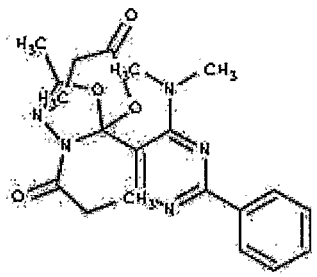
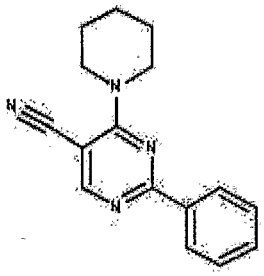
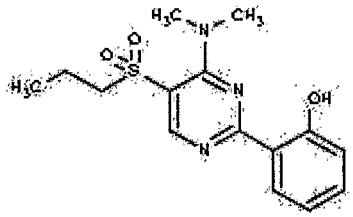
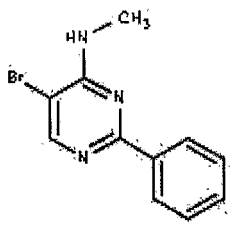
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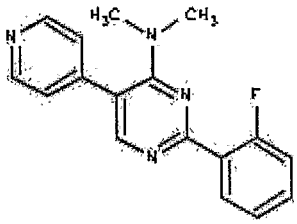
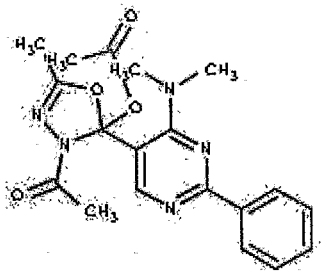
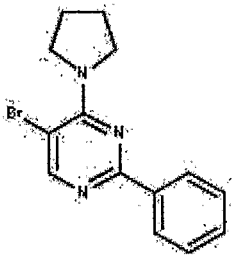
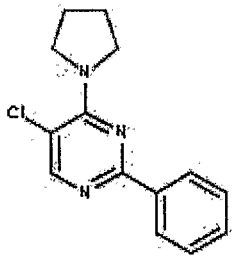
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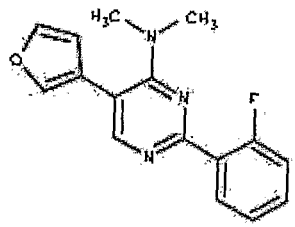
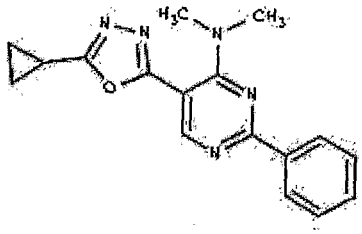
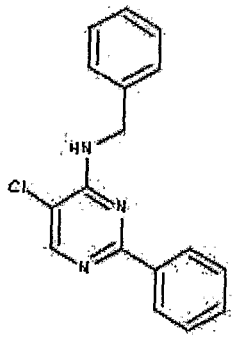
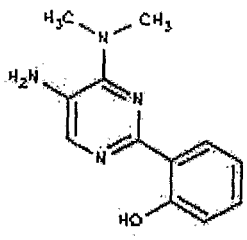
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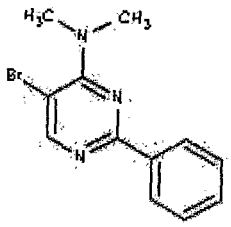
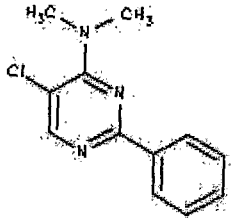
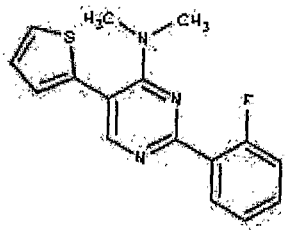
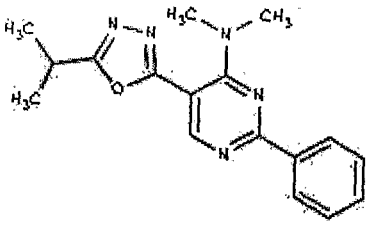
Cmpd #	Compound
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269	
270	
271	

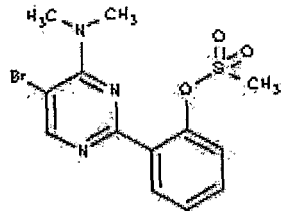
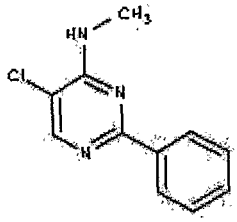
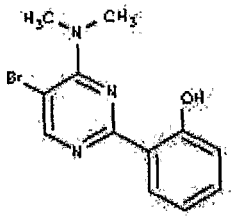
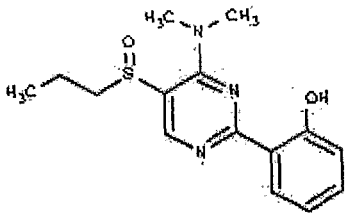
Cmpd #	Compound
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273	
274	
275	

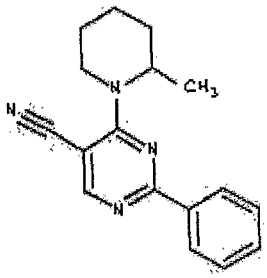
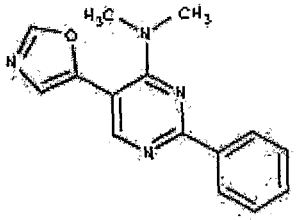
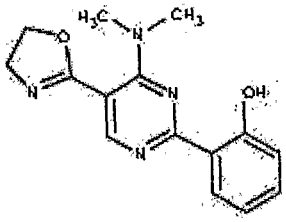
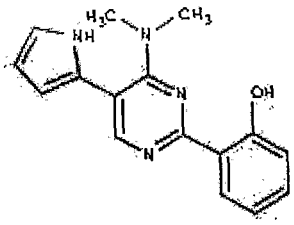
Cmpd #	Compound
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277	
278	
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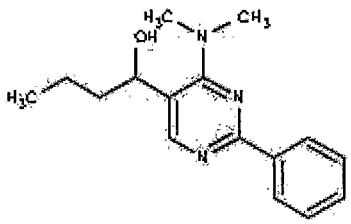
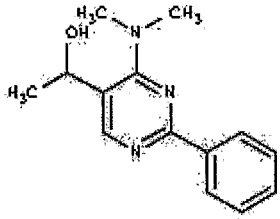
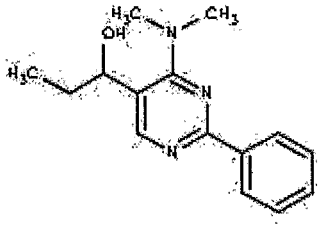
Cmpd #	Compound
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281	
282	
283	

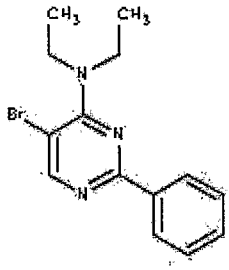
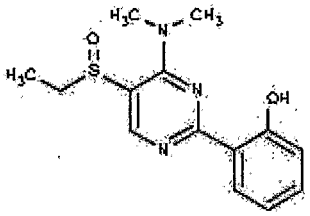
Cmpd #	Compound
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286	
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Cmpd #	Compound
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Cmpd #	Compound
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Cmpd #	Compound
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299	

Cmpd #	Compound
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301	
302	

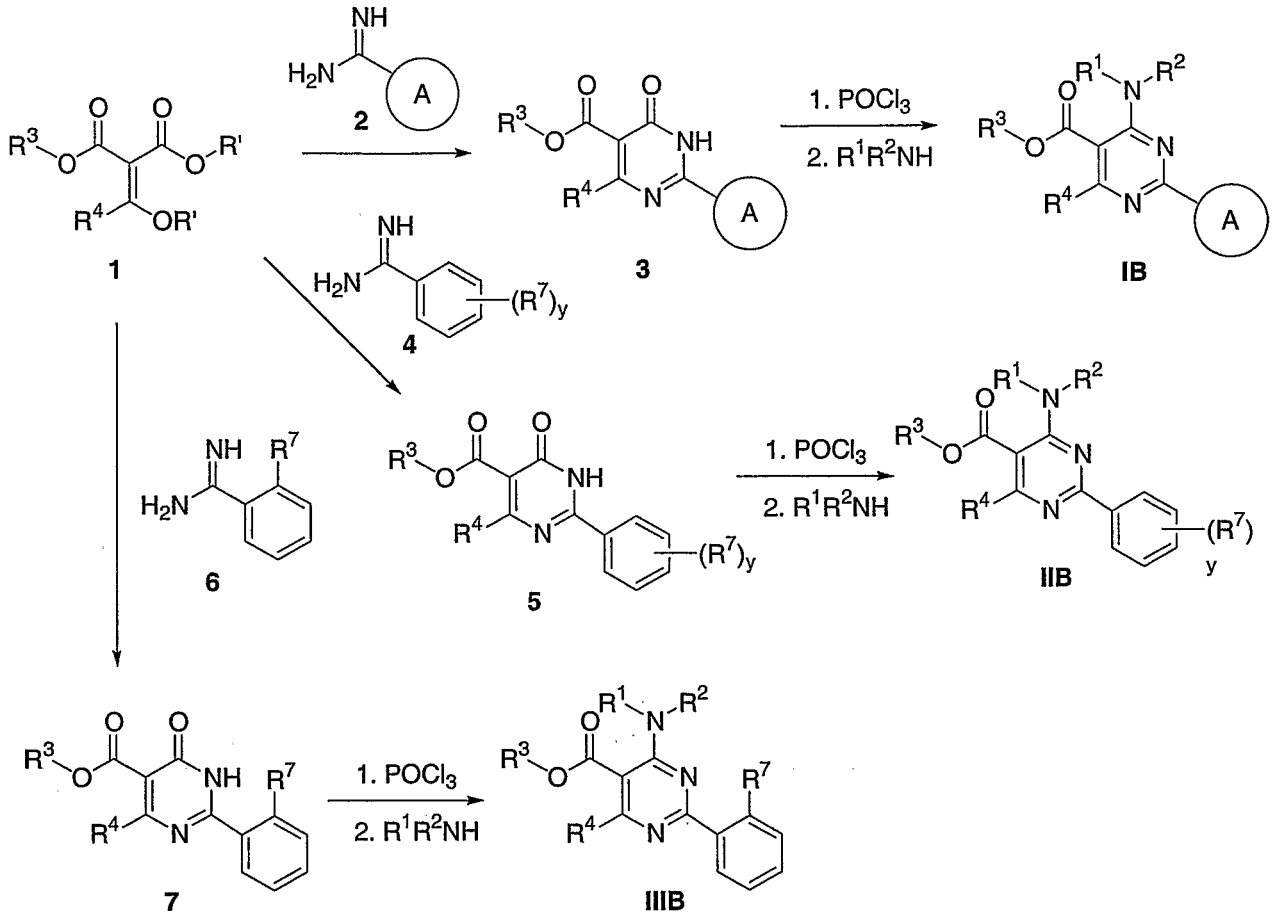
Cmpd #	Compound
303	
304	

[00207] *4. General Synthetic Methodology:*

[00208] 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.

[00209] Scheme I below depicts general conditions for the synthesis of compounds of formulas **IB, IIB, IIIB** via amidines and alkoxyalkylidine malonates.

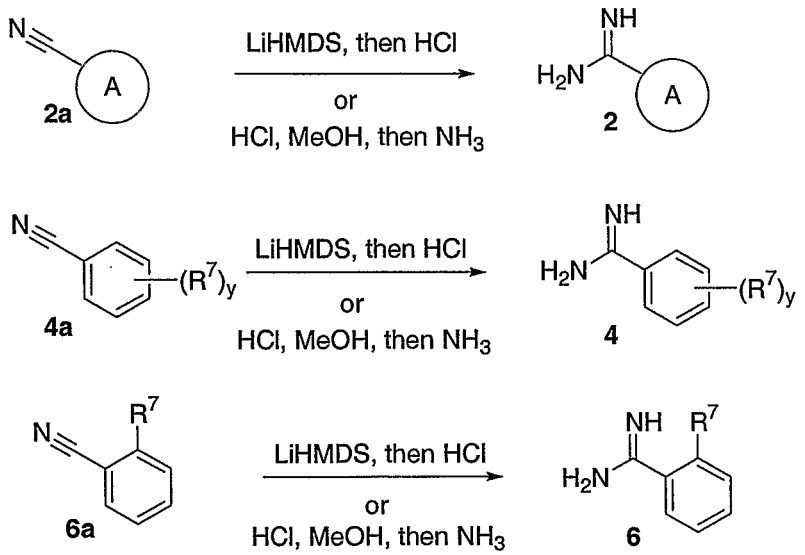
[00210] **Scheme I:**



[00210] Treatment of the appropriate alkoxyalkylidine malonate **1** (*vide infra*, Scheme III) with an amidine **2**, **4**, **6** (*vide infra*, Scheme II) generates the corresponding pyrimidinones **3**, **5**, **7**. Subsequent chlorination and nucleophilic displacement with the amine R^1R^2NH gives the pyrimidines **IB**, **IIB**, **IIIB**.

[00211] Scheme II below depicts synthesis of the requisite amidines **2**, **4**, **6** required for the preparation of **IB**, **IIB**, **IIIB** in the above Scheme I.

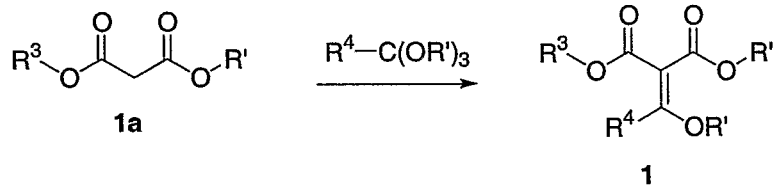
[00212] **Scheme II:**



[00213] Treatment of nitriles **2a**, **4a**, **4c** with lithium hexamethyldisilazide, followed by acidic desilylation, generates amidines **2**, **4**, **6**. Alternatively, Pinner reaction of **2a**, **4a**, **4c** generates amidines **2**, **4**, **6**.

[00214] Scheme III below depicts synthesis of the requisite alkoxyalkylidine malonates **1** required for the preparation of **IB**, **IIB**, **IIIB** in the above Scheme I.

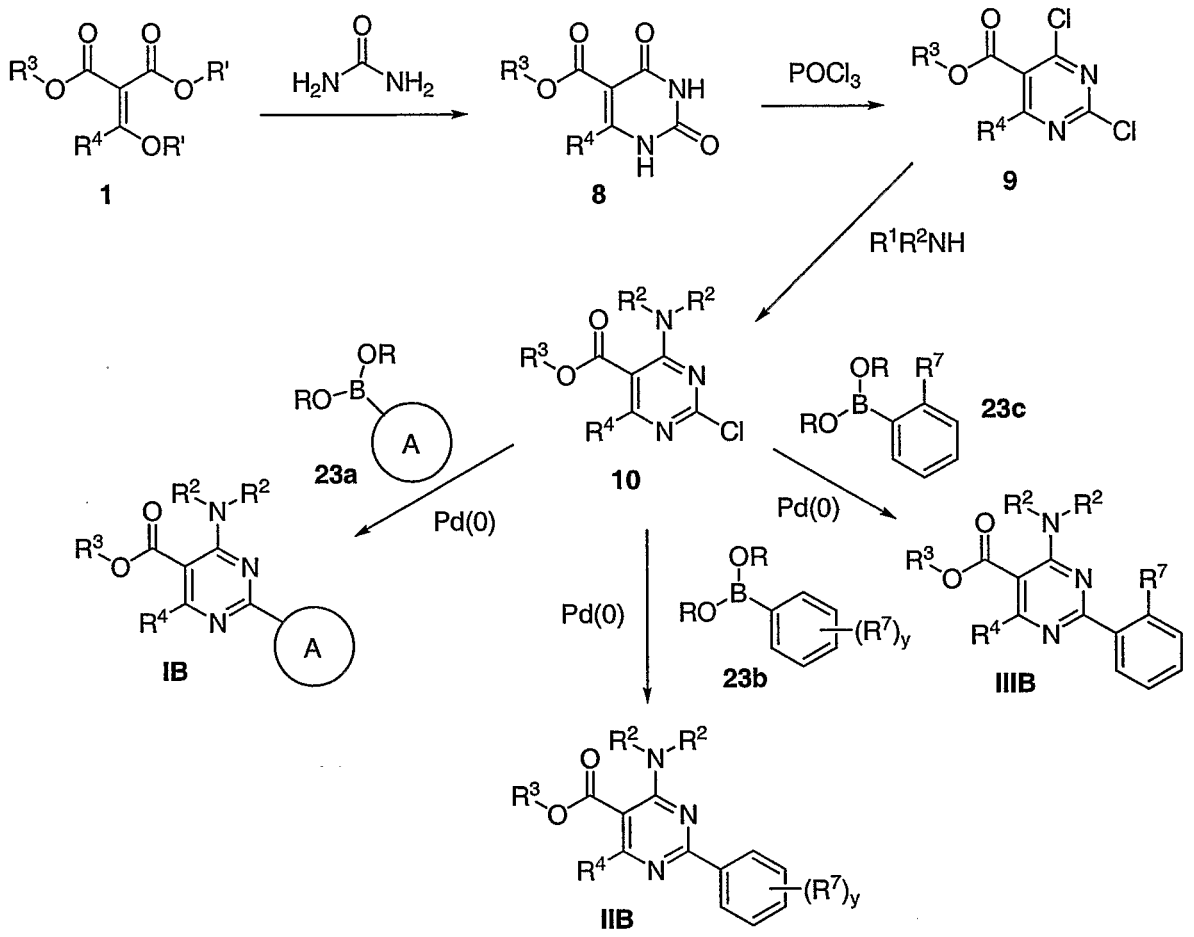
[00215] **Scheme III:**



[00216] Treatment of malonates **1a** with the appropriate orthoformate gives alkoxyalkylidine malonate **1**.

[00217] Scheme IV below depicts synthesis of **IB**, **IIB**, **IIIB** via cross coupling reactions using C2 halopyrimidines.

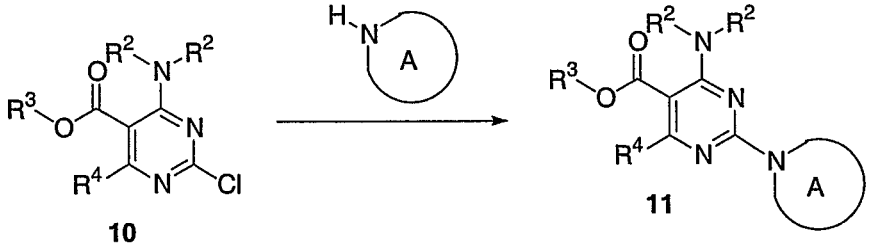
[00218] **Scheme IV:**



[00219] Treatment of alkoxyalkylidine malonate **1** with urea generates carboxyuracil **8**, which is subsequently converted to dichloropyrimidine **9** with phosphorous oxychloride. Amination proceeds at position 4 to yield 2-chloropyrimidine **10**, with Suzuki coupling at C2 giving the desired pyrimidines **IB**, **IIB**, **IIIB**.

[00220] Scheme V below depicts synthesis of C2 aza substituted pyrimidines using C2 halopyrimidines, via displacement at C2 of the pyrimidine with an incoming heteroatom nucleophile.

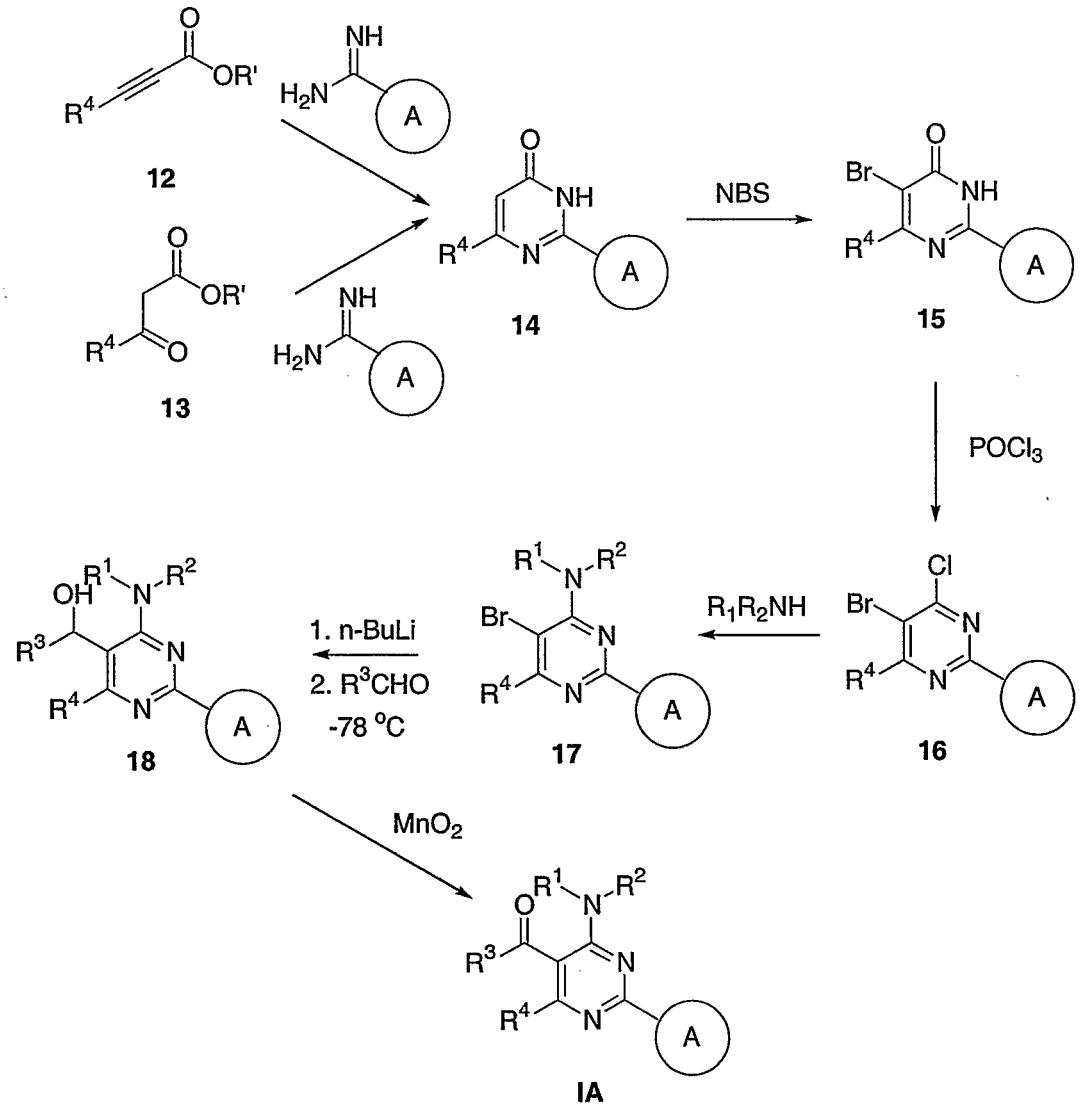
[00221] **Scheme V:**



Treatment of chloropyrimidine **10** with the appropriate nucleophilic amine in the presence of a proton scavenger generates **11**; in cases where the incoming amine is not sufficiently nucleophilic, generation of the amine anion with strong base such as sodium hydride followed by arylation with electrophile **10** gives **11**.

[00222] Scheme VI below depicts synthesis of compounds **IA** using C5 halopyrimidines.

[00223] **Scheme VI:**

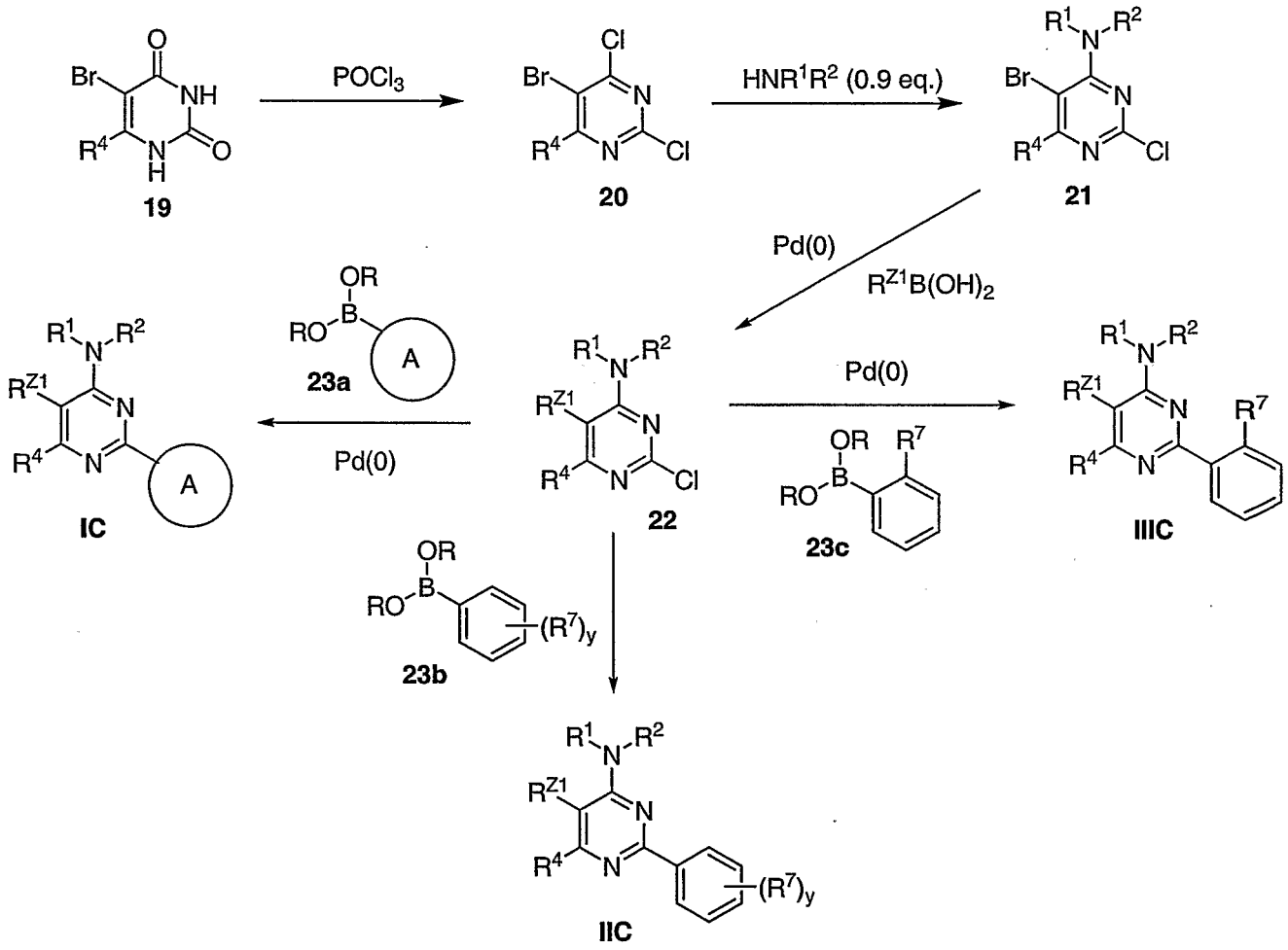


[00224] Treatment the appropriate alkynoate **12** or ketoester **13** with an amidine generates pyrimidinone **14**, which undergoes electrophilic bromination at C5 to yield bromopyrimidinone

15. Chlorination with phosphorus oxychloride followed by displacement with a suitable amine gives **17**. C5 metallation followed by reaction with an aldehyde yields hydroxypyrimidine **18**, which can be readily oxidized by Mn(IV) to give **IA**.

[00225] Scheme VII below depicts synthesis of compounds **IC**, **IIC**, **IIIC** via a tandem Suzuki strategy.

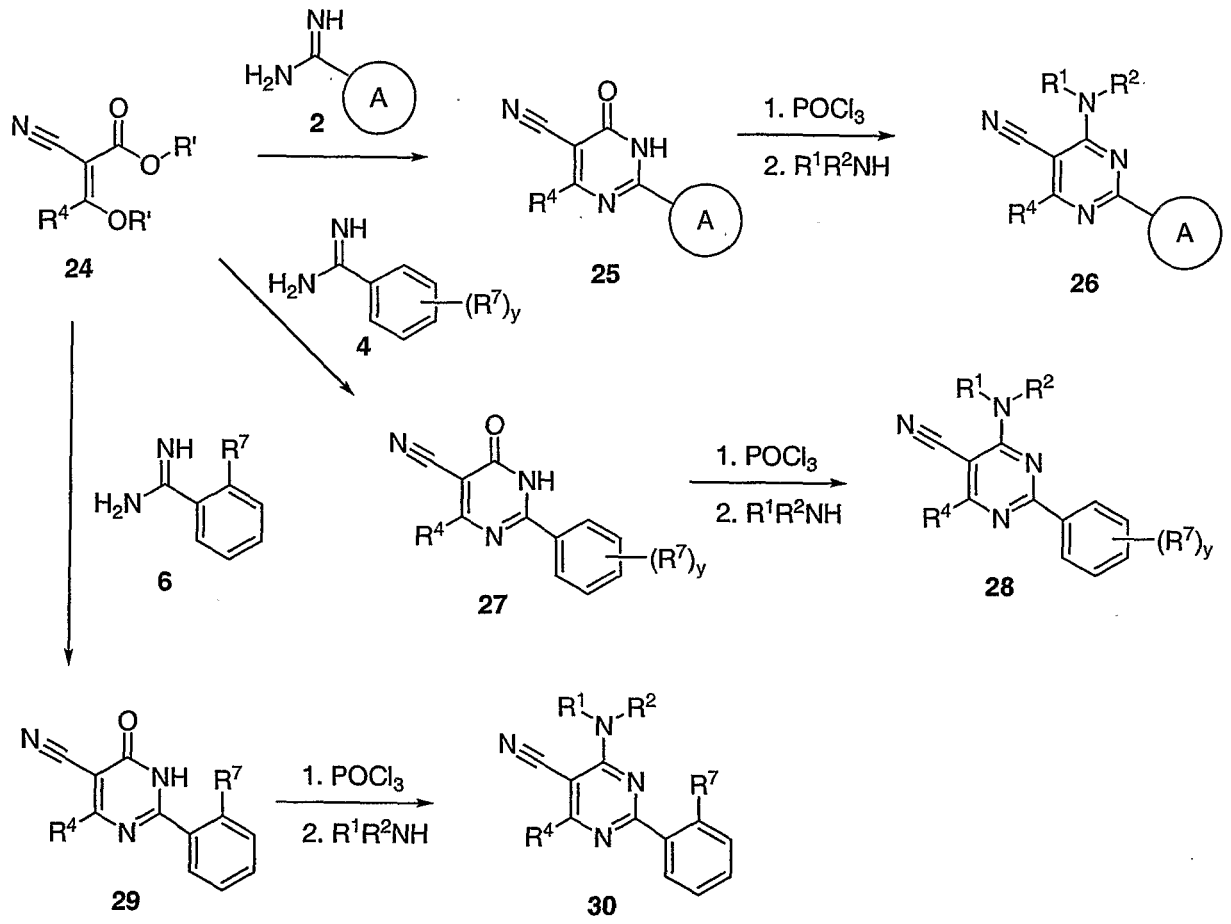
[00226] **Scheme VII:**



[00227] Chlorination of bromouracil **19** affords dichlorobromopyrimidine **20**, which undergoes amination at C4 by treatment with the appropriate amine R^1R^2NH. Suzuki cross coupling occurs at C5 to yield 2-chloropyrimidine **22**, which is subsequently cross coupled with boronates **23a**, **23b**, **23c** to give **IC**, **IIC**, **IIIC**.

[00228] Scheme VIII below depicts synthesis of C5 nitrile analogs of **26. 28, 30** using malononitriles **24**.

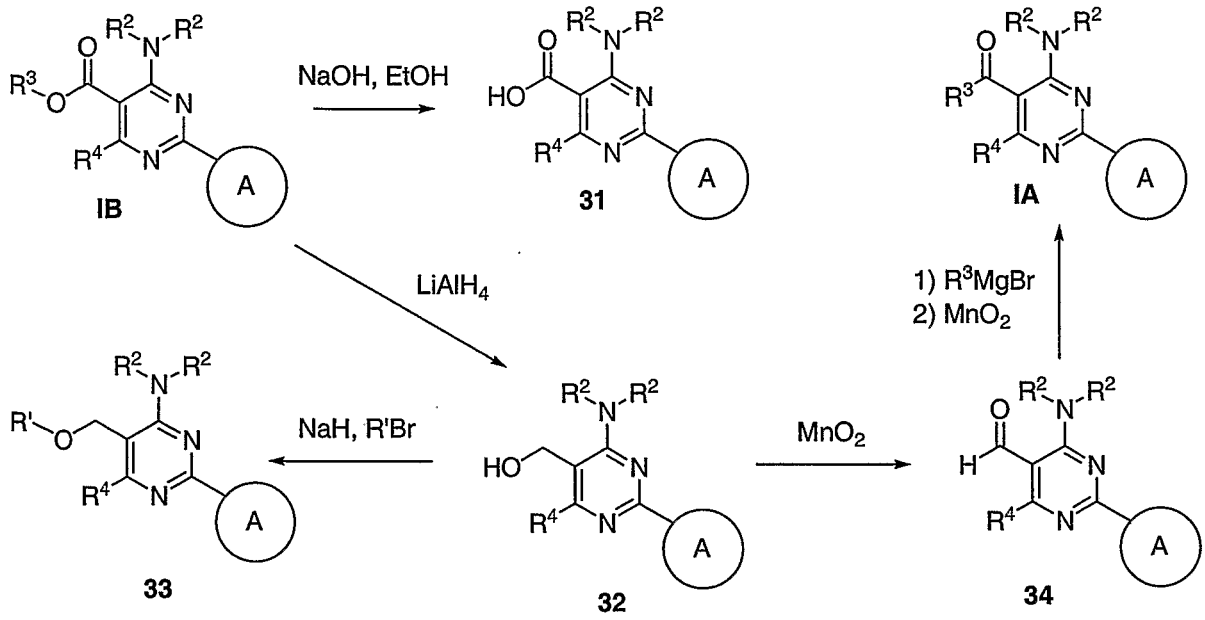
[00229] **Scheme VIII:**



[00230] Treatment of alkoxyalkylidine malononitrile **24** with amidines **2, 4, 6** affords the 5-cyanopyrimidinones **25, 27, 29.** Chlorination and amination at C4 by treatment with amine R^1R^2NH gives the C5 cyano derivatives **26, 28, 30,** which are themselves useful precursors to **IC, IIC, IIIC.**

[00231] Scheme **IX** depicts the preparation of **IB** derivatives **31, 32, 33, 34,** which also facilitate synthesis of compounds **IA.**

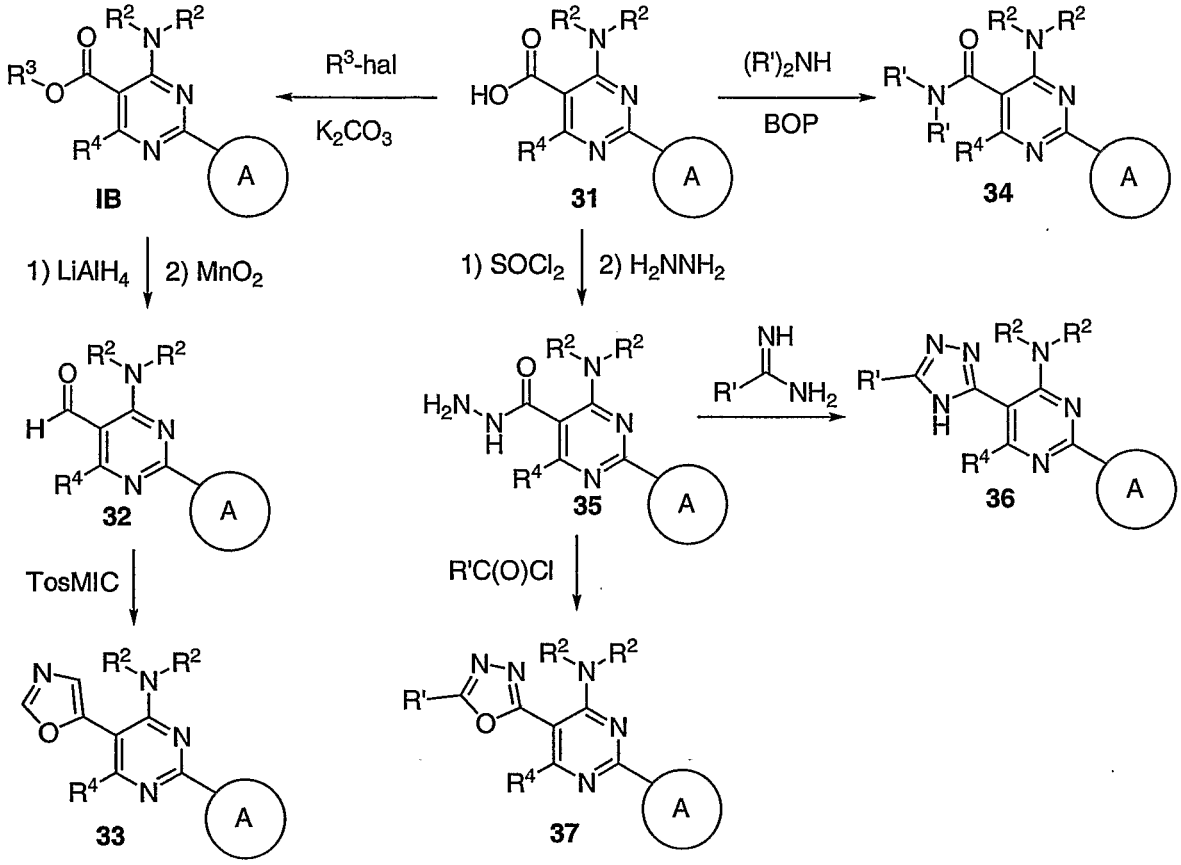
[00232] **Scheme IX:**



[00233] Saponification of **IB** affords C5 carboxylate **31** (*vide infra*, Scheme **X**); alternatively reduction using lithium aluminum hydride gives alcohol **32**, which can either be derivatized using a Williamson ether synthesis or oxidized using Mn(IV) to give aldehyde **34**. In addition to the formation of **IA** via Grignard addition and reoxidation, aldehyde **34** has utility as shown in Scheme **X** (*vide infra*).

[00234] Scheme **X** depicts the utility of carboxylate **31** in the preparation of C5 derivatives **IC** and **IB**, for example C5 derivatives **34** and C5 heteroaryl systems **33**, **36**, **37**.

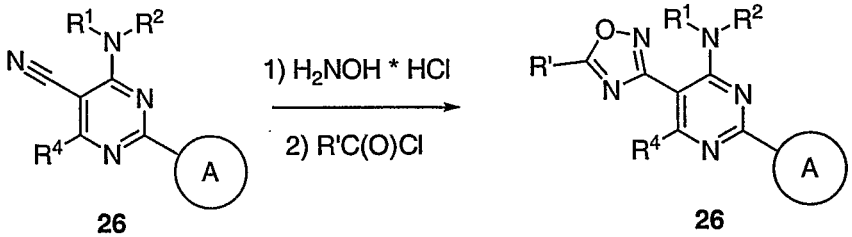
[00235] **Scheme X:**



[00236] Alkylation of carboxylate **31** (*vide supra*, Scheme **IX**) yields **IB**, with subsequent conversion to aldehyde **32** and reaction with tosylmethylisocyanide yielding oxazoles **33**. Alternatively, activation of the C5 carboxylate of **31** and reaction with a suitable nucleophile gives C5 amido derivatives **34**, while reaction of the activated carboxylate with hydrazine affords hydrazide **35**. Hydrazide **35** can be converted to a variety of heterocycles, for example triazoles **36** and oxadiazoles **37**.

[00237] Sheme **XI** depicts further utility of nitrile **26** in the preparation of oxadiazoles.

[00238] **Scheme XI:**



[00239]

[00240] Treatment of nitrile **26** with hydroxylamine hydrochloride and subsequent acylation and cyclodehydration with an acyl chloride give 1, 3, 4-oxadiazoles.

[00241] 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.

[00242] *5. Uses, Formulation and Administration*

[00243] *Pharmaceutically acceptable compositions*

[00244] 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.

[00245] 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.

[00246] 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.

[00247] 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.

[00248] 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.

[00249] *Uses of Compounds and Pharmaceutically Acceptable Compositions*

[00250] 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.

[00251] 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.

[00252] 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.

[00253] 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.

[00254] 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.

[00255] 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.

[00256] 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.

[00257] 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.

[00258] 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.

[00259] 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.

[00260] 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.

[00261] 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.

[00262] 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.

[00263] 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.

[00264] 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.

[00265] 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".

[00266] 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.

[00267] 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.

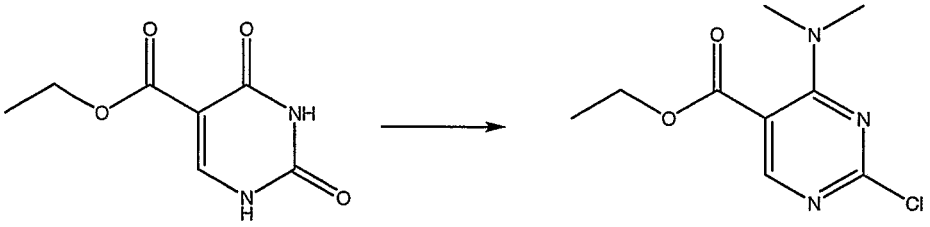
[00268] Another aspect of the invention relates to inhibiting NaV1.1, NaV1.2, NaV1.3, NaV1.4, NaV1.5, NaV1.6, NaV1.7, NaV1.8, NaV1.9, or CaV2.2 activity in a biological sample or a patient, which method comprises administering to the patient, or contacting said biological sample with a compound of formula **I** or a composition comprising said compound. The term "biological sample", as used herein, includes, without limitation, cell cultures or extracts thereof; biopsied material obtained from a mammal or extracts thereof; and blood, saliva, urine, feces, semen, tears, or other body fluids or extracts thereof.

[00269] 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.

[00270] 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.

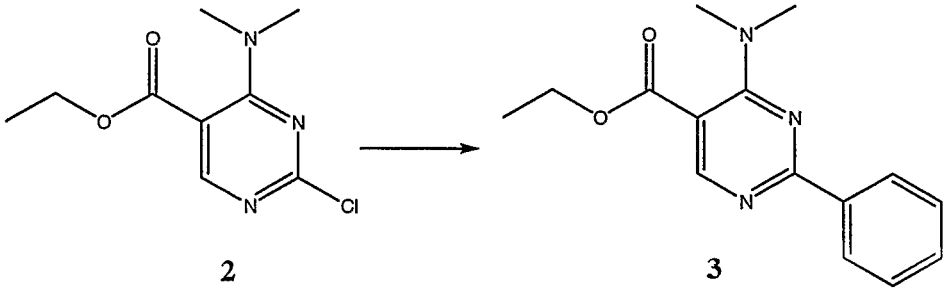
EXAMPLES

[00271] Example 1:



1 2

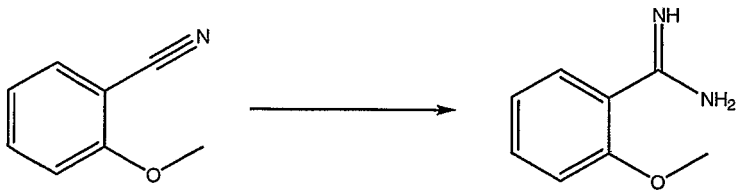
[00272] To a stirring suspension of 5-carbethoxyuracil **1** (3.00 g, 16.3 mmol) and phosphorus oxychloride (20 mL) in a 250 mL three-necked round-bottomed flask equipped with a magnetic stirrer and reflux condenser, was added N, N-dimethylaniline (2.10 mL, 16.3 mmol) in a single portion. The suspension was heated at reflux for 30 minutes and slowly formed a clear solution. The solution was concentrated under reduced pressure and the residue was poured onto ice (100 g). The solution was basified to pH = 9.0 using concentrated aqueous sodium bicarbonate solution. The mixture was partitioned between CH_2Cl_2 and H_2O. The organic portion was dried ($MgSO_4$) and evaporated to dryness under reduced pressure. The residue was dissolved in anhydrous THF (30 mL) and cooled to 0 °C. Dimethylaniline (16.3 mL, 32.6 mmol, 2.0 M in THF) was added dropwise, with stirring, over a period of 10 minutes. The solution was then stirred at 0 °C for 1 hour. The solution was concentrated under reduced pressure and the residue was purified by silica gel chromatography using (90% hexanes, 10% ethyl acetate) to obtain **2** (1.70 g, 7.34 mmol, 45% yield) as a yellow oil. M+1 (obs) = 230.1; R_t = 3.49.



2 3

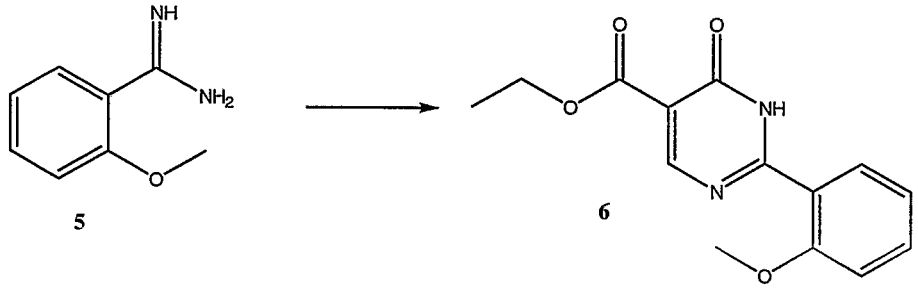
[00273] A 5 mL microwave reaction vessel was charged with a mixture of **2** (50 mg, 0.22 mmol), phenylboronic acid (39 mg, 0.32 mmol), tetrakis(triphenylphosphine)-palladium(0) (25 mg, 0.02 mmol), sodium carbonate (0.55 mL, 0.22 mmol, 0.40 M aqueous solution), and acetonitrile (0.55 mL). The vessel was sealed and heated, with stirring, at 150 °C for 10 minutes

via microwave irradiation. The organic portion was concentrated under reduced pressure and the residue was purified by silica gel chromatography using (90% hexanes, 10% ethyl acetate) to obtain **3** (54 mg, 0.20 mmol, 92% yield) as a white solid. ^{1}H NMR($CDCl_3$) δ 1.41 (t, 3H), 3.18 (s, 6H), 4.39 (q, 2H), 7.48-7.52 (m, 3H), 8.39-8.43 (m, 2H), 8.79 (s, 1H); M+1 (obs) = 272.3; R_t = 2.97.



4 5

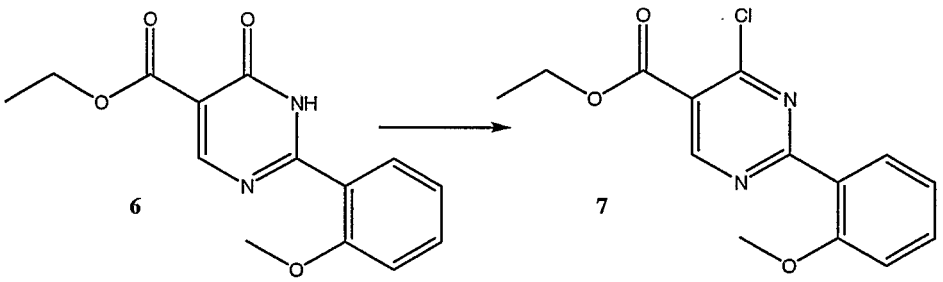
[00274] To a stirring solution of 2-methoxybenzonitrile **4** (3.00 g, 22.5 mmol) and anhydrous Et_2O (50 mL) in a 500 mL three-necked round-bottomed flask equipped with a magnetic stirrer was added lithium hexamethyldisilazane (45.0 mL, 45.0 mmol, 1.0 M in hexane) dropwise over 10 minutes, at 0 °C. The solution was stirred at ambient temperature for 24 hours. 2.0 N aqueous HCl solution was carefully added dropwise over a 30 minute period at 0 °C. The solution was stirred at ambient temperature for 2 hours. The aqueous portion was made strongly basic by the addition of saturated aqueous KOH solution (50 mL). The mixture was extracted with CH_2Cl_2 (5 x 40 mL). The organic portions were combined, dried ($MgSO_4$), and evaporated to dryness under reduced pressure to obtain **5** (1.20 g, 7.99 mmol, 36% yield) as a light tan solid. M+1 (obs) = 151.2; R_t = 0.85.



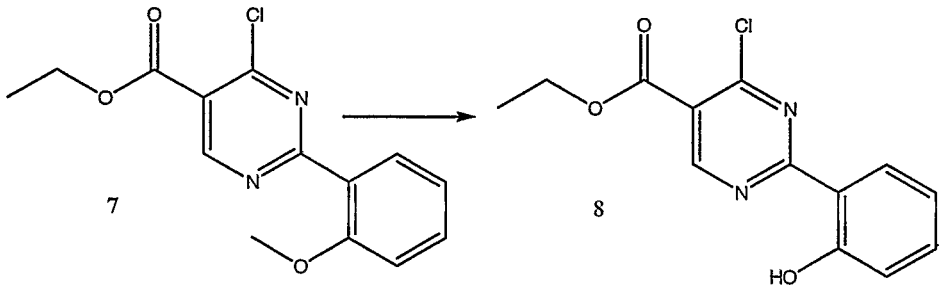
5 6

[00275] To a stirring solution of 2-methoxybenzamidine **5** (3.00 g, 20.0 mmol), diethyl ethoxymethylenemalonate (4.00 mL, 4.30 g, 20.0 mmol) and anhydrous EtOH (25 mL) in a 250 mL three-necked round-bottomed flask equipped with a magnetic stirrer was added sodium ethoxide (7.50 mL, 20.0 mmol, 21% in EtOH) dropwise over 10 minutes, at 0 °C. The solution

was stirred at ambient temperature for 1 hour. The mixture was poured into H_2O (50 mL) and the solution was acidified to pH = 4 with conc. HCl. The mixture was partitioned between CH_2Cl_2 and H_2O. The organic portion was dried ($MgSO_4$) and evaporated to dryness under reduced pressure to obtain **6** (4.82 g, 17.6 mmol, 88% yield) as a white solid. M+1 (obs) = 275.4; R_t = 2.90.

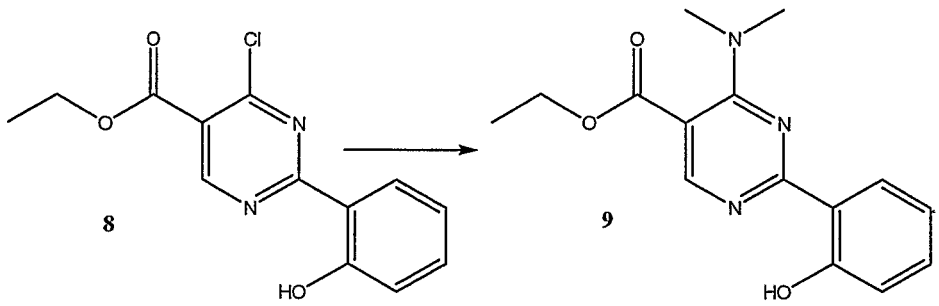


[00276] To a stirring suspension of **6** (4.50 g, 16.3 mmol) and phosphorus oxychloride (25 mL) in a 250 mL three-necked round-bottomed flask equipped with a magnetic stirrer and reflux condenser, was added N, N-dimethylaniline (2.10 mL, 16.3 mmol) in a single portion. The suspension was heated at reflux for 1 hour and slowly formed a clear solution. The solution was concentrated under reduced pressure and the residue was poured onto ice (100 g). The solution was basified to pH = 9.0 using concentrated aqueous sodium bicarbonate solution. The mixture was partitioned between CH_2Cl_2 and H_2O. The organic portion was dried ($MgSO_4$) and evaporated to dryness under reduced pressure to obtain **7** (3.10 g, 10.6 mmol, 65% yield) as a white solid. M+1 (obs) = 293.2; R_t = 3.79.



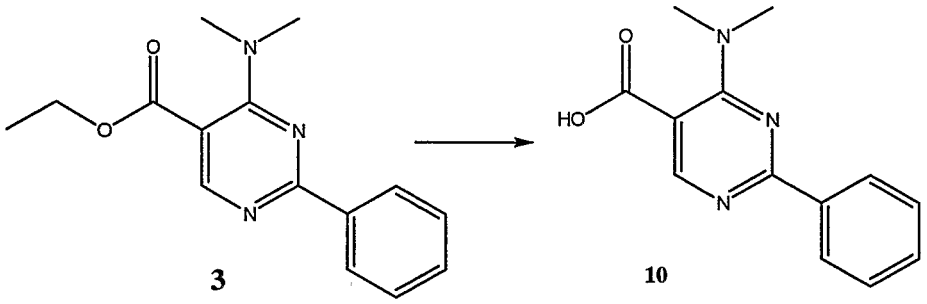
[00277] To a stirring solution of **7** (100 mg, 0.34 mmol) and CH_2Cl_2 (10 mL) in a 50 mL three-necked round-bottomed flask equipped with a magnetic stirrer was added boron tribromide (3.4 mL, 3.4 mmol, 1.0 M in CH_2Cl_2) dropwise over 10 minutes, at -78 °C. The solution was stirred at -78 °C for 1 hour and then poured into a saturated aqueous solution of $NaHCO_3$ (20

mL). The organic portion was dried ($MgSO_4$) and evaporated to dryness under reduced pressure to obtain **8** (94 mg, 0.34mmol, 100% yield) as a white solid. M+1 (obs) = 279.1; R_t = 4.50.



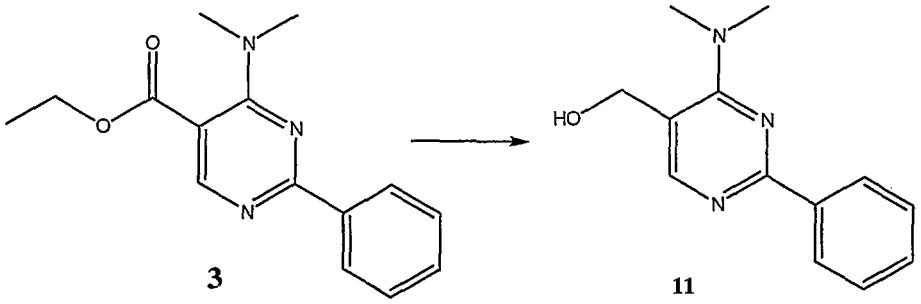
8 **9**

[00278] To a stirring solution of **9** (95 mg, 0.34 mmol), Et_3N (0.15 mL, 1.10 mmol), and THF (2.0 mL) in a 50 mL three-necked round-bottomed flask equipped with a magnetic stirrer was added dimethylaniline (0.55 mL, 1.10 mmol, 2.0 M in THF) dropwise, with stirring, over a period of 2 minutes. The solution was then stirred at ambient temperature for 1 hour. The solution was concentrated and purified by HPLC (10% to 99% CH_3CN) to obtain **9** as a trifluoroacetic acid salt (112 mg, 0.28 mmol, 82% yield) as a white solid. M+1 (obs) = 288.0; R_t = 3.47.



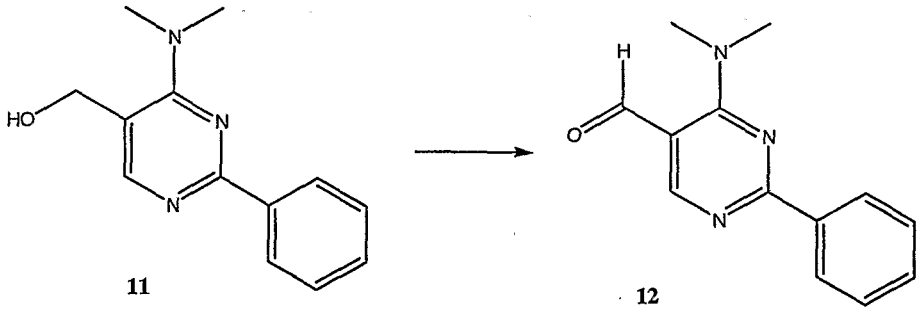
3 **10**

[00279] To a stirring solution of **3** (1.00 g, 3.70 mmol) and EtOH (50 mL) in a 250 mL three-necked round-bottomed flask equipped with a magnetic stirrer was added 1.0 N aqueous NaOH solution (26.0 mL, 26.0 mmol). The solution was stirred at 70 °C for 2 hour. The solution was acidified to pH = 4.0 using conc. HCl followed by basification with Et_3N. The mixture was concentrated under reduced pressure and the residue was purified by silica gel chromatography using (90% CH_2Cl_2, 10% MeOH) to obtain **10** (0.71 g, 2.90 mmol, 79% yield) as a white solid. M+1 (obs) = 244.4; R_t = 1.98.



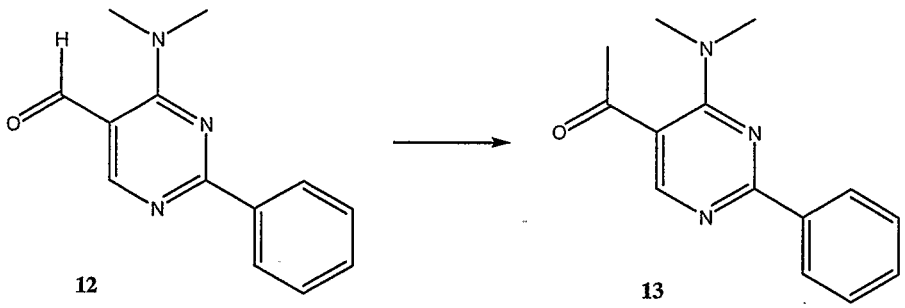
3 11

[00280] To a stirring solution of **3** (1.00 g, 3.70 mmol) and anhydrous THF (30 mL) in a 250 mL three-necked round-bottomed flask equipped with a magnetic stirrer was added lithium aluminum hydride (5.60 mL, 5.60 mmol, 1.0 M in THF) dropwise over a 10 minute period. The solution was stirred at room temperature for 20 minutes. To this solution was added H_2O (10 mL), at 0 °C, over a 5 minute period. The mixture was partitioned between CH_2Cl_2 and H_2O. The organic portion was dried ($MgSO_4$) and evaporated to dryness under reduced pressure to obtain **11** (0.72 g, 3.15 mmol, 85% yield) as a white solid. M+1 (obs) = 230.3; R_t = 2.16.



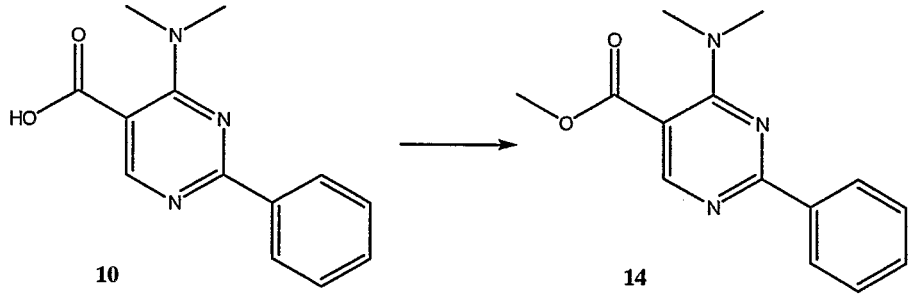
11 12

[00281] To a stirring solution of **11** (750 mg, 3.27 mmol) and CH_2Cl_2 (10 mL) in a 100 mL three-necked round-bottomed flask equipped with a magnetic stirrer was added manganese(IV) oxide (2.87 g, 33.0 mmol) in a single portion. The mixture was stirred at room temperature for 3 hours. The mixture was filtered through a bed of Celite® and the filtrate was evaporated to dryness under reduced pressure to obtain **12** (710 mg, 3.12 mmol, 96% yield) as a white solid. M+1 (obs) = 228.2; R_t = 3.42.



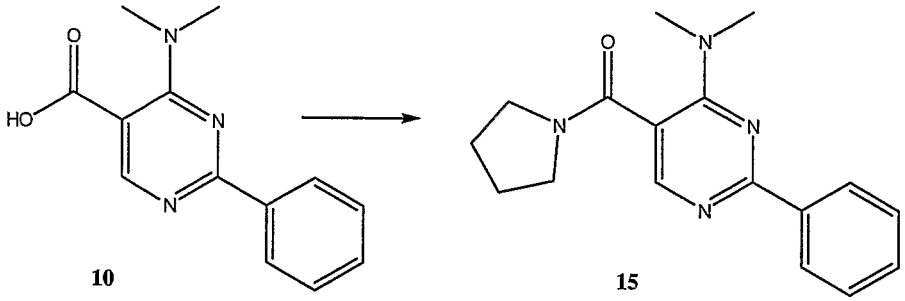
12 13

[00282] To a stirring solution of **12** (200 mg, 0.88 mmol) and Et_2O (15 mL) in a 100 mL three-necked round-bottomed flask equipped with a magnetic stirrer was added methylmagnesium bromide (0.60 mL, 1.76 mmol, 3.0 M in Et_2O) dropwise, at 0 °C, over a 5 minute period. The mixture was stirred at room temperature for 30 minutes. The mixture was partitioned between EtOAc and H_2O. The organic portion was dried ($MgSO_4$) and evaporated to dryness under reduced pressure. The obtained residue was dissolved in CH_2Cl_2 (10 mL). Manganese(IV) oxide (2.87 g, 33.0 mmol) was added in a single portion and the mixture was stirred at room temperature for 3 hours. The mixture was filtered through a bed of Celite® and the filtrate was evaporated to dryness under reduced pressure. The residue was purified by HPLC (10% to 99% CH_3CN) to obtain **13** as a trifluoroacetic acid salt (196 mg, 0.55 mmol, 63% yield) as a white solid. M+1 (obs) = 242.1; R_t = 2.95.



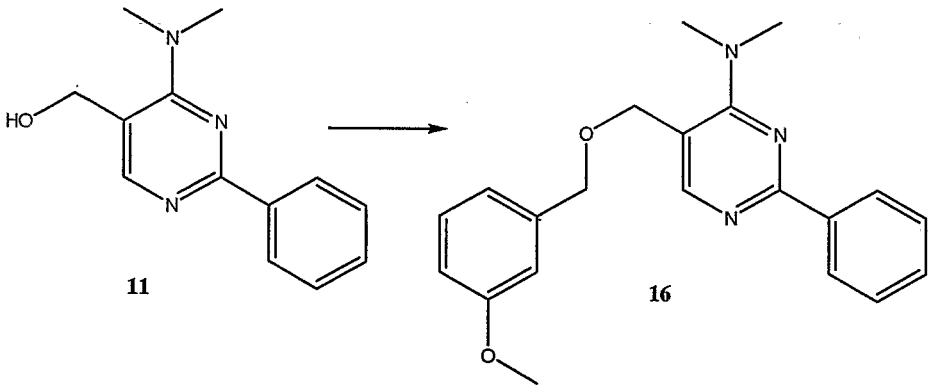
10 14

[00283] To a stirring solution of **10** (100 mg, 0.41 mmol), potassium carbonate (170 mg, 1.23 mmol) and anhydrous DMF (0.50 mL) in a 1 mL single-necked reaction vessel equipped with a magnetic stirrer was added iodomethane (0.05 mL, 0.82 mmol) in a single portion. The mixture was stirred at room temperature for 2 hours. The mixture was filtered and the filtrate purified by HPLC (10% to 99% CH_3CN) to obtain **14** as a trifluoroacetic acid salt (111 mg, 0.30 mmol, 72% yield) as a white solid. M+1 (obs) = 258.2; R_t = 2.44.



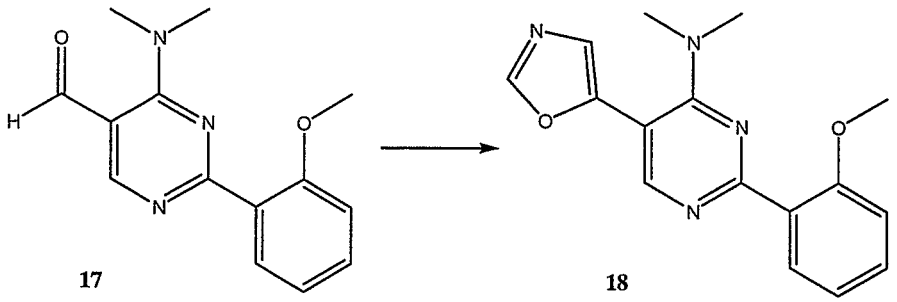
10 15

[00284] To a stirring solution of **10** (100 mg, 0.41 mmol), pyrrolidine (29 mg, 0.41 mmol), Et_3N (83 mg, 0.82 mmol), and anhydrous DMF (1.0 mL) in a 1 mL single-necked reaction vessel equipped with a magnetic stirrer was added benzotriazol-1-yloxy-tris(dimethylamino)phosphonium hexafluorophosphate (181 mg, 0.41 mmol) in a single portion. The mixture was stirred at room temperature for 20 minutes. The mixture was filtered and the filtrate purified by HPLC (10% to 99% CH_3CN) to obtain **15** as a trifluoroacetic acid salt (135 mg, 0.33 mmol, 81% yield) as a white solid. M+1 (obs) = 297.4; R_t = 2.23.



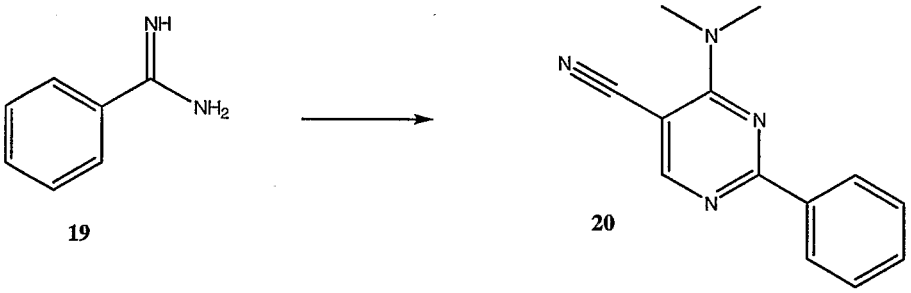
11 16

[00285] To a stirring solution of **11** (50 mg, 0.22 mmol) and anhydrous DMF (0.50 mL) in a 1 mL single-necked reaction vessel equipped with a magnetic stirrer was added sodium hydride (9.0 mg, 0.22 mmol, 60% in mineral oil) in a single portion. The mixture was stirred at room temperature for 15 minutes. To this solution was added 3-methoxybenzyl bromide (66 mg, 0.33 mmol) in a single portion. The mixture was filtered and the filtrate purified by HPLC (10% to 99% CH_3CN) to obtain **16** as a trifluoroacetic acid salt (65 mg, 0.14 mmol, 63% yield) as a white solid. M+1 (obs) = 350.4; R_t = 3.06.



17 18

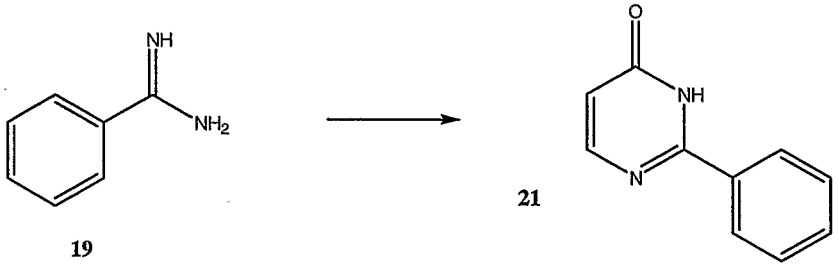
[00286] To a stirring solution of **17** (100 mg, 0.39 mmol) and anhydrous MeOH (0.50 mL) in a 1 mL single-necked reaction vessel equipped with a magnetic stirrer was added potassium carbonate (180 mg, 1.30 mmol) in a single portion. The mixture was stirred at room temperature for 5 minutes. Tosylmethyl isocyanide (91 mg, 0.47 mmol) was added in a single portion and the mixture was heated at 60 °C for 17 hours. The solution was concentrated under reduced pressure and the residue was purified by silica gel chromatography using (97% CH_2Cl_2, 3% MeOH) to obtain **18** (105 mg, 0.35 mmol, 90% yield) as a white solid. M+1 (obs) = 297.2; R_t = 2.83.



19 20

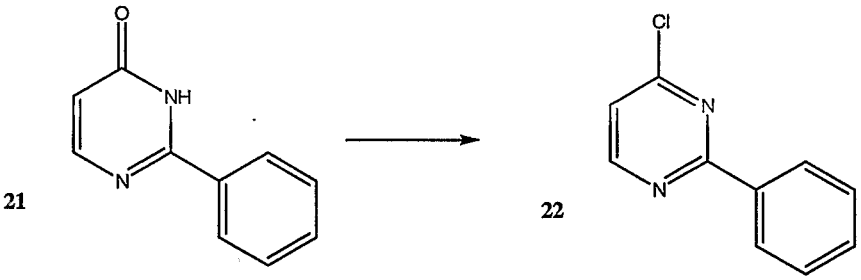
[00287] To a stirring solution of benzamidine hydrochloride **19** (735 mg, 4.70 mmol), diethyl ethoxymethylenemalonate (794 mg, 4.70 mmol) and anhydrous EtOH (10 mL) in a 100 mL three-necked round-bottomed flask equipped with a magnetic stirrer was added sodium ethoxide (3.50 mL, 9.41 mmol, 21% in EtOH) dropwise over 10 minutes, at 0 °C. The solution was heated at reflux for 1 hour. The mixture was poured into H_2O (25 ml) and the solution was acidified to pH = 3 with conc. HCl. The precipitate was filtered and the residual solid was vacuum dried to obtain the intermediate pyrimidinone as a white solid (500 mg, 2.54 mmol). The obtained pyrimidinone was suspended in phosphorus oxychloride (3 mL) in a 50 mL three-necked round-bottomed flask equipped with a magnetic stirrer and reflux condenser. To this suspension was added dimethylaniline (0.32 mL, 2.54 mmol) in a single portion. The suspension was heated at reflux for 1 hour and slowly formed a clear solution. The solution was concentrated under reduced pressure and the residue was poured onto ice (100 g). The solution

was basified to pH = 9.0 using concentrated aqueous sodium bicarbonate solution. The mixture was partitioned between CH_2Cl_2 and H_2O. The organic portion was dried ($MgSO_4$) and evaporated to dryness under reduced pressure. To the obtained residue was added Et_3N (0.35 mL, 2.54 mmol), and THF (2.0 mL) in a 50 mL three-necked round-bottomed flask equipped with a magnetic stirrer. To this solution was added dimethylaniline (3.81 mL, 7.62 mmol, 2.0 M in THF) dropwise, with stirring, over a period of 2 minutes. The solution was then stirred at ambient temperature for 1 hour. The solution was concentrated under reduced pressure and the residue was purified by silica gel chromatography using (80% hexanes, 20% ethyl acetate) to obtain **20** (256 mg, 1.14 mmol, 24% yield) as a clear oil. M+1 (obs) = 225.1; R_t = 3.83.



19 21

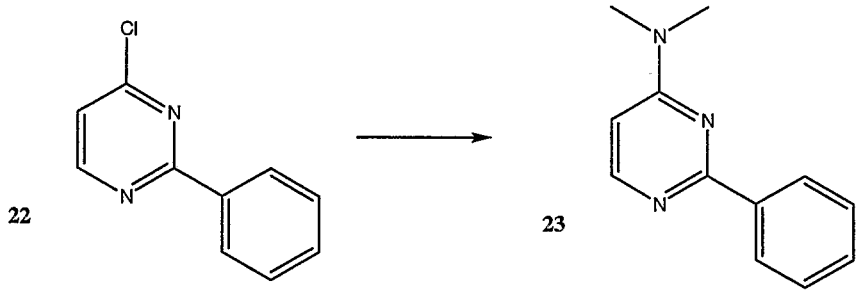
[00288] To a stirring solution of benzamidine hydrochloride **19** (5.00 g, 31.9 mmol), ethyl propiolate (3.50 mL, 34.3 mol) and anhydrous EtOH (50 mL) in a 250 mL three-necked round-bottomed flask equipped with a magnetic stirrer was added sodium ethoxide (6.51 mL, 63.8 mmol, 21% in EtOH) dropwise over 10 minutes, at 0 °C. The solution was heated at reflux for 2.5 hour. The mixture was poured into H_2O (25 mL) and the solution was acidified to pH = 3 with conc. HCl. The precipitate was filtered and the residual solid was vacuum dried to obtain **21** (2.9 g, 16.8 mmol, 53% yield) as a white solid. M+1 (obs) = 173.20; R_t = 1.74.



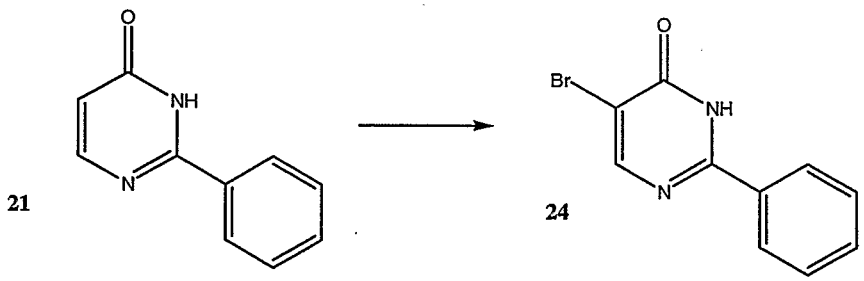
21 22

[00289] A stirring suspension of **21** (2.50 g, 14.5 mmol) and phosphorus oxychloride (17 mL) in a 100 mL three-necked round-bottomed flask equipped with a magnetic stirrer and reflux

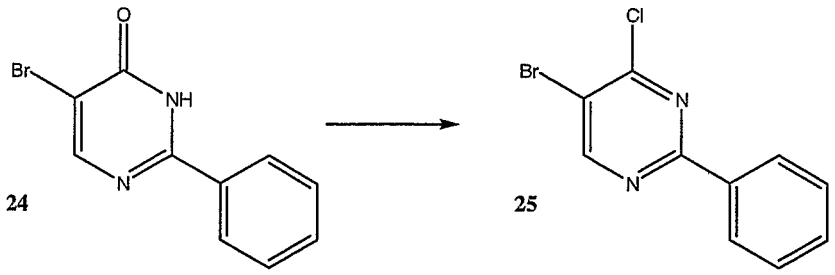
condenser, was heated at reflux for 3 hours and slowly formed a clear solution. The solution was concentrated under reduced pressure and the residue was poured onto ice (40 g). The obtain precipitate was filtered, washed with water, and vacuum dried to give **22** (2.10 g, 11.0 mmol, 76% yield) as a white solid. M+1 (obs) = 191.0; R_t = 4.22.



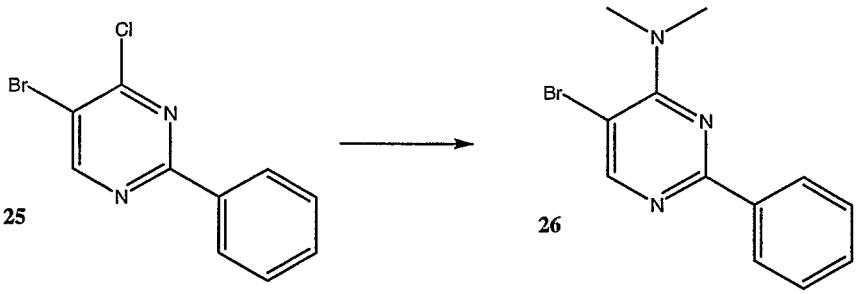
[00290] To a stirring solution of **22** (150 mg, 0.80 mmol) and H_2O (1.5 mL) in a 5 mL microwave vessel was added dimethylaniline (1.50 mL, 3.00 mmol, 2.0 M in MeOH). The solution was then heated via microwave irradiation to 150 °C for 5 minutes. The solution was purified by HPLC (10% to 99% CH_3CN) to obtain **23** as a trifluoroacetic acid salt (130 mg, 0.28 mmol, 52% yield) as a white solid. M+1 (obs) = 200.2; R_t = 2.32.



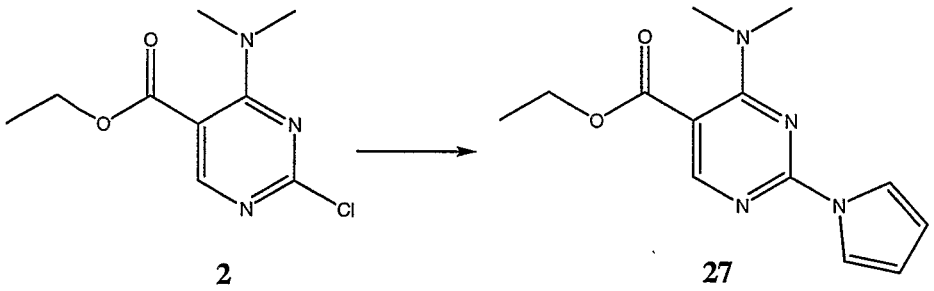
[00291] To a stirring solution of **21** (100 mg, 0.58 mmol) and acetic acid (2.0 ml) in a 50 mL three-necked round-bottomed flask equipped with a magnetic stirrer and reflux condenser, was added N-bromosuccinimide (103 mg, 0.58 mmol). The mixture was heated at 60 °C for 1 hour. The solution was concentrated under reduced pressure and the residue was purified by silica gel chromatography using (97% CH_2Cl_2, 3% MeOH) to obtain **24** (110 mg, 0.44 mmol, 76% yield) as a white solid. ^{1}H NMR(DMSO-D_6) δ 7.44-7.61 (m, 3H), 8.04-8.16 (m, 2H), 8.44 (s, 1H) 13.23 (s, 1H); M+1 (obs) = 251.1; R_t = 2.98.



[00292] A stirring suspension of **24** (100 mg, 0.40 mmol) and phosphorus oxychloride (2.0 mL) in a 50 mL three-necked round-bottomed flask equipped with a magnetic stirrer and reflux condenser, was heated at reflux for 1 hour and slowly formed a clear solution. The solution was concentrated under reduced pressure and the residue was poured onto ice (10 g). The solution was basified to pH = 9.0 using concentrated aqueous sodium bicarbonate solution. The mixture was partitioned between CH_2Cl_2 and H_2O. The organic portion was dried ($MgSO_4$) and evaporated to dryness under reduced pressure to obtain **25** (95 mg, .035 mmol, 88% yield) as a white solid. M+1 (obs) = 271.0; R_t = 4.67.

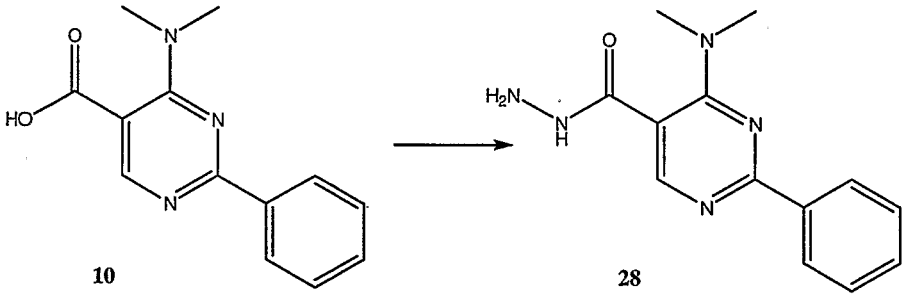


[00293] To a stirring solution of **25** (80 mg, 0.30 mmol) Et_3N (0.10 mL, 0.70 mL) and THF (2.0 mL) in a 1 mL reaction vessel was added dimethylaniline (1.0 mL, 2.0 mmol, 2.0 M in THF). The solution was stirred at room temperature for 15 minutes. The solution was purified by HPLC (10% to 99% CH_3CN) to obtain **26** as a trifluoroacetic acid salt (94 mg, 0.24 mmol, 79% yield) as a white solid. M+1 (obs) = 277.8; R_t = 3.23.



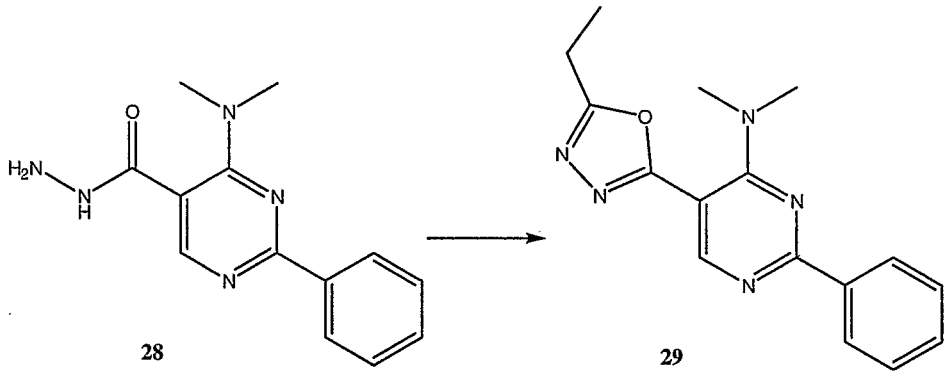
2 27

[00294] To a stirring solution of pyrrole (23 mg, 0.33 mmol) and anhydrous THF (0.50 mL) in a 2 mL microwave vessel was added sodium hydride (5.0 mg, 0.12 mmol, 60% in mineral oil). The mixture was stirred at ambient temperature for 10 minutes. To this solution was added **2** (25 mg, 0.11 mmol). The solution was then heated via microwave to 150 °C for 5 minutes. The solution was purified by HPLC (10% to 99% CH_3CN) to obtain **27** as a trifluoroacetic acid salt (30 mg, 0.08 mmol, 74% yield) as a white solid. M+1 (obs) = 261.0; R_t = 4.28.



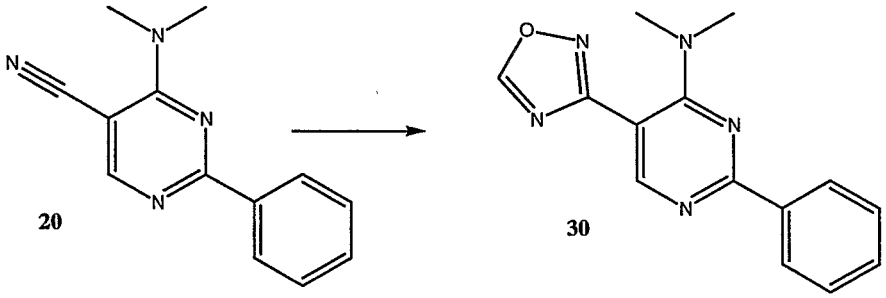
10 28

[00295] To a stirring solution of **10** (500 mg, 1.84 mmol), thionyl chloride (1.50 mL) and benzene (10 mL) in a 100 mL three-necked round-bottomed flask equipped with a magnetic stirrer and reflux condenser, was added a single drop of DMF. The solution was heated at reflux for 2 hours. The solution was concentrated under reduced pressure and the residue was azeotroped with toluene (2 x 10 mL). The residue was dissolved in CH_2Cl_2 (10 mL) follwed by the addition of Et_3N (0.50 mL, 3.60 mmol) and hydrazine (0.11 mL, 3.6 mmol). The solution was stirred at ambient temperature for 30 minutes. The mixture was evaporated to dryness under reduced pressure. The residue was purified by silica gel chromatography using (90% CH_2Cl_2, 10% MeOH) to obtain **28** (350 mg, 1.36 mmol, 74% yield) as a white solid. M+1 (obs) = 258.0; R_t = 1.66.



28 29

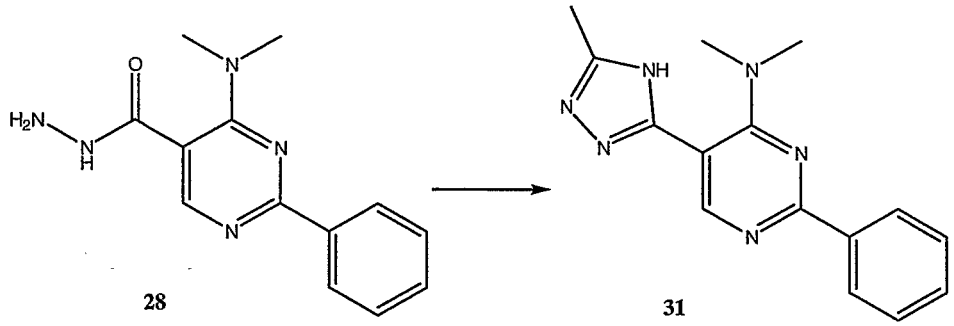
[00296] To a stirring solution of **28** (20 mg, 0.13 mmol), Et_3N (0.05 mL, 0.39 mmol), and CH_2Cl_2 (3.0 mL)) in a 50 mL three-necked round-bottomed flask equipped with a magnetic stirrer, was added propionyl chloride (0.02 mL, 0.26 mmol). The solution was stirred at ambient temperature for 30 minutes. The mixture was partitioned between CH_2Cl_2 and H_2O. The organic portion was dried ($MgSO_4$) and evaporated to dryness under reduced pressure. The residue was dissolved in anhydrous CH_3CN (2 mL) followed by the addition of $POCl_3$ (0.06 mL, 0.65 mmol). The solution was heated via microwave to 170 °C for 5 minutes in a 5 mL microwave vessel. The solution was purified by HPLC (10% to 99% CH_3CN) to obtain **29** as a trifluoroacetic acid salt (33 mg, 0.08 mmol, 59% yield) as a white solid. M+1 (obs) = 296.4; R_t = 3.18.



20 30

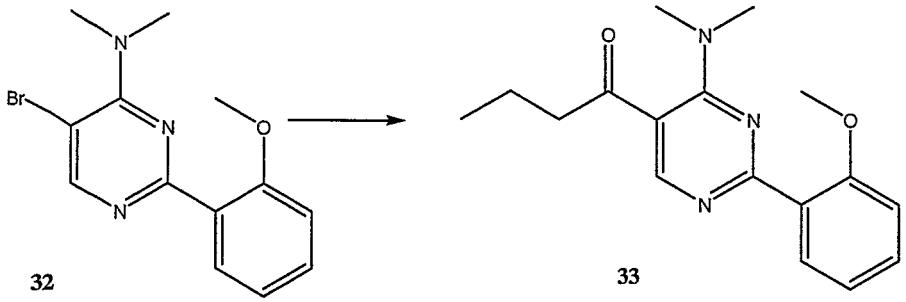
[00297] To a stirring solution of **20** (100 mg, 0.41 mmol), hydroxylamine hydrochloride (68 mg, 0.98 mmol) and anhydrous EtOH (0.50 mL) in a 10 mL three-necked round-bottomed flask equipped with a magnetic stirrer and reflux condenser, was added Et_3N (0.14 mL, 1.00 mmol) in a single portion. The suspension was heated at reflux for 24 hours. The solution was concentrated under reduced pressure and the residue was poured onto ice (100 g). The mixture

was partitioned between CH_2Cl_2 and H_2O. The organic portion was dried ($MgSO_4$) and evaporated to dryness under reduced pressure. The residue was dissolved in anhydrous CH_2Cl_2 (2.0 mL) followed by the addition of Et_3N (0.17 mL, 1.20 mmol), and Acetyl chloride (92 mg, 1.20 mmol). The solution was then stirred at ambient temperatues for 1 hour. The solution was concentrated under reduced pressure. The residue was dissolved in anhydrous DMF (0.50 mL) followed by the addition of 1,1'-carbonyldiimidazole (11 mg, 0.07 mmol). The solution was heated at 115 °C for 1 hour. The solution was purified by HPLC (10% to 99% CH_3CN) to obtain **30** as a trifluoroacetic acid salt (19 mg, 0.05 mmol, 12% yield) as a white solid. M+1 (obs) = 282.2; R_t = 3.02.



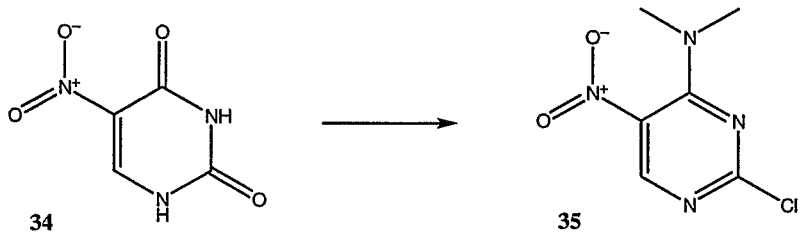
28 31

[00298] To a stirring solution of acetamidine hydrochloride (44 mg, 0.47 mmol) and anhydrous EtOH (10 mL) in a 50 mL three-necked round-bottomed flask equipped with a magnetic stirrer, was added sodium methoxide (0.94 mL, 0.047 mmol, 0.5 M in MeOH) in a single portion. The suspension was stirred at ambient temperature for 30 minutes. The mixture was filtered and to the filtrate was added **28** (80 mg, 0.31 mmol). The solution was stirred at ambient temperature for 24 hours. The mixture was partitioned between CH_2Cl_2 and H_2O. The organic portion was dried ($MgSO_4$) and evaporated to dryness under reduced pressure. The residue was dissolved in a solution of xylenes/octanol (2.0 mL, 20/1). The solution was then heated at reflux for 17 hours with the incorporation of a Dean-Stark apparatus for removal of H_2O. The solution was concentrated under reduced pressure and purified by HPLC (10% to 99% CH_3CN) to obtain **31** as a trifluoroacetic acid salt (79 mg, 0.20 mmol, 43% yield) as a white solid. M+1 (obs) = 282.1; R_t = 3.01.



32 33

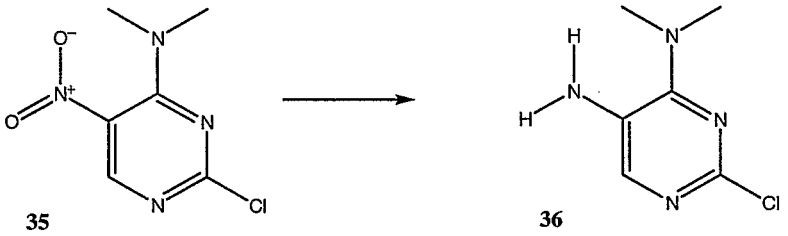
[00299] To a stirring solution of **32** (50.0 mg, 0.16 mmol) and toluene (1.0 mL) in a 20 mL two-necked round-bottomed flask equipped with a magnetic stirrer was added n-butyllithium (0.10 mL, 0.16 mmol, 1.60 M in hexane) dropwise at –78 °C over a period of 2 minutes. The mixture was stirred at –78 °C for 5 minutes followed by the dropwise addition of butyraldehyde (0.02 mL, 0.24 mmol) over a 2 minute period. The mixture was allowed to warm to room temperature over a period of 20 minutes. The resulting solution was then portioned between saturated aqueous NH_4Cl and EtOAc. The organic portion dried ($MgSO_4$) and evaporated to dryness under reduced pressure. The obtained oil was dissolved in CH_2Cl_2 (5.0 mL) followed by the addition of manganese(IV) oxide (139 mg, 1.6 mmol). The mixture was stirred at ambient temperature for 17 hours. The mixture was filtered through a bed of Celite® and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel chromatography using (10% EtOAc, 90% Hexane) to obtain **33** (15 mg, 0.05 mmol, 31% yield) as a clear oil. M+1 (obs) = 300.3; R_t = 2.55.



34 35

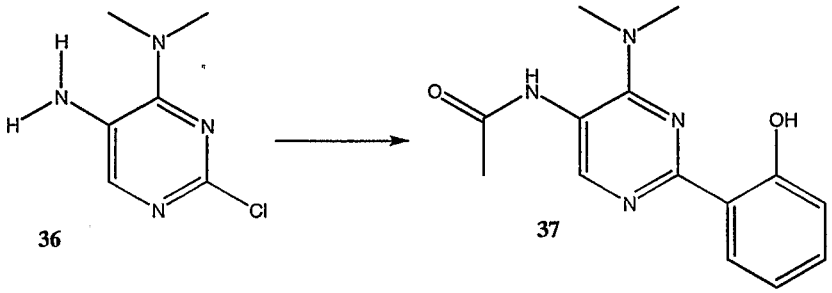
[00300] A stirring solution of **34** (10.0 g, 63.6 mmol), phosphorus oxychloride (25.0 mL), and N,N-dimethylaniline(17.0 g, 140 mmol) in a 200 mL three-necked round-bottomed flask equipped with a magnetic stirrer was heated at 80 °C for a period of 20 minutes. The solution was concentrated under reduced pressure. The residue was residue was poured into ice-water (300 g) and the mixture was basified with saturated aqueous $NaHCO_3$ solution. The mixture was

partitioned between CH_2Cl_2 and water. The organic portion was dried ($MgSO_4$) and cooled to –78 °C. To this solution was added Et3N (8.70 mL, 63.0 mmol) followed by the dropwise addition of dimethylamine (31.8 mL, 63.6 mmol, 2.0 M in THF) at –78 °C over a period of 10 minutes. The mixture was concentrated under reduced pressure. The residue was purified by silica gel chromatography using (30% EtOAc, 70% Hexane) to obtain **35** (3.9 g, 19.2 mmol, 30% yield) as a yellow solid. ^{1}H NMR ($CDCl_3$) δ 3.01 (s, 6H), 8.62(s, 1H).



35 36

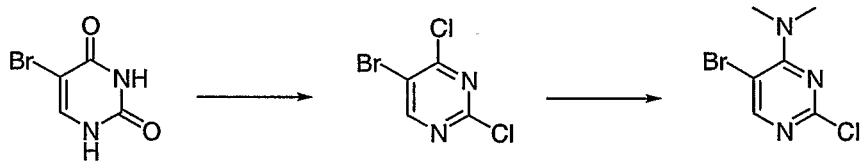
[00301] To a stirring solution of **35** (500 mg, 2.0 mmol) and acetic acid (3.0 mL) in a 50 mL single-necked round-bottomed flask equipped with a magnetic stirrer was added zinc dust (810 mg, 1.2 mmol) portionwise over a period of 5 minutes. The mixture was stirred at ambient temperature for 1 hour. The mixture was poured into a solution of saturated aqueous $NaHCO_3$ (100 mL). The mixture was filtered and partitioned between CH_2Cl_2 and water. The organic portion was dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by silica gel chromatography using (30% EtOAc, 70% Hexane) to obtain **36** (50 mg, 0.29 mmol, 15% yield) as a tan solid. M+1 (obs) = 173.2; R_t = 2.96.



36 37

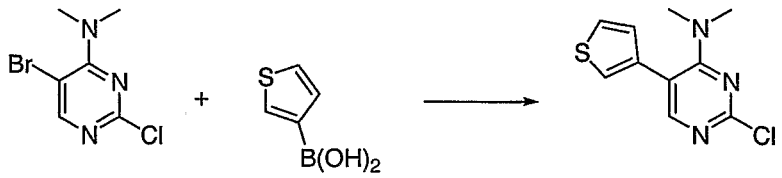
[00302] To a stirring solution of **36** (50.0 mg, 0.29 mmol), Et_3N (59.0 mg, 0.58 mmol), and anhydrous CH_2Cl_2 (10.0 mL) in a 50 mL single-necked reaction vessel equipped with a magnetic stirrer was added acetyl chloride (34.0 mg, 0.43 mmol) in a single portion. The

mixture was stirred at room temperature for 20 minutes. The solution concentrated under reduced pressure and the residue was purified via silica gel chromatography using (3% MeOH, 97% CH_2Cl_2) to obtain the amide intermediate. The amide intermediate was added to a microwave vessel followed by the addition of CH_3CN (0.50 mL), 2-(4,4,55-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenol (83 mg, 0.38 mmol) $Pd(PPh_3)_4$ (30.0 mg, 0.03 mmol), and sodium carbonate (0.50 mL, 0.40 M in H_2O). The mixture was heated via microwave irradiation at 170 °C for 5 minutes. The mixture was filtered and the filtrate purified by HPLC (10% to 99% CH_3CN) to obtain **37** as a trifluoroacetic acid salt (26 mg, 0.07 mmol, 23% yield) as a white solid. M+1 (obs) = 273.2; R_t = 1.77.



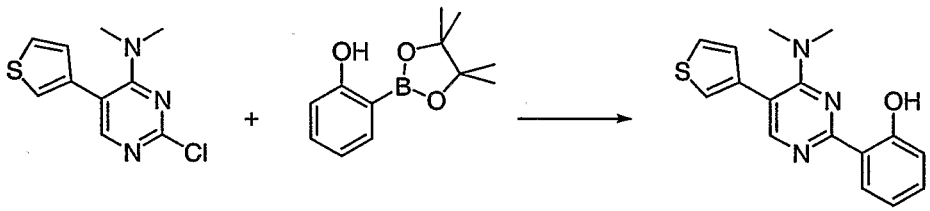
1 2 3

[00303] A solution of 5-bromouracil **1** (6.00 g, 31.4 mmol), *N,N*-dimethylaniline (12.0 mL, 94.7 mmol) in phosphoryl chloride (18 mL) was heated to 120 °C for 2h. After cooling to RT, the reaction mixture was concentrated *in vacuo*. The residue was dissolved in CH_2Cl_2 (100 mL), and the pH was adjusted to pH 8-9 by careful addition of a saturated aqueous $NaHCO_3$ solution. The phases were separated, and the aqueous phase was extracted with CH_2Cl_2 (2 × 100 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated *in vacuo* to give compound **2** which was used without further purification in the next reaction step: To a solution of compound **2** (ca. 31 mmol) in THF (100 mL) at –78 °C was slowly added a solution of dimethylamine in THF (2.0 M, 13.8 mL, 27.6 mmol) over 15 Min. The cooling bath was removed and stirring was continued for 2h at RT. The solvent was removed *in vacuo*. Chromatography over silica (EtOAc in hexanes, 0-15%) afforded compound **3** (2.7 g, 36%) as a yellow solid. LC/MS (10-99%) m/z: 238, retention time: 3.19 min. ^{1}H-NMR (400 MHz, DMSO): δ 8.29 (s, 1H), 3.20 (s, 6H).



3 4

[00304] A mixture of compound **3** (237 mg, 1.00 mmol), 3-thiophene boronic acid (128 mg, 1.00 mmol), $Pd(PPh_3)_4$ (58 mg, 0.05 mmol, 5 mol%) and aqueous Na_2CO_3 (0.4 M, 5 mL, 2.00 mmol) in acetonitrile (5 mL) was heated to reflux for 75 Min. After cooling to RT, CH_2Cl_2 (10 mL) was added and the phases were separated. The aqueous phase was extracted with CH_2Cl_2 (2 × 10 mL), and the combined organic extracts were dried over $MgSO_4$ and concentrated *in vacuo*. Chromatography over silica (EtOAc in hexanes, 0-20%) afforded compound **4** (132 mg, 55%) as a yellow oil. LC/MS (10-99%) m/z: 241, retention time: 3.61 min. ^{1}H-NMR (400 MHz, DMSO): δ 7.98 (s, 1H), 7.65 (m, 1H), 7.57 (m, 1H), 7.17 (m, 1H), 2.86 (s, 6H).



4 5

[00305] A mixture of compound **4** (36 mg, 0.15 mmol), 2-(4,4,5,5)-tetramethyl-1,3,2-dioxaborolan-2-yl)phenol (32 μL, 0.15 mmol), $Pd(PPh_3)_4$ (17 mg, 0.015 mmol, 10 mol%) and aqueous Na_2CO_3 (0.4 M, 0.75 mL, 0.30 mmol) in DME (0.75 mL) was heated by mirowave irradiation to 180 °C for 600s. The reaction mixture was filtered and purified by preparative HPLC to give compound **5** as a white solid (TFA salt). LC/MS (10-99%) m/z: 298, retention time: 2.89 min.

[00306] The characterizaton data for compounds of general formula I prepared by the above methods or methods substantially similar to those above is depicted in Table 3 below.

[00307] Table 3

Cmpd No.	LC/MS (m/z) Obs. $[M+H]^+$	LCMS RT Min
1	242.1	2.95
2	274.2	2.76
3	280.20	1.08
4	316.00	3.14
5	314.00	3.27
6	273.10	2.76
7	358.00,358.00	3.27,3.39
8	326.30	3.33
9	300.20	3.27
10	350.20	3.83
11	325.20	3.18
12	427.00	3.11
13	299.4	2.31
14	332.2	3.57
15	328.30	2.52
16	314.00	3.78
17	296.2	3.97
18	287.20	1.69
19	298.2	3.10
20	342.20	3.42
21	262.00	3.55
22	308.00,308.30	3.23,3.09
23	368.20	3.29
24	320.00	2.87
25	356.20	3.07
26	287.00	2.58
27	281.20	2.13
28	353.00	4.91
29	288.2	3.21
30	378.3	4.12
31	271.18	3.06
32	320.10	3.11
33	340.30	4.19
34	304.10	3.50
35	326.4	1.74
36	324.00	4.65
37	288.00	3.51
38	228.2	3.42
39	306.00	4.48
40	328.00	4.31
41	340.20	3.60
42	300.4	3.08
43	313.20,327.40	3.93,4.07
44	340.20	3.60
45	339.00	4.91
46	299.30	3.76

Cmpd No.	LC/MS (m/z) Obs. $[M+H]^+$	LCMS RT Min
47	375.27	4.34
48	314.10	3.36
49	326.20	2.66
50	388.00	3.66
51	357.20	2.19
52	328.2	3.58
53	314.00	2.40
54	314.10	2.67
55	343.20	2.12
56	405.4	2.96
57	300.00	3.69
58	306.10	3.88
59	258.0	3.22
60	328.20	3.05
61	410.29	3.84
62	332.00	4.75
63	272.2	2.85
64	296.00	3.75
65	360.2	4.11
66	292.00	2.36
67	271.4	2.00
68	300.30	3.10
69	300.20	3.37
70	364.00	3.11
71	327.2	2.60
72	272.20	2.41
73	328.20	1.89
74	344.00	2.47
75	329.00	3.55
76	330.00	2.94
77	342.00	3.36
78	400.00	3.41
79	284.00	2.88
80	312.20	3.49
81	286.10,286.10,286.10	3.49,3.16,2.86,3.25
82	334.20	2.56
83	326.2	3.55
84	312.00	2.45
85	290.30	3.49
86	311.21	3.21
87	326.2	3.82
88	346.2	3.94
89	259.20	3.37
90	364.00	3.80
91	390.2	4.04
92	314.00	3.72
93	333.00	3.66
94	308.20	3.46
95	340.00	2.79
96	344.00	3.65
97	313.20	3.79

Cmpd No.	LC/MS (m/z) Obs. $[M+H]^+$	LCMS RT Min
98	314.00	3.00
99	286.10	2.81
100	273.30	3.50
101	302.00	3.76
102	294.00	4.80
103	312.2	3.62
104	379.00	5.09
105	309.20	2.82
106	342.2	2.84
107	364.2	3.19
108	335.20	3.53
109	346.00	2.67
110	244.4	2.05
111	278.00	4.06
112	408.30	5.41
113	317.00	3.28
114	334.23	3.39
115	339.80	3.57
116	326.00	3.56
117	351.00	3.06
118	294.40	1.77
119	288.00	3.80
120	336.0	3.87
121	336.20	3.25
122	290.00	3.00
123	376.26	3.80
124	324.20	1.17
125	339.2	2.80
126	297.4	2.23
127	378.00	2.99
128	278.0	3.09
129	330.20	2.90
130	261.00	4.28
131	301.40	3.77
132	342.00	2.95
133	318.00	3.41
134	334.2	3.46
135	301.40	3.86
136	316.00	3.04
137	282.2	2.66
138	314.10	3.15
139	288.00	3.51
140	338.00	3.12
141	285.19	3.00
142	297.20	3.71
143	286.1	3.39
144	300.40	3.09
145	359.80	2.79
146	300.30	2.55
147	328.00	3.75
148	300.4	3.08

Cmpd No.	LC/MS (m/z) Obs. $[M+H]^+$	LCMS RT Min
149	314.2	3.26
150	342.00	3.52
151	306.2	3.36
152	298.20	2.96
153	304.0	3.28
154	325.22	3.40
155	244.4	3.11
156	270.2	3.07
157	299.30	3.35
158	387.28	4.49
159	300.20	3.45
160	358.00	2.60
161	295.00	3.50
162	364.00	3.10
163	312.0	3.38
164	295.20	3.59
165	274.00	3.08
166	354.00	3.42
167	286.2	2.87
168	318.00	4.58
169	443.10	3.66
170	302.2	2.56
171	262.00,262.00	3.19,2.54
172	347.24	3.84
173	332.20	2.40
174	300.40	3.12
175	299.30	3.66
176	361.00	1.94
177	290.00	3.96
178	300.4	3.28
179	309.20	2.76
180	314.10	3.23
181	302.2	3.34
182	380.00	3.31
183	259.20	3.57
184	273.30	3.39
185	264.00	4.28
186	348.00	3.27
187	311.00	4.48
188	302.00	4.01
189	278.0	3.79
190	374.26	3.70
191	265.00	2.81
192	348.00	3.99
193	301.40	1.77
194	341.20	2.06
195	376.2	3.67
196	361.2	2.93
197	328.20	3.28
198	300.20	3.20
199	354.0	3.67

Cmpd No.	LC/MS (m/z) Obs. $[M+H]^+$	LCMS RT Min
200	328.00	3.58
201	348.24	3.44
202	350.2	3.44
203	287.00	2.41
204	345.00	2.09
205	328.4	3.26
206	351.00	3.06
207	386.00	3.53
208	306.2	2.84
209	328.30	2.48
210	262.00	2.64
211	258.2	2.44
212	333.2	2.59
213	316.20	3.16
214	287.8	2.99
215	259.00	2.83
216	302.00	2.78
217	302.00	3.95
218	332.00	3.20
219	322.20	2.65
220	355.80	4.22
221	345.2	3.31
222	288.00	3.03
223	328.00	4.03
224	335.40	4.26
225	373.00	2.10
226	304.00	4.29
227	260.0	3.94
228	290.30	3.21
229	347.24	4.05
230	243.4	1.88
231	373.27	4.17
232	311.2	2.39
233	316.00	4.24
234	272.20	2.53
235	355.80	4.04
236	409.30	5.06
237	356.00	3.97
238	378.2	3.90
239	314.00	2.58
240	301.20	3.13
241	313.30,327.30	3.50,3.35
242	328.00	2.85
243	404.2	4.21
244	388.27	3.81
245	248.00	3.59
246	279.20	2.99
247	333.23	4.35
248	292.2	3.72
249	282.00	3.01
250	293.00	1.99

Cmpd No.	LC/MS (m/z) Obs. $[M+H]^+$	LCMS RT Min
251	295.00	0.80
252	323.20	2.20
253	273.20	1.77
254	225.1	3.83
255	289.4	2.41
256	282.20	3.02
257	282.10	3.01
258	297.20	2.83
259	296.20	3.23
260	426.20	4.01
261	253.2	4.09
262	274.4	3.90
263	283.30	3.79
264	283.00	1.99
265	362.00	2.46
266	290.00	3.41
267	275.80	3.07
268	306.2	3.11
269	259.80	2.46
270	293.00	2.13
271	262.0	3.37
272	317.9	4.24
273	384.10	3.43
274	251.0	4.07
275	282.00	2.69
276	296.40	3.18
277	265.2	4.23
278	322.20	3.63
279	264.0	2.34
280	295.00	0.90
281	282.20	2.96
282	304.2	2.96
283	260.2	2.96
284	284.00	2.44
285	308.20	3.25
286	296.4	3.46
287	231.20	1.85
288	278.0	2.83
289	234.2	2.83
290	300.00	2.55
291	310.20	3.40
292	374.00	2.67
293	220.2	2.25
294	294.00	3.63
295	306.20	2.88
296	279.0	4.63
297	267.00	2.83
298	285.00	2.12
299	281.00	2.22
300	272.0	2.97
301	244.2	3.36

Cmpd No.	LC/MS (m/z) Obs. $[M+H]^+$	LCMS RT Min
302	258.0	2.81
303	306.2	3.34
304	264.20	2.28

[00308] **ASSAYS FOR DETECTING AND MEASURING NaV INHIBITION PROPERTIES OF COMPOUNDS**

[00309] A) Optical methods for assaying NaV inhibition properties of compounds:

[00310] 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).

[00311] B) VIPR® optical membrane potential assay method with chemical stimulation

[00312] Cell Handling and Dye Loading

[00313] 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.

[00314] Analysis of VIPR® Data:

[00315] 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:

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

[00316] 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.

[00317] 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

[00318] Cell Culture

[00319] 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.

[00320] C) VIPR® optical membrane potential assay method with electrical stimulation

[00321] 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.

[00322] 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.

[00323] ***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)

[00324] ***Loading protocol:***

[00325] **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.

[00326] **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 .

[00327] 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.

[00328] 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.

[00329] Reagents

[00330] 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

[00331] 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.

[00332] Data Analysis

[00333] 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:

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

[00334] 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.

[00335] 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.

[00336] ELECTROPHYSIOLOGY ASSAYS FOR NaV ACTIVITY AND INHBITION OF TEST COMPOUNDS

[00337] 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.

[00338] VOLTAGE-CLAMP assay in DRG neurons

[00339] 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).

[00340] 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.

[00341] Solutions

[00342] 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.

[00343] 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}).

[00344] CURRENT-CLAMP assay for NaV channel inhibition activity of compounds

[00345] 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.

[00346] Compounds of the invention as shown in Table 2 were found modulate voltage-gated sodium channels.

[00347] ASSAYS FOR DETECTING AND MEASURING CaV INHIBITION PROPERTIES OF COMPOUNDS

[00348] A) Optical methods for assaying CaV inhibition properties of compounds:

[00349] 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).

[00350] VIPR® optical membrane potential assay method with electrical stimulation

[00351] 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.

[00352] 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

[00353] Loading rotocol:

[00354] **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.

[00355] **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.

[00356] **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.

[00357] 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.

[00358] Assay Protocol

[00359] Insert or use electrodes into each well to be assayed.

[00360] 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.

[00361] Data Analysis

[00362] 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:

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

[00363] 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.

[00364] 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.

[00365] ELECTROPHYSIOLOGY ASSAYS FOR CaV ACTIVITY AND INHBITION OF TEST COMPOUNDS

[00366] 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.

[00367] VOLTAGE-CLAMP assay in HEK293 cells expressing CaV2.2

[00368] 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).

[00369] 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.

[00370] Solutions

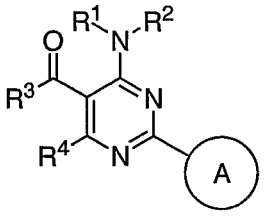
[00371] Intracellular solution (in mM): Cs-F (130), NaCl (10), $MgCl_2$ (1), EGTA (1.5), $CaCl_2$ (0.1), HEPES (10), glucose (2), pH = 7.42, 290 mOsm.

[00372] 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).

[00373] 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 having formula **IA**:



IA

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 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^3, 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 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; and each occurrence of R^X is independently selected from R', halogen, NO_2, or CN;

wherein each occurrence of R is independently selected from hydrogen or an optionally substituted C_{1-6} aliphatic group; and 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 R^3 is bonded to the carbon atom of the carbonyl group through a atom other than oxygen; and further provided that:

a) when ring A is unsubstituted phenyl, R^3 is methyl, and R^4 is =S or –SMe, then R^1 and R^2 taken together cannot be N-morpholino, N-pyrrolidinyl, or optionally substituted piperazinyl;

b) when ring A is N-morpholino, R^3 is H, and R^4 is Cl or Me, then R^1 is not Et, when R^2 is 4-Cl-phenyl, or R^1 and R^2, taken together, cannot be N-morpholino;

c) when ring A is N-pyrrolidinyl and R^3 is H, then:

i) when R^4 is $-N(CH_3)COPh$, then R^1 and R^2, taken together, cannot be pyrrolidinyl; and

ii) when R^4 is Cl, then R^1 is not Et, when R^2 is 4-Me-phenyl;

d) when ring A is N-piperidinyl, R^3 is hydrogen, and R^4 is methyl, then R^1 and R^2, taken together, cannot be N-piperidinyl;

e) when ring A is optionally substituted piperazinyl, R^3 is hydrogen, and R^4 is chloro, then when R^1 is Et, then R^2 is not 4-Cl-phenyl, 4-Me-phenyl, or 4-F-phenyl, or R^1 and R^2, taken together, cannot be thiomorpholino;

f) when ring A is 2,5-dimethyl-1H-pyrrol-1-yl, R^3 is hydrogen, and R^4 is OMe, then when R^1 is Me, then R^2 is not benzyl;

g) when ring A is 1-oxido-4-thiomorpholinyl, R^3 is hydrogen, and R^4 is OEt, then R^1 and R^2, taken together, cannot be piperizinyl;

h) when R^3 is CH_3 or optionally substituted phenyl R^1 is hydrogen, R^2 is optionally substituted phenyl, methyl, ethyl, COR', NR', or CONHR', and R^4 is =S, Me ,SMe, or SCH_2CO_2Me, SCH_2CN, then ring A is not unsubstituted phenyl or 4-Cl-phenyl;

i) when R^3 is CH_3, R^1 is hydrogen, R^2 is ethyl, and R^4 is hydrogen, then ring A is not N-pyrrolidinyl, piperazin-1-yl, N-morpholinyl, or 1-piperidinyl;

j) when R^3 is $N(R')_2$, R^1 is hydrogen, R^2 is 3-,5-Cl-phenyl, 4-Cl-phenyl, methyl, optionally substituted cyclohexyl, 3-Cl, 4-OMe-benzyl, 4-Ac-phenyl, ethyl, i-propyl, 4-OEt-phenyl, 4-OMe-phenyl, benzyl, or $(CH_2)_2OR$, and R^4 is CH_3, hydrogen, or SMe, then ring A is not unsubstituted phenyl, piperidinyl, optionally substituted piperazinyl, morpholinyl, optionally substituted pyrrolidinyl, 5,8-dihydro-1,7-naphthyridin-7(6H)-yl, or 5,6-dihydro-8-imidazo[1,2-a]pyrazin-7-yl;

k) when R^3 is $-CH=CHN(CH_3)_2$, CH_3, $-(CH_2)_2$-N-morpholino, $-(CH_2)_2$-OMe, $-(CH_2)_2$-OH, $-CH_2OMe$, n-butyl, pyridin-2-ylmethyl, pyridin-2-yl, pyrimidin-5-yl, CH_2SO_2Me, $-(CH_2)_2$-NMe_2, $-(CH_2)_2$-N-(4-methylpiperazyl), $-(CH_2)_2$-NH-pyridin-3-yl, $-(CH_2)_2$-NH-CH_2-pyridin-3-yl, 1-methyl-1H-imidazol-2-yl, 5-amino-1,2-dimethyl-1H-imidazol-4-yl, 4-(dimethylamino)phenyl, 3,4-(methylenedioxy)phenyl, $-CH_2=CH_2$, $-CH=CH_2$, or -CH(CN)COOEt, R^1 is hydrogen, R^2 is optionally substituted benzyl or ethyl, R^4 is SMe or hydrogen, then ring A is not unsubstituted phenyl or optionally substituted pyrrolidinyl;

l) when R^1 is hydrogen and R^2 is hydrogen or 4,6-dimethylpyrimidin-2-yl, ring A is optionally substituted phenyl, R^3 is Me or unsubstituted phenyl, then R^4 is not SMe, =S, Me, or unsubstituted phenyl;

m) when R^1 is hydrogen and R^2 is optionally substituted benzyl, then R^3 is not 3,4,5-trimethoxyphenyl;

n) when R^1 and R^2 are both hydrogen, ring A is (2-fluorophenylmethyl)-1H-pyrazolo[3,4-b]pyridin-3-yl, R^3 is ethyl or 2-ethoxyethyl, then R^4 is not hydrogen;

o) when R^1 is hydrogen, R^2 is benzoyl, then R^3, R^4, and ring A are all not simultaneously unsubstituted phenyl;

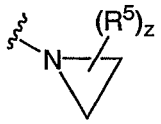
p) when R^1 and R^2 are both hydrogen, ring A is 4-(4'-morpholinyl)-5-methyl-2-phenylthieno[2,3-d]pyrimidin-6-yl, 4-amino-5-methyl-2-phenylthieno[2,3-d]pyrimidin-6-yl, 4-(4-(4-fluorophenyl)-piperazyl)-5-methyl-2-phenylthieno[2,3-d]pyrimidin-6-yl, 4-(4,6-dimethyl-pyrimidin-2-yl)amino-5-methyl-2-phenylthieno[2,3-d]pyrimidin-6-yl, 4-(N-pyrrolidinyl)-5-methyl-2-phenylthieno[2,3-d]pyrimidin-6-yl,or unsubstituted phenyl, R^3 is methyl, then R^4 is not methyl or SMe;

q) when R^1 and R^2 both are hydrogen, R^3 is methyl, R^4 is =S or unsubstituted phenyl, then ring A is not unsubstituted phenyl;

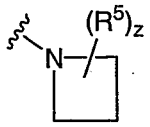
r) when R^1 and R^2 taken together form a N-pyrrolidinyl ring, R^3 is $-NHCH_2$(4-trifluoromethylphenyl), R^4 is H, then ring A is not N-pyrrolidinyl, 3,4-dimethoxyphenyl, 2-methoxyphenyl, thiophen-3-yl, or thiophen-2-yl; and

2. The compound according to claim 1, 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, sulfur, or oxygen.

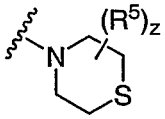
3. The compound according to claim 2, wherein R^1 and R^2, taken together with the nitrogen atom to which they are bound, form an optionally substituted 3-8 membered heterocyclyl ring selected from:



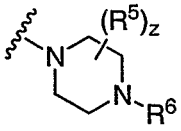
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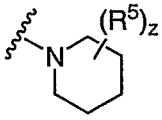
bb



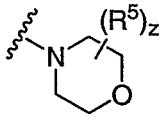
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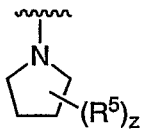
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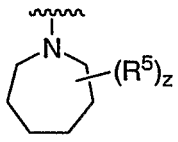
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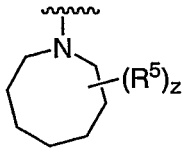
ff



gg



hh



jj

wherein z is 0-4.

4. The compound according to claim 3, wherein R^1 and R^2, taken together with the nitrogen atom to which they are bound, form ring **bb**, **dd**, **ee**, **ff**, or **gg**.

5. The compound according to claim 1, 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 replaced with NR, O, (CO)O, O(CO), NR(CO), (CO)NR, SO_2(NR), or (NR)SO_2.

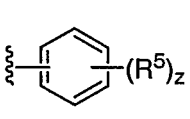
6. The compound according to claim 1, wherein one of R^1 or R^2 is hydrogen and the other of R^1 or R^2 is an optionally substituted C_{1-4}aliphatic group, wherein one or more methylene units in the C_{1-4}aliphatic group are optionally replaced with NR, O, (CO)O, O(CO), NR(CO), (CO)NR, SO_2(NR), or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

7. The compound according to claim 5, or 6, wherein R^1 and R^2 groups is selected from 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.

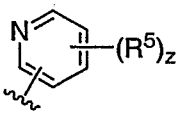
8. The compound according to claim 5 or 7, wherein R^1 and R^2 are identical.

9. The compound according to claim 1, 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.

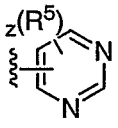
10. The compound according to claim 9, wherein one of R^1 or R^2 is hydrogen and the other of R^1 or R^2 is selected from:



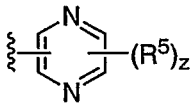
a



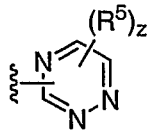
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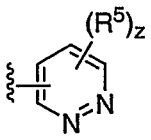
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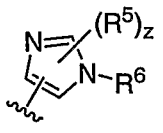
d



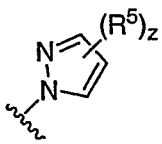
e



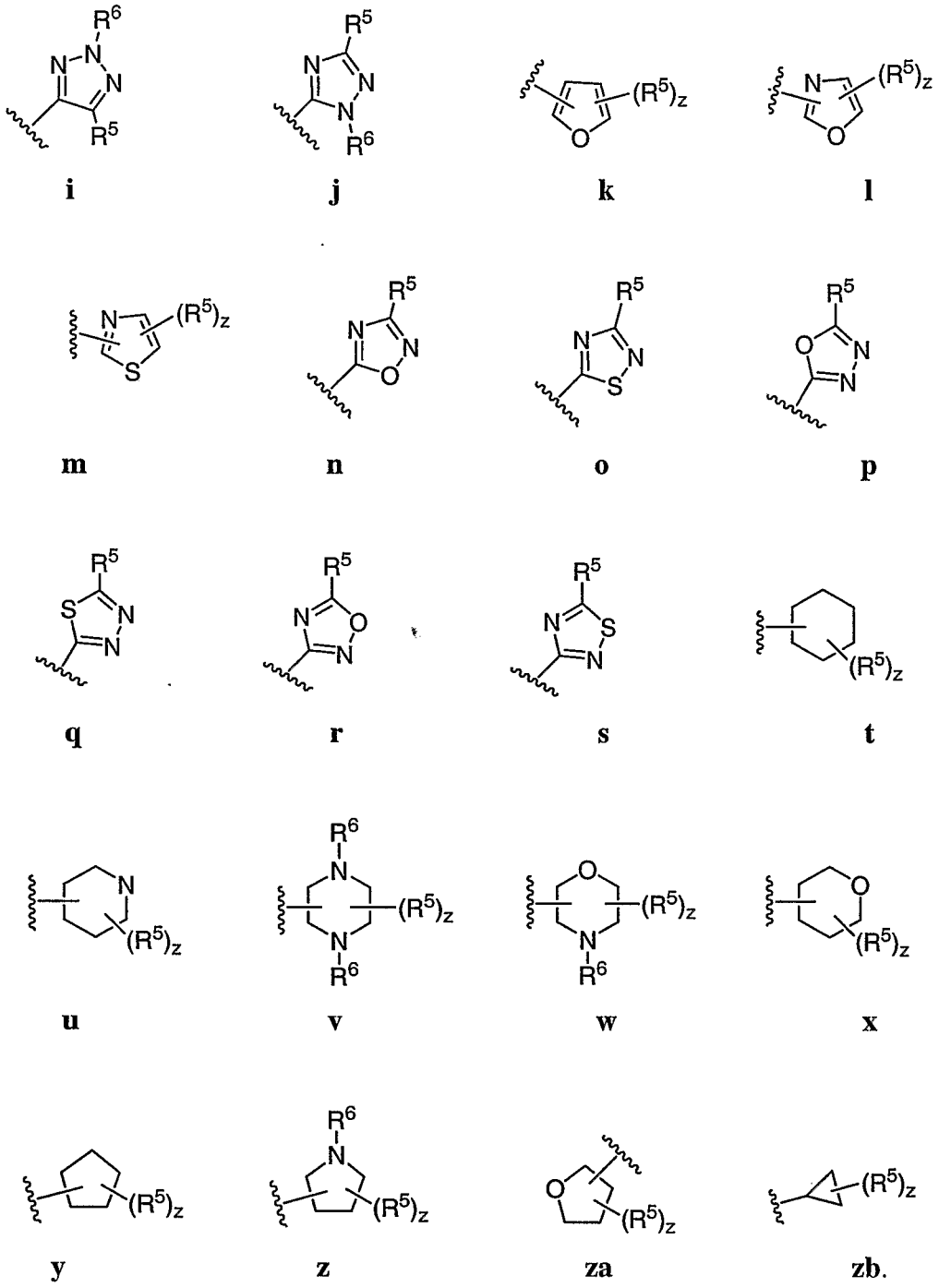
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11. The compound according to claim 3 or 10, wherein R^6 is hydrogen, or an optionally substituted group selected from C_{1-6}alkyl, aryl, aryl(C_{1-6})alkyl, -N(R')$_2$, -CH_2N(R')$_2$, -CH_2OR', -CH_2SR', -$(CH_2)_2$N(R')$_2$, -$(CH_2)_2$OR', -$(CH_2)_2$SR', -COR', -CON(R')$_2$, or -$S(O)_2$N(R')$_2$.

12. The compound according to claim 11, wherein R^6 is independently H, Me, CF_3, ethyl, propyl, butyl, pentyl, $CO(C_1\text{-}C_4alkyl)$, $-CONH_2$, $-COO(C_1\text{-}C_4alkyl)$, $-CH_2OH$, $-SO_2NH_2$, $SO_2N(CH_3)_2$, or optionally substituted phenyl.

13. The compound according to claim 1, wherein R^4 is 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 $-S(O)_2N(R')_2$.

14. The compound according to claim 13, wherein R^4 is 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.

15. The compound according to claim 1, wherein R^3 is $-CF_2H$, $-CF_3$, $-CHCl_2$, $-CHBr_2$, CH_2CN, $-CH_2OR'$, $-CH_2SR'$, $-CH_2N(R')_2$, or as $Q\text{-}R^X$; wherein Q is an optionally substituted $C_2\text{-}C_6$ alkylidene chain wherein up to two non-adjacent methylene units of Q are optionally 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; and each occurrence of R^X is independently selected from R', halogen, NO_2, or CN, provided that Q is bonded to the carbon atom of the carbonyl group through a carbon atom.

16. The compound of claim 15, wherein R^3 is $-CF_2H$, $-CF_3$, $-CHCl_2$, $-CHBr_2$, CH_2CN, $-CH_2OR'$, $-CH_2SR'$, $-CH_2N(R')_2$, or as $Q\text{-}R^X$; wherein Q is a bond, and R^X is an optionally substituted group selected from $C_{2\text{-}8}$ aliphatic, $C_{6\text{-}10}$ aryl, a heteroaryl ring having 5-10 ring atoms, or a heterocyclyl ring having 3-10 ring atoms.

17. The compound of claim 1, wherein R^3 is 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', $-CON(R')_2$, or $-S(O)_2N(R')_2$.

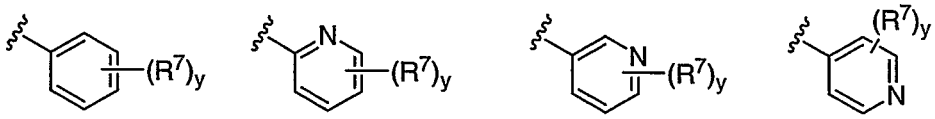
18. The compound of claim 17, wherein R^3 is H, Me, CF_3, ethyl, propyl, butyl, pentyl, $CO(C_1\text{-}C_4alkyl)$, $-CONH_2$, $-COO(C_1\text{-}C_4alkyl)$, $-CH_2OH$, $-SO_2NH_2$, $SO_2N(CH_3)_2$, or optionally substituted phenyl.

19. The compound according to claim 1, wherein ring A is selected from 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, wherein said ring is optionally substituted at one or more carbon atoms with y occurrences of $-R^7$, and at one or more substitutable nitrogen atoms with $-R^8$, wherein y is 0-5.

20. The compound according to claim 19, wherein ring A is selected from phenyl, piperidyl, thiophenyl, indolyl, or pyrrolidinyl, wherein ring A has 0-2 occurrences of $-R^7$ and 0-1 occurrences of $-R^8$ at a substitutable nitrogen atom.

21. The compound according to claim 20, wherein ring A is phenyl, piperidyl, or pyrrolidinyl.

22. The compound according to claim 19, wherein ring A is selected from:



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

wherein y is 0-5.

23. The compound according to claim 19, wherein y is 0-2.

24. The compound according to claim 23, wherein y is 0 and ring A is unsubstituted.

25. The compound according to claim 23, wherein each R^7 is independently selected from 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 -$S(O)_2N(R')_2$.

26. The compound according to claim 25, wherein each R^7 is independently H, Cl, Br, F, CF_3, Me, Et, CN, NO_2, -COOH, NH_2, –$N(CH_3)_2$, -$N(Et)_2$, -$N(iPr)_2$, -$O(CH_2)_2OCH_3$, -$CONH_2$, -$COOCH_3$, -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.

27. The compound according to claim 23, wherein each R^8 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', -$(CH_2)_2N(R')_2$, -$(CH_2)_2OR'$, -$(CH_2)_2SR'$, -COR', -$CON(R')_2$, or -$S(O)_2N(R')_2$.

28. The compound according to claim 27, wherein each 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_2NH_2, $SO_2N(CH_3)_2$, or optionally substituted phenyl.

29. The compound according to claim 1, wherein R^1 and R^2 both are optionally substituted C_{1-4} aliphatic, R^3 is C_{1-4} aliphatic, R^4 is hydrogen, and ring A is optionally substituted phenyl.

30. The compound according to claim 29, wherein R^1 and R^2 are both methyl, ethyl, or propyl, R^3 is ethyl, propyl or butyl, and ring A is phenyl having up to one Q- R^X substituent, 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 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; and each occurrence of R^X is independently selected from R', halogen, NO_2, or CN.

31. The compound according to claim 1, R^1 and R^2 are both C_{1-4} aliphatic or R^1 and R^2 taken together form a 5-6 membered heterocyclic ring, R^3 is optionally substituted C_{1-4} aliphatic or aryl, R^4 is hydrogen, and ring A is optionally substituted phenyl.

32. The compound according to claim 31, wherein R^1 and R^2 are both methyl, ethyl, or propyl, or R^1 and R^2, taken together form an optionally substiuted 1-pyrrolidinyl or 1-piperidinyl, R^3 is optionally substituted ethyl, propyl, butyl, or phenyl, and ring A is phenyl having up to one $Q\text{-}R^X$ substituent, 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 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; and each occurrence of R^X is independently selected from R', halogen, NO_2, or CN.

33. The compound according to claim 32, wherein, R^1 and R^2 both are methyl or ethyl, R^3 is ethyl or propyl, R^4 is hydrogen, and ring A is a 2-substituted phenyl, wherein said substituent is $Q\text{-}R^X$, wherein Q is a bond.

34. The compound according to claim 1, wherein R^1 and R^2 are both C_{1-4} aliphatic, R^3 is optionally substituted C_{1-4} aliphatic, R^4 is hydrogen, and ring A is optionally substituted phenyl.

35. The compound according to claim 34, wherein R^1 and R^2 include methyl or ethyl, R^3 is optionally substituted ethyl, or propyl, ring A is phenyl having up to one $Q\text{-}R^X$ substituent, 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 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; and each occurrence of R^X is independently selected from R', halogen, NO_2, or CN.

36. The compound according to claim 35, wherein R^1 and R^2 are both methyl or ethyl, R^3 is ethyl or propyl, R^4 is hydrogen, and ring A is phenyl optionally substituted with halo, or OH.

37. The compound according to claim 1, wherein R^1 and R^2 are both C_{1-4} alphatic or R^1 and R^2 taken together form a 4-6 membered heterocyclic ring, R^3 is optionally substituted C_{1-4} aliphatic or aryl, R^4 is hydrogen, and ring A is optionally substituted phenyl, 5-membered heteroaryl, or six-membered heterocyclyl.

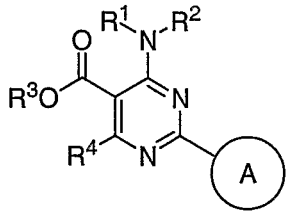
38. The compound according to claim 37, wherein R^1 and R^2 are both methyl, ethyl, or propyl; or R^1 and R^2, taken together form a 1-azetidinyl, 1-pyrrolidinyl, or 2,5-dihydropyrrolyl ring, R^3 is optionally substituted ethyl, propyl, butyl, or phenyl, and ring A is phenyl having up to one Q-R^X substituent, 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 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; and each occurrence of R^X is independently selected from R', halogen, NO_2, or CN.

39. The compound according to claim 38, wherein R^1 and R^2 are both methyl or ethyl, R^3 is ethyl or propyl, R^4 is hydrogen, and ring A is phenyl optionally substituted with halo, or OH.

40. The compound according to claim 1, wherein R^1 and R^2 are both C_{1-4} aliphatic, R^3 is R^3 is C_{1-4} aliphatic, R^4 is hydrogen, and ring A is phenyl having up to two Q- R^X substituents, 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 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; and each occurrence of R^X is independently selected from R', halogen, NO_2, or CN.

41. The compound according to claim 40, wherein R^1 and R^2 are both methyl or ethyl, R^3 is propyl, n-butyl, or isobutyl, R^4 is hydrogen, and ring A is phenyl having up to two substituents selected from halo, OH, OMe, OCF_3, or C_{1-4} aliphatic.

42. A compound having formula **IB**:



IB;

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 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^3, 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 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; and each occurrence of R^X is independently selected from R', halogen, NO_2, or CN;

wherein each occurrence of R is independently selected from hydrogen or an optionally substituted C_{1-6} aliphatic group; and 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 R^3 is ethyl; R^4 is hydrogen; ring A is unsubstituted phenyl, and R^1 is hydrogen, then R^2 is not optionally substituted 2-pyridinyl, optionally substituted phenyl, optionally substituted benzyl, $-CH_2CO_2H$, $-CH_2CN$, n-propyl, methyl, ethyl, $-CH_2$(4-OMe-phenyl), $-CH_2CON(Me)CH_2Ph$, $-CH_2C{\equiv}CH$, $-CH_2CH_2OMe$, $-CH_2CH{=}CH_2$, or $-(CH_2)_3OH$;

b) when R^3 is ethyl; R^4 is hydrogen; ring A is thienyl; and R^1 is hydrogen; then R^2 is not optionally substituted phenyl;

c) when R^3 is ethyl; R^4 is hydrogen; ring A is unsubstituted phenyl; then when R^1 is methyl, ethyl, CH_2CH_2Ph, $-CH_2CH_2$morpholino, $-CH_2CH_2NEt_2$, $-CH_2CH_2OMe$, n- butyl, or optionally substituted phenyl, then R^2 is not $-CH_2CH_2CN$, $-CH_2CN$, or $-CH_2CH_2OAc$, or R^1 and R^2 taken together are not optionally substituted piperidinyl, morpholino, or thiomorpholino;

d) when R^3 is ethyl; R^4 is NH_2, Cl, Me, or Br, ring A is unsubstituted phenyl or morpholino, and R^1 is hydrogen, then R^2 is not optionally substituted phenyl, or COR';

e) when R^3 is ethyl, R^4 is hydrogen; and ring A is unsubstituted phenyl, then R^1 and R^2 are not simultaneously methyl;

f) when R^3 is methyl, then ring A, R^4, and R^1 and R^2 taken together, are not simultaneously piperidinyl;

g) when R^3 is ethyl, R^1 is hydrogen, R^2 is unsubstituted phenyl, and R^4 is methyl or thiomorpholino, then ring A is not unsubstituted phenyl, 4-OMe-phenyl, 2-pyridinyl, 4-Cl-phenyl, 2-Cl-phenyl, 3,4-dichlorophenyl, 4-Me-phenyl, 3,5-dichlorophenyl, 4-OH-phenyl, or $3CF_3$-,4-Cl-phenyl;

h) when R^3 is ethyl, methyl, or isopropyl, R^1 is hydrogen or ethyl, and R^2 is ethyl, $COCH_3$, isopropyl, $-CH_2CH_2CN$, benzyl, $-CH_2CH_2NEt_2$, $-CH_2CH_2COOEt$, or R^1 and R^2, taken together are piperazinyl, and R^4 is hydrogen, then ring A is not optionally substituted piperazinyl, pyrrolidinyl, morpholino, or piperidinyl;

i) when R^3 is ethyl, and R^1 is hydrogen, then R^2 is not optionally substituted cyclohexyl;

j) when R^3 is methyl, and R^4 is N(Me)COPh, then ring A and R^1 and R^2, taken together, are not simultaneously N-pyrrolidinyl;

k) when R^3 is ethyl, R^4 is optionally substituted phenyl, ring A is optionally substituted phenyl, and R^1 is hydrogen, then R^2 is not optionally substituted naphthyl, methyl, optionally substituted phenyl, or R^1 and R^2, taken together are not morpholino;

l) when R^3 is ethyl, then when one of R^1 and R^2, taken together or ring A is optionally substituted piperazinyl, then the other of R^1 and R^2, taken together or ring A is not thiomorpholino or morpholino;

m) R^1 and R^2, taken together and ring A are not simultaneously morpholino or thiomorpholino;

o) when R^3 is methyl, R^4 is hydrogen or OMe, ring A is unsubstituted phenyl, and R^1 is hydrogen, then R^2 is not methyl, 2,3-dimethylphenyl, or 3-CF_3phenyl;

p) when R^3 is ethyl, R^4 is hydrogen, and ring A is unsubstituted phenyl, then:

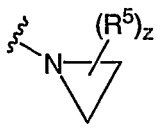
i) R^1 and R^2 taken together do not form a 1-pyrrolidinyl, 4-methylpiperazinyl, or 1-piperidyl;

ii) R^1 and R^2 both are not hydrogen, methyl, or ethyl;

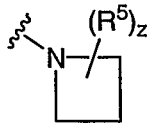
iii) when R^1 is hydrogen then R^2 is not 2-hydroxyethyl.

43. The compound according to claim 42, 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, sulfur, or oxygen.

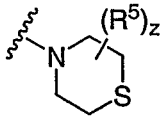
44. The compound according to claim 43 wherein R^1 and R^2, taken together with the nitrogen atom to which they are bound, form an optionally substituted 3-8 membered heterocyclyl ring selected from:



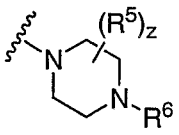
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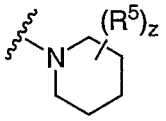
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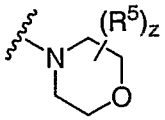
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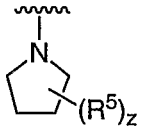
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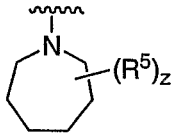
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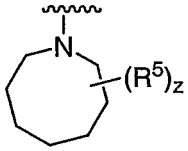
ff



gg



hh



jj

wherein z is 0-4.

45. The compound according to claim 44, wherein R^1 and R^2, taken together with the nitrogen atom to which they are bound, form ring **bb**, **dd**, **ee**, **ff**, or **gg**.

46. The compound according to claim 42, 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 replaced with NR, O, (CO)O, O(CO), NR(CO), (CO)NR, SO_2(NR), or (NR)SO_2.

47. The compound according to claim 42, 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 replaced with NR, O, (CO)O, O(CO), NR(CO), (CO)NR, SO_2(NR), or (NR)SO_2.

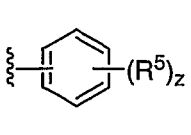
48. The compound according to claim 46, or 47, wherein R^1 and R^2 groups is selected from methyl, ethyl, cyclopropyl, n-propyl, propenyl, cyclobutyl, $(CO)OCH_2CH_3$, $(CH_2)_2OCH_3$, $CH_2(CO)OCH_2CH_3$, $CH_2(CO)OCH_3$, $CH(CH_3)CH_2CH_3$, or t-butyl, or n-butyl.

49. The compound according to claim 46 or 48, wherein R^1 and R^2 are identical.

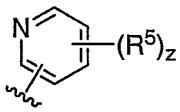
50. The compound according to claim 42, wherein one of R^1 or R^2 is hydrogen and the other of R^1 or R^2 is a 5-6 membered aryl ring having 0-5 heteroatoms independently selected

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.

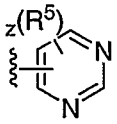
51. The compound according to claim 50, wherein one of R^1 or R^2 is hydrogen and the other of R^1 or R^2 is selected from:



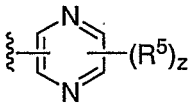
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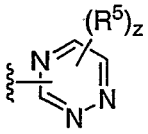
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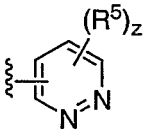
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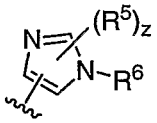
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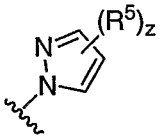
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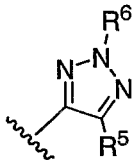
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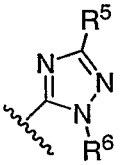
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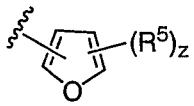
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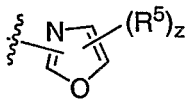
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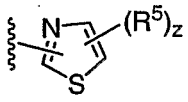
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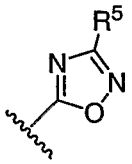
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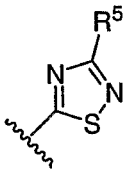
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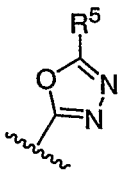
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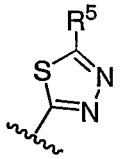
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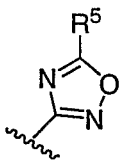
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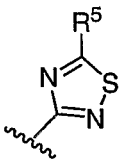
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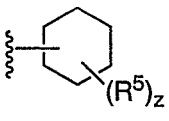
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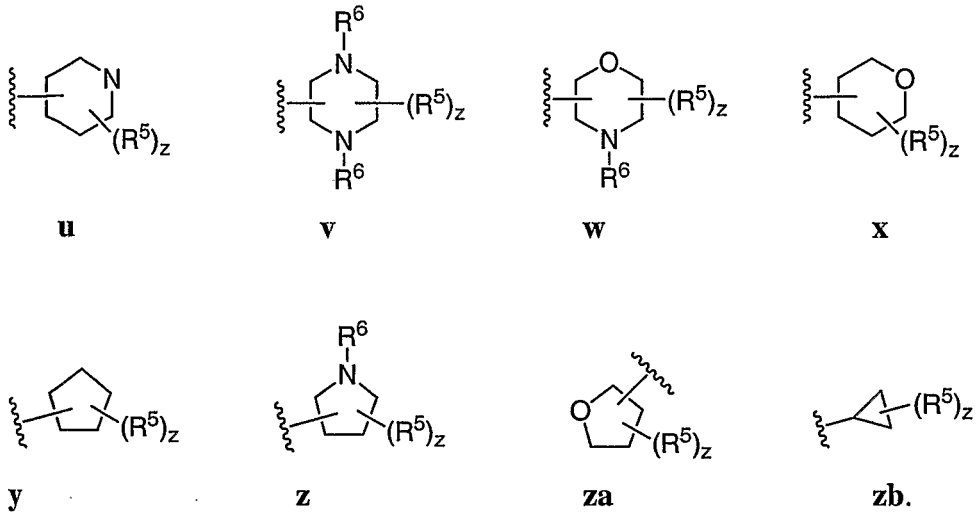
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s



t



u v w x

y z za zb.

52. The compound according to claim 44 or 51, wherein R^6 is 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')$_2$.

53. The compound according to claim 52, wherein R^6 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_2NH_2, $SO_2N(CH_3)_2$, or optionally substituted phenyl.

54. The compound according to claim 42, wherein 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')$_2$.

55. The compound according to claim 54, wherein R^4 is 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.

56. The compound according to claim 42, wherein R^3 is -CF_2H, -CF_3, -$CHCl_2$, -$CHBr_2$, CH_2CN, -CH_2OR', -CH_2SR', -CH_2N(R')$_2$, or as Q-R^X; wherein Q is an optionally substituted C_2-

C_6 alkylidene chain wherein up to two non-adjacent methylene units of Q are optionally 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; and each occurrence of R^X is independently selected from R', halogen, NO_2, or CN, provided that Q is bonded to the carbon atom of the carbonyl group through a carbon atom.

57. The compound of claim 56, wherein R^3 is $-CF_2H$, $-CF_3$, $-CHCl_2$, $-CHBr_2$, CH_2CN, $-CH_2OR'$, $-CH_2SR'$, $-CH_2N(R')_2$, or as $Q-R^X$; wherein Q is a bond, and R^X is an optionally substituted group selected from C_{2-8} aliphatic, C_{6-10} aryl, a heteroaryl ring having 5-10 ring atoms, or a heterocyclyl ring having 3-10 ring atoms.

58. The compound of claim 42, wherein R^3 is 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 $-S(O)_2N(R')_2$.

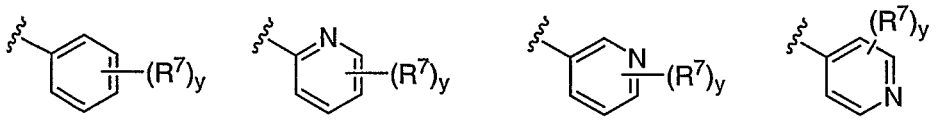
59. The compound of claim 58, wherein R^3 is H, Me, CF_3, ethyl, propyl, butyl, pentyl, $CO(C_1-C_4alkyl)$, $-CONH_2$, $-COO(C_1-C_4alkyl)$, $-CH_2OH$, $-SO_2NH_2$, $SO_2N(CH_3)_2$, or optionally substituted phenyl.

60. The compound according to claim 42, wherein ring A is selected from 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, wherein said ring is optionally substituted at one or more carbon atoms with y occurrences of $-R^7$, and at one or more substitutable nitrogen atoms with $-R^8$, wherein y is 0-5.

61. The compound according to claim 60, wherein ring A is selected from phenyl, piperidyl, thiophenyl, indolyl, or pyrrolidinyl, wherein ring A has 0-2 occurrences of $-R^7$ and 0-1 occurrences of $-R^8$ at a substitutable nitrogen atom.

62. The compound according to claim 62, wherein ring A is phenyl, piperidyl, or pyrrolidinyl.

63. The compound according to claim 60, wherein ring A is selected from:



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

wherein y is 0-5.

64. The compound according to claim 60, wherein y is 0-2.

65. The compound according to claim 65, wherein y is 0 and ring A is unsubstituted.

66. The compound according to claim 64, wherein each R^7 is independently selected from 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')$_2$.

67. The compound according to claim 66, wherein each 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.

68. The compound according to claim 64, wherein each R^8 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')$_2$.

69. The compound according to claim 68, wherein each 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_2NH_2, $SO_2N(CH_3)_2$, or optionally substituted phenyl.

70. The compound according to claim 42, wherein R^1 and R^2 both are optionally substituted C_{1-4} aliphatic, R^3 is C_{1-4} aliphatic, R^4 is hydrogen, and ring A is optionally substituted 5-6 membered aryl, heteroaryl, or heterocyclic ring.

71. The compound according to claim 70, wherein R^1 and R^2 are both methyl, ethyl, or propyl, R^3 is ethyl, propyl or butyl, ring A is phenyl or a 5-6 membered heteroaryl or heterocyclyl ring having one nitrogen ring atom, wherein ring A has up to one Q- R^X substituent, 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 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; and each occurrence of R^X is independently selected from R', halogen, NO_2, or CN.

72. The compound according to claim 42, wherein R^1 and R^2 are both C_{1-4} alphatic or R^1 and R^2 taken together form a 3-6 membered heterocyclic ring having up to 2 heteroatoms, R^3 is optionally C_{1-4} aliphatic, R^4 is hydrogen, and ring A is optionally substituted phenyl, 5 membered heteroaryl, or 6-membered heterocyclyl, having up to 3 heteroatoms selected from oxygen, nitrogen, or sulfur.

73. The compound according to clailm 72, wherein R^1 and R^2 both are methyl, ethyl, propyl; or R^1 and R^2, taken together form an optionally substituted 1-azetidinyl, 1-pyrrolidinyl, 1-piperidinyl, or 1-piperazinyl, R^3 is optionally substituted ethyl, propyl, or butyl, ring A is phenyl or a 5-membered heteroaryl having 1 heteroatom, wherein said ring A has up to two Q-R^X substituents, 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 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; and each occurrence of R^X is independently selected from R', halogen, NO_2, or CN.

74. The compound according to claim 73, wherein R^1 and R^2 both are methyl or ethyl, or R^1 and R^2, taken together form a 1-pyrrolidinyl ring, R^3 is ethyl or propyl, R^4 is hydrogen, and ring A is optionally substituted phenyl, piperidyl, or pyrrolyl, wherein ring A has up to two substituents selected from halo, OH, OCF_3, or C_{1-4} aliphatic.

75. The compound according to claim 74, wherein R^1 and R^2 both are methyl or ethyl, R^3 is ethyl, R^4 is hydrogen, and ring A is phenyl, 1-piperidyl, or 1-pyrrolyl, wherein ring A has up to two substituents selected from halo or OH.

76. The compound according to claim 42, wherein R^1 and R^2 are both C_{1-4} alphatic or R^1 and R^2 taken together form a 4-6 membered heterocyclic ring having up to 2 nitrogen heteroatoms, R^3 is optionally substituted C_{1-4} aliphatic, R^4 is hydrogen, and ring A is optionally substituted phenyl or 5-membered heteroaryl.

77. The compound according to claim 76, wherein R^1 and R^2 are both methyl, ethyl, propyl; or R^1 and R^2, taken together form an optionally substituted 1-pyrrolidinyl or 1-piperazinyl, R^3 is optionally substituted ethyl, propyl, or butyl, ring A is phenyl or a 5-membered heteroaryl having 1 heteroatom, wherein said ring A has up to two Q- R^X substituents, 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 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; and each occurrence of R^X is independently selected from R', halogen, NO_2, or CN.

78. The compound according to claim 77, wherein R^1 and R^2 both are methyl or ethyl, or R^1 and R^2, taken together form a 1-pyrrolidinyl ring, R^3 is ethyl or propyl, R^4 is hydrogen, and ring A is phenyl, piperidyl, or pyrrolyl, optionally substituted with up to two substituents selected from halo, OH, OCF_3, or C_{1-4} aliphatic.

79. The compound according to claim 78, wherein R^1 and R^2 are both methyl or ethyl, R^3 is ethyl, R^4 is hydrogen, and ring A is phenyl, 1-piperidyl, or 1-pyrrolyl, wherein ring A has up to two substituents selected from halo or OH.

80. The compound according to clailm 42, wherein R^1 and R^2 are both C_{1-4} alphatic or R^1 and R^2 taken together form a 4-6 membered heterocyclic ring having up to 2 nitrogen heteroatoms, R^3 is optionally substituted C_{1-4} aliphatic, R^4 is hydrogen, and ring A is optionally subsituted phenyl, 5-6 membered heterocyclic or heteroaryl ring.

81. The compound according to claim 80, wherein R^1 and R^2 both are methyl, ethyl, propyl; or R^1 and R^2, taken together form an optionally substituted 1-azetidinyl, 1-pyrrolidinyl, 2,5-dihydro-1H-pyrrolyl, 1-piperidinyl, or 1-piperazinyl, R^3 is optionally substituted ethyl, propyl, or butyl, and ring A is phenyl or a 5-membered heteroaryl having 1 heteroatom, wherein said ring A has up to two Q- R^X substituents, 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 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; and each occurrence of R^X is independently selected from R', halogen, NO_2, or CN.

82. The compound according to claim 81, wherein R^1 and R^2 are both C_{1-4} alphatic, R^3 is ethyl, propyl, or butyl, R^4 is hydrogen, ring A is phenyl, 1-pyrrolidyl, or 1-pyrrolyl, having up to two substituents selected from halo, OH, OCF_3, or C_{1-4} aliphatic.

83. The compound according to claim 82, wherein R^1 and R^2 are both methyl or ethyl, R^3 is ethyl, R^4 is hydrogen, ring A is phenyl, 1-pyrrolidyl, or 1-pyrrolyl, having up to two substituents selected from halo, OH, OCF_3, or C_{1-4} aliphatic.

84. The compound according to claim 82, wherein ring A is optionally substituted 1-piperidyl or 1-pyrrolyl.

85. The compound according to claim 42, wherein R^1 and R^2 are both C_{1-4} aliphatic, or R^1 and R^2 together form an optionally substituted 5-6 membered heterocyclic ring having up to 2 heteroatoms, R^3 is C_{1-4} aliphatic, R^4 is hydrogen, and ring A is aryl or 5-10 membered heteroaromatic or heterocyclyl, having up to four Q- R^X substituents, wherein Q is a bond or is a

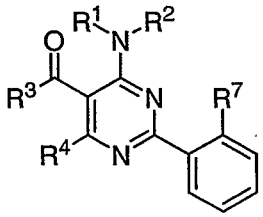
C_1-C_6 alkylidene chain wherein up to two non-adjacent methylene units of Q are optionally replaced by CO, CO_2, COCO, CONR, OCONR, NRNR, NRNRCO, NRCO, $NRCO_2$, NRCONR, SO, SO_2, $NRSO_2$, SO_2NR, $NRSO_2NR$, O, S, or NR; and each occurrence of R^X is independently selected from R', halogen, NO_2, or CN.

86. The compound according to claim 85, wherein R^1 and R^2 are both C_{1-4} aliphatic, or R^1 and R^2 together form an optionally substituted 5-6 membered heterocyclic ring having up to 2 heteroatoms, R^3 is C_{1-4} aliphatic, R^4 is hydrogen, and ring A is phenyl, indolyl, or pyrrolyl having up to two substituents selected from halo, OH, OMe, OCF_3, or C_{1-4} aliphatic.

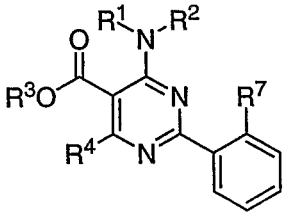
87. The compound according to clailm 86, wherein R^1 and R^2 are both methyl or ethyl, or R^1 and R^2 together form an optionally substituted pyrrolidinyl or piperidinyl ring, R^3 is methyl or ethyl, R^4 is hydrogen, and ring A is phenyl or pyrrolyl having up to two substituents selected from halo, OH, OMe, OCF_3, or C_{1-4} aliphatic.

88. The compound according to claim 87, wherein R^1 and R^2 are both methyl or ethyl, or R^1 and R^2 together form a pyrrolidinyl or 3-hydroxy-piperidinyl ring, R^3 is methyl or ethyl, R^4 is hydrogen, and ring A is phenyl or pyrrolyl having up to two substituents selected from halo, OH, OMe, OCF_3, or C_{1-4} aliphatic.

89. The compound according to claim 1 or 42, having formula **IIIA** or formula **IIIB**:



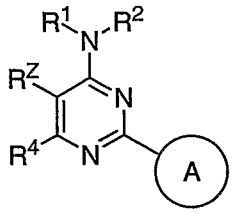
IIIA



IIIB.

90. A composition comprising a compound according to claim 1 or 42, a pharmaceutically acceptable carrier, vehicle, or diluent, and optionally an additional therapeutic agent.

91. 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 of formula **I**:



I

or a pharmaceutically acceptable salt thereof, wherein:

R^Z is $-C(O)R^3$, $-C(O)OR^3$, or R^{Z1};

R^{Z1} is $-C(O)N(R')_2$, $-SO_2R'$, $-SO_2NHR'$, $-NHSO_2R'$, $-P(O)(OR')_2$, $-C(O)N(CN)R'$, an optionally substituted 5-membered heteroaryl ring having1-4 heteroatoms selected from O, S, or N, or an optionally substituted pyran-4-one-yl;

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 aryl ring 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^3, 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 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; and each occurrence of R^X is independently selected from R', halogen, NO_2, or CN, provided that when R^Z is $-OR^3$, then $Q\text{-}R^X$ is bonded to the oxygen atom through a carbon atom;

wherein each occurrence of R is independently selected from hydrogen or an optionally substituted C_{1-6} aliphatic group; and 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 when R^Z is R^3, then R^3 is bonded to the carbon atom of the carbonyl group through an atom other than oxygen, preferably, through a carbon atom.

92. The method according to claim 91, wherein the disease, condition, or disorder is implicated in the activation or hyperactivity of voltage-gated sodium channels.

93. The method according to claim 92, wherein the disease, condition, or disorder is implicated in the activation or hyperactivity of voltage-gated calcium channels.

94. The method according to claim 91, wherein the disease, condition, or diorder is acute, chronic, neuropathic, or inflammatory pain.

95. The method according to claim 91, wherein the disease, condition, or diorder is radicular pain, sciatica, back pain, head pain, or neck pain.

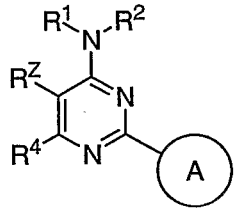
96. The method according to claim 91, wherein the disease, condition, or diorder is severe or intractable pain, acute pain, postsurgical pain, back pain, or cancer pain.

97. 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:

R^Z is $-C(O)R^3$, $-C(O)OR^3$, or R^{Z1};

R^{Z1} is $-C(O)N(R')_2$, $-SO_2R'$, $-SO_2NHR'$, $-NHSO_2R'$, $-P(O)(OR')_2$, $-C(O)N(CN)R'$, an optionally substituted 5-membered heteroaryl ring having1-4 heteroatoms selected from O, S, or N, or an optionally substituted pyran-4-one-yl;

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 aryl ring 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^3, 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 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; and each occurrence of R^X is independently selected from R', halogen, NO_2, or CN, provided that when R^Z is $-OR^3$, then $Q\text{-}R^X$ is bonded to the oxygen atom through a carbon atom;

wherein each occurrence of R is independently selected from hydrogen or an optionally substituted C_{1-6} aliphatic group; and 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 when R^Z is R^3, then R^3 is bonded to the carbon atom of the carbonyl group through an atom other than oxygen, preferably, through a carbon atom.

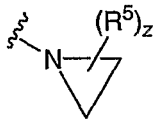
98. The method according to claim 91 or 97, wherein R^Z is $-C(O)R^3$.

99. The method according to claim 91 or 97, wherein R^Z is $-C(O)OR^3$.

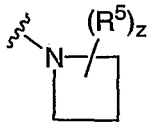
100. The method according to claim 91 or 97, wherein R^Z is R^{Z1}.

101. The method according to claim 91 or 97, 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, sulfur, or oxygen.

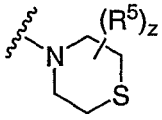
102. The method according to claim 101, wherein R^1 and R^2, taken together with the nitrogen atom to which they are bound, form an optionally substituted 3-8 membered heterocyclyl ring selected from:



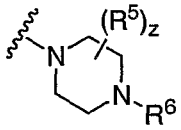
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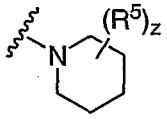
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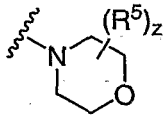
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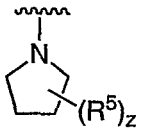
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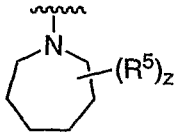
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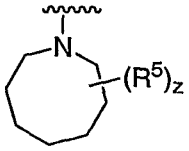
ff



gg



hh



jj

wherein z is 0-4.

103. The method according to claim 102, wherein R^1 and R^2, taken together with the nitrogen atom to which they are bound, form ring **bb**, **dd**, **ee**, **ff**, or **gg**.

104. The method according to claim 91 or 97, 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 replaced with NR, O, (CO)O, O(CO), NR(CO), (CO)NR, SO_2(NR), or (NR)SO_2.

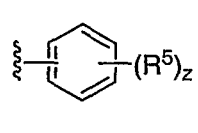
105. The method according to claim 1, wherein one of R^1 or R^2 is hydrogen and the other of R^1 or R^2 is an optionally substituted C_{1-4}aliphatic group, wherein one or more methylene units in the C_{1-4}aliphatic group are optionally replaced with NR, O, (CO)O, O(CO), NR(CO), (CO)NR, SO_2(NR), or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

106. The method according to claim 104 or 105, wherein R^1 and R^2 groups is selected from 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.

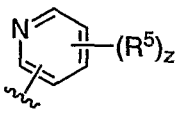
107. The method according to claim 104 or 106, wherein R^1 and R^2 are identical.

108. The method according to claim 91 or 97, 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.

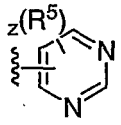
109. The method according to claim 108, wherein one of R^1 or R^2 is hydrogen and the other of R^1 or R^2 is selected from:



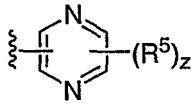
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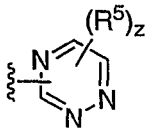
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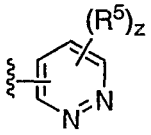
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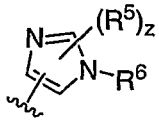
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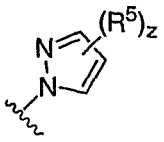
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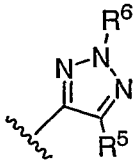
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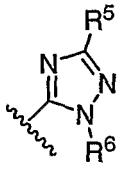
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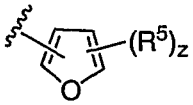
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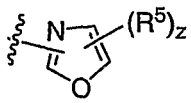
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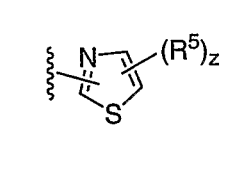
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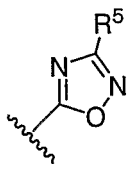
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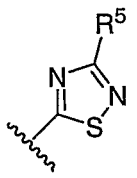
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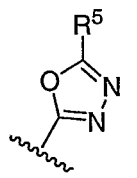
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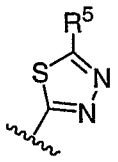
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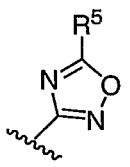
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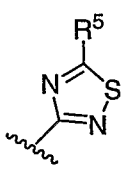
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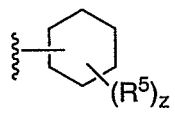
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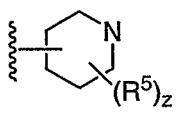
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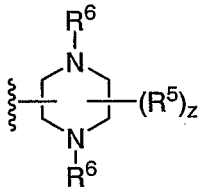
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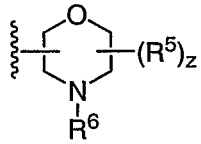
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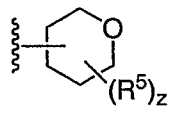
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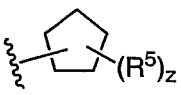
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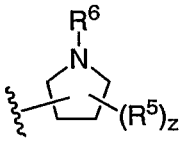
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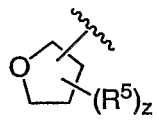
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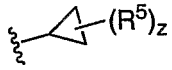
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za



zb.

110. The method according to claim 102 or 109, wherein R^6 is 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')$_2$.

111. The method according to claim 110, wherein R^6 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_2NH_2, $SO_2N(CH_3)_2$, or optionally substituted phenyl.

112. The method according to claim 91 or 97, wherein 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 -$S(O)_2N(R')_2$.

113. The method according to claim 112, wherein R^4 is 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.

114. The method according to claim 91 or 97, wherein R^3 is -CF_2H, -CF_3, -$CHCl_2$, -$CHBr_2$, CH_2CN, -CH_2OR', -CH_2SR', -$CH_2N(R')_2$, or as Q-R^X; wherein Q is an optionally substituted C_2-C_6 alkylidene chain wherein up to two non-adjacent methylene units of Q are optionally 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; and each occurrence of R^X is independently selected from R', halogen, NO_2, or CN, provided that Q is bonded to the carbon atom of the carbonyl group through a carbon atom.

115. The method of claim 114, wherein R^3 is -CF_2H, -CF_3, -$CHCl_2$, -$CHBr_2$, CH_2CN, -CH_2OR', -CH_2SR', -$CH_2N(R')_2$, or as Q-R^X; wherein Q is a bond, and R^X is an optionally substituted group selected from C_{2-8} aliphatic, C_{6-10} aryl, a heteroaryl ring having 5-10 ring atoms, or a heterocyclyl ring having 3-10 ring atoms.

116. The method of claim 91 or 97, wherein R^3 is 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 -$S(O)_2N(R')_2$.

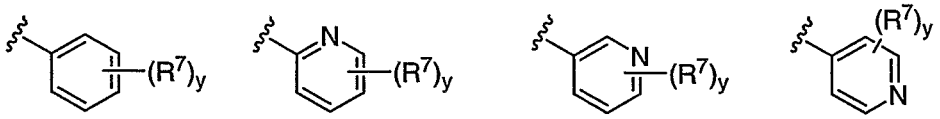
117. The method of claim 116, wherein R^3 is H, Me, CF_3, ethyl, propyl, butyl, pentyl, CO(C_1-C_4alkyl), -$CONH_2$, -COO(C_1-C_4alkyl), -CH_2OH, -SO_2NH_2, $SO_2N(CH_3)_2$, or optionally substituted phenyl.

118. The method according to claim 91 or 97, wherein ring A is selected from 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, wherein said ring is optionally substituted at one or more carbon atoms with y occurrences of $-R^7$, and at one or more substitutable nitrogen atoms with $-R^8$, wherein y is 0-5.

119. The method according to claim 118, wherein ring A is selected from phenyl, piperidyl, thiophenyl, indolyl, or pyrrolidinyl, wherein ring A has 0-2 occurrences of $-R^7$ and 0-1 occurrences of $-R^8$ at a substitutable nitrogen atom.

120. The method according to claim 119, wherein ring A is phenyl, piperidyl, or pyrrolidinyl.

121. The method according to claim 118, wherein ring A is selected from:



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

wherein y is 0-5.

122. The method according to claim 118, wherein y is 0-2.

123. The method according to claim 122, wherein y is 0 and ring A is unsubstituted.

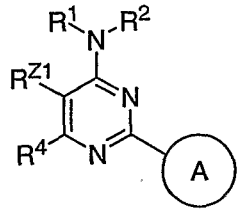
124. The method according to claim 118, wherein each R^7 is independently selected from hydrogen, halogen, CN, NO_2, or an optionally substituted group selected from C_{1-6}alkyl, aryl, aryl(C_{1-6})alkyl, -N(R')$_2$, -CH_2N(R')$_2$, OR', -CH_2OR', SR', -CH_2SR', COOR', -NRCOR', -(CH_2)$_2$N(R')$_2$, -(CH_2)$_2$OR', -(CH_2)$_2$SR', -COR', -CON(R')$_2$, or -S(O)$_2$N(R')$_2$.

125. The method according to claim 124, wherein each R^7 is independently H, Cl, Br, F, CF_3, Me, Et, CN, NO_2, -COOH, NH_2, $-N(CH_3)_2$, $-N(Et)_2$, $-N(iPr)_2$, $-O(CH_2)_2OCH_3$, $-CONH_2$, $-COOCH_3$, -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.

126. The method according to claim 125, wherein each R^8 is independently selected from hydrogen, or an optionally substituted group selected from C_{1-6}alkyl, aryl, aryl(C_{1-6})alkyl, $-N(R')_2$, $-CH_2N(R')_2$, $-CH_2OR'$, $-CH_2SR'$, $-(CH_2)_2N(R')_2$, $-(CH_2)_2OR'$, $-(CH_2)_2SR'$, -COR', $-CON(R')_2$, or $-S(O)_2N(R')_2$.

127. The method according to claim 126, wherein each R^8 is independently H, Me, CF_3, ethyl, propyl, butyl, pentyl, $CO(C_1$-C_4alkyl), $-CONH_2$, $-COO(C_1$-C_4alkyl), $-CH_2OH$, $-SO_2NH_2$, $SO_2N(CH_3)_2$, or optionally substituted phenyl.

128. A compound having formula **IC**:



IC

or a pharmaceutically acceptable salt thereof;

wherein R^{Z1} is halo, cyano, $-SO_2R'$, $-SO_2NHR'$, $-NHSO_2R'$, $-P(O)(OR')_2$, $-C(O)N(CN)R'$, an optionally substituted 5-membered heteroaryl ring having1-4 heteroatoms selected from O, S, or N, or an optionally substituted pyran-4-one-yl;

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 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^3, 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 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; and each occurrence of R^X is independently selected from R', halogen, NO_2, or CN;

wherein each occurrence of R is independently selected from hydrogen or an optionally substituted C_{1-6} aliphatic group; and 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 R^{Z1} is tetrazolyl, R^1 is hydrogen, R^2 is hydrogen or optionally substituted phenyl, R^4 is hydrogen, then ring A is not unsubstituted 1-pyrrolidinyl, 1-piperidyl, N-morpholinyl, 1-azepanyl, or phenyl;

b) when R^{Z1} is $-P(O)(OR')_2$ and R' is C_{1-4} aliphatic, R^1 and R^2 are both hydrogen, and R^4 is hydrogen, methyl, anino, $-OCH_2OH$, then ring A is not 1-[(2-fluorophenyl)methyl]-1H-pyrazolo[3,4-b]pyridin-3-yl or unsubstituted phenyl.

c) when R^{Z1} is $-SO_2NHR'$and R' is hydrogen, R^1 and R^2 are both hydrogen, R^4 is amino, then ring A is not N-morpholino.

129. The compound according to claim 128, wherein R^{Z1} is $-SO_2R'$, $-SO_2NHR'$, or $-NHSO_2R'$.

130. The compound according to claim 128, wherein R^{Z1} is $-P(O)(OR')_2$.

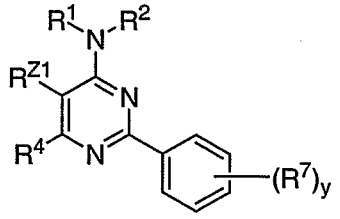
131. The compound according to claim 128, wherein R^{Z1} is an optionally substituted 5-membered heteroaryl ring having1-4 heteroatoms selected from O, S, or N.

132. The compound according to claim 131, wherein R^{Z1} is an optionally substituted oxazolyl, triazolyl, thiophenyl, furanyl, or tetrazolyl ring.

133. The compound according to claim 128, wherein R^{Z1} is an optionally substituted pyran-4-one-yl.

134. The compound according to claim 128, wherein R^{Z1} is $-C(O)N(CN)R'$.

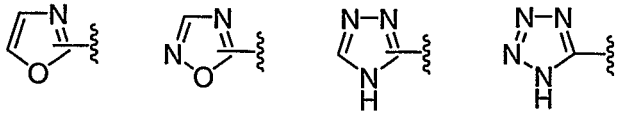
135. The compound according to claim 128, having formula **IIC**:



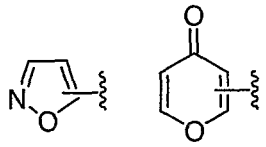
IIC

wherein y is 0-5;

R^{Z1} is halo, $-SO_2R'$, $-SO_2NHR'$, $-NHSO_2R'$, $-P(O)(OR')_2$, $-C(O)N(CN)R'$, or an optionally substituted ring selected from:



z-a **z-b** **z-c** **z-d**



z-e z-f.

136. The compound according to claim 135, whereincR^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 replaced with NR, O, (CO)O, O(CO), NR(CO), (CO)NR, SO_2(NR), or (NR)SO_2.

137. The compound according to claim 136, wherein 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.

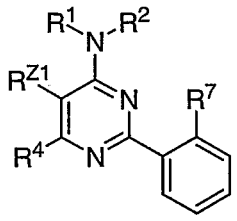
138. The compound according to claim 137, wherein R^4 is independently hydrogen, halogen, CN, NO_2, or an optionally substituted group selected from C_{1-6}alkyl, aryl, aryl(C_{1-6})alkyl, -N(R')$_2$, -CH_2N(R')$_2$, OR', -CH_2OR', SR', -CH_2SR', COOR', -NRCOR', -$(CH_2)_2$N(R')$_2$, -$(CH_2)_2$OR', -$(CH_2)_2$SR', -COR', -CON(R')$_2$, SO_2R', or -SO_2N(R')$_2$.

139. The compound according to claim 138, wherein R^4 is 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.

140. The compound according to claim 135, wherein R^7 is Cl, Br, F, CF_3, OCF_3, Me, Et, propyl, n-butyl, t-butyl, 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), -$CONH_2$, CON$(CH_3)_2$, -$COOCH_3$, -OH, -SCH_3, -CH_2OH, -

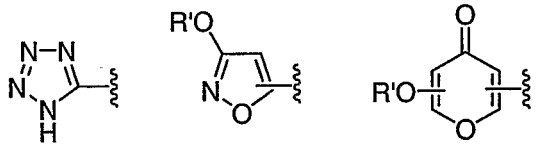
$NHCOCH_3$, $-SO_2(C_1-C_4alkyl)$, $-SO_2NH_2$, $-SO_2N(CH_3)_2$, piperidinyl, piperizinyl, morpholino, or an optionally substituted group selected from C_{1-4}alkoxy, phenyl, phenyloxy, benzyl, or benzyloxy.

141. The compound according to claim 135, having formula **IIIC**:



IIIC

wherein R^{Z1} is $-SO_2R'$, $-NHSO_2R'$, $-C(O)N(CN)R'$, or an optionally substituted ring selected from:



z-dd **z-ee** **z-ff** .

142. The compound according to claim 141, wherein R^1 and R^2 are identical, and they both are methyl or ethyl. Or, R^1 and R^2 are taken together to form a 1-piperidyl, 1-piperazyl, or 1-pyrrolidinyl.

142. A compound selected from Table 2.

143. A composition comprising a compound according to claim 128 or 142, and a pharmaceutically acceptable carrier, vehicle, or diluent.

144. The composition according to claim 143, further comprising a therapeutic agent.