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(54) Title: COMPOSITIONS USEFUL AS INHIBITORS OF VOLTAGE-GATED SODIUM CHANNELS

(57) Abstract: The present invention relates to compounds useful as inhibitors of voltage-gated sodium 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.

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COMPOSITIONS USEFUL AS INHIBITORS OF VOLTAGE-GATED SODIUM CHANNELS

TECHNICAL FIELD OF THE INVENTION

[00146] 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

[00147] 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).

[00148] 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).

[00149] Table 1 (Abbreviations: CNS = central nervous system, PNS = peripheral nervous sytem, DRG = dorsal root ganglion, TG = Trigeminal ganglion):

Na Isoform	**Tissue**	**TTX IC50**	**Indications**
NaV1.1	CNS, PNS soma of neurons	10nM	Pain, Epilepsy, neurodegeneration
NaV1.2	CNS, high in axons	10nM	Neurodegeneration Epilepsy
NaV1.3	CNS, embryonic, injured nerves	15nM	Pain, Epilepsy
NaV1.4	Skeletal muscle	25nM	Myotonia
NaV1.5	Heart	2μM	Arrythmia, long QT
NaV1.6	CNS widespread, most abuntant	6nM	Pain, movement disorders
NaV1.7	PNS, DRG, terminals neuroendocrine	25nM	Pain, Neuroendocrine disorders
NaV1.8	PNS, small neurons in DRG & TG	>50μM	Pain
NaV1.9	PNS, small neurons in DRG & TG	1μM	Pain

[00150] 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.

[00151] 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.

[00152] 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.

[00153] 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.

[00154] In neuropathic pain states there is a remodeling of Na channel distribution and subtype. In the injured nerve, expression of NaV1.8 and NaV1.9 are greatly reduced whereas expression of the TTX sensitive subunit NaV1.3 is significantly upregulated in animal models of neuropathic pain (See, Dib-Hajj, S. D., J. Fjell, et al. (1999) "Plasticity of sodium channel expression in DRG neurons in the chronic constriction injury model of neuropathic pain." Pain **83**(3): 591-600 and Kim, C.H., Youngsuk, O., et al. (2001) "The changes in expression of three subtypes of

TTX sensitive sodium channels in sensory neurons after spinal nerve ligation". Mol. Brain Res. **95**:153-61.) The timecourse of the increase in NaV1.3 parallels the appearance of allodynia in animal models subsequent to nerve injury. Up-regulation of Nav1.3 transcription is also observed in a rat model of diabetic neuropathy. (See, Craner, M.J., Klein, J.P. et al. (2002) "Changes of sodium channel expression in experimental painful diabetic neuropathy." Ann Neurol. **52**(6): 786-92. The biophysics of the NaV1.3 channel is distinctive in that it shows very fast repriming after inactivation following an action potential. This allows for sustained rates of high firing as is often seen in the pathophysiological activity accompanying neuropathic pain (See, Cummins, T. R., F. Aglieco, et al. (2001) "Nav1.3 sodium channels: rapid repriming and slow closed-state inactivation display quantitative differences after expression in a mammalian cell line and in spinal sensory neurons" J Neurosci **21**(16): 5952-61.). Human NaV1.3 channel proteins are expressed in the central and peripheral systems of man. (See, Chen, Y.H., Dale, T.J., et al. (2000) "Cloning, distribution and functional analysis of the type III sodium channel from human brain." Eur. J. Neurosci. **12**: 4281-89). Furthermore, in the periphery, NaV1.3 channel proteins are detectable in injured but not uninjured human nerves indicating that NaV1.3 plays important physiological roles under pathophysiological conditions in humans as well. Given the strong correlation between increased NaV1.3 channel expression and neuronal hyperexcitability, inhibitors of NaV1.3 channels, and in particular selective ones, might therefore provide efficacious therapeutic agents with less-severe side effects than nonselective Na_+ channel inhibitors in the treatment of painful neuropathies. Similarly, NaV1.3 overexpression may also be associated with

increased epipleptic neuronal activity as it is significantly upregulated in hippocampal pyramidal neurons of epileptic humans (See, Whitaker, W.R.J., Faull, M., et al. (2001) "Changes in the mRNAs encoding voltage-gated sodium channel types II and III in human epileptic hippocampus." Neurosci. **106**(2): 275-285.); inhibitors with some selectivity against Nav1.3 could also be particularly attractive anticonvulsants and neuroprotectants.

[00155] 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/Navl.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.

[00156] 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 may 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).

[00157] 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)

[00158] 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).

[00159] 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).

[00160] Voltage-gated calcium channels are membrane-spanning, multi-subunit proteins that open in response to membrane depolarization, allowing Ca entry from the extracellular milieu. Calcium channels were initially classified based on the time and voltage-dependence of channel opening and on the sensitivity to pharmacological block. The categories were low-voltage activated (primarily T-type) and high-voltage activated (L,N,P,Q or R-type). This classification scheme was replaced by a nomenclature based upon the molecular subunit composition, as summarized in Table I (Hockerman, G. H., et. al. (1997) Annu. Rev. Pharmacol. Toxicol. **37**: 361-96; Striessnig, J. (1999) Cell. Physiol. Biochem. **9**: 242-69). There are four primary subunit types that make up calcium channels - $\alpha_1, \alpha_2\delta, \beta$ and γ (See, e.g., De Waard et al. Structural and functional diversity of voltage-activated calcium channels. In Ion Channels, (ed. T. Narahashi) 41-87, (Plenum Press, New York, 1996)). The α_1 subunit is the primary determinant of the pharmacological properties and contains the channel pore and voltage sensor (Hockerman, G. H., et. al. (1997) Annu. Rev. Pharmacol. Toxicol. **37**: 361-96; Striessnig, J. (1999) Cell. Physiol. Biochem. **9**: 242-69). Ten isoforms of the α_1 subunit are known, as indicated in Table I. The $\alpha_2\delta$ subunit consists of two disulfide linked subunits, α_2, which is primarily extracellular and a transmembrane δ subunit. Four isoforms of $\alpha_2\delta$ are known, $\alpha_2\delta$-1, $\alpha_2\delta$-2, $\alpha_2\delta$-3 and $\alpha_2\delta$-4. The β subunit is a non-glycosylated cytoplasmic protein that binds to the α_1 subunit. Four isoforms are known, termed β_1 to β_4. The γ subunit is a transmembrane protein that has been biochemically isolated as a component of Ca_v1 and Ca_v2 channels. At least 8 isoforms are known (γ_1 to γ_8) (Kang, M.G. and

K. P. Campbell (2003) J. Biol. Chem. **278**: 21315-8). The nomenclature for voltage-gated calcium channels is based upon the content of the α_1 subunit, as indicated in Table I. Each type of α_1 subunit can associate with a variety of β, $\alpha_2\delta$ or γ subunits, so that each Ca_v type corresponds to many different combinations of subunits.

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

[00161] Ca_v2 currents are found almost exclusively in the central and peripheral nervous system and in neuroendocrine cells and constitute the predominant forms of presynaptic voltage-gated calcium current. Presynaptic action potentials cause channel opening and neurotransmitter release is steeply dependent upon the subsequent calcium entry. Thus, Ca_v2 channels play a central role in mediating neurotransmitter release.

[00162] $Ca_v2.1$ and $Ca_v2.2$ contain high affinity binding sites for the peptide toxins ω-conotoxin-MVIIC and ω-conotoxin-GVIA, respectively, and these peptides have been used to determine the

distribution and function of each channel type. $Ca_V2.2$ is highly expressed at the presynaptic nerve terminals of neurons from the dorsal root ganglion and neurons of lamina I and II of the dorsal horn (Westenbroek, R. E., et al. (1998) J. Neurosci. **18**: 6319-30; Cizkova, D, et al. (2002) Exp. Brain Res. **147**: 456-63). $Ca_V2.2$ channels are also found in presynaptic terminals between second and third order interneurons in the spinal cord. Both sites of neurotransmission are very important in relaying pain information to the brain.

[00163] Pain can be roughly divided into three different types: acute, inflammatory, and neuropathic. Acute pain serves an important protective function in keeping the organism safe from stimuli that may produce tissue damage. Severe thermal, mechanical, or chemical inputs have the potential to cause severe damage to the organism if unheeded. Acute pain serves to quickly remove the individual from the damaging environment. Acute pain by its very nature generally is short lasting and intense. Inflammatory pain, on the other hand, may last for much longer periods of time and its intensity is more graded. Inflammation may occur for many reasons including tissue damage, autoimmune response, and pathogen invasion. Inflammatory pain is mediated by a variety of agents that are released during inflammation, including substance P, histamines, acid, prostaglandin, bradykinin, CGRP, cytokines, ATP, and other agents (Julius, D. and A. I. Basbaum (2001) Nature **413** (6852): 203-10). The third class of pain is neuropathic and involves nerve damage arising from nerve injury or viral infection and results in reorganization of neuronal proteins and circuits yielding a pathologic "sensitized" state that can produce chronic pain lasting for years. This type

of pain provides no adaptive benefit and is particularly difficult to treat with existing therapies.

[00164] Pain, particularly neuropathic and intractable pain is a large unmet medical need. Millions of individuals suffer from severe pain that is not well controlled by current therapeutics. The current drugs used to treat pain include NSAIDS, COX-2 inhibitors, opioids, tricyclic antidepressants, and anticonvulsants. Neuropathic pain has been particularly difficult to treat as it does not respond well to opioids until high doses are reached. Gabapentin is currently the most widely used therapeutic for the treatment of neuropathic pain, although it works in only 60% of patients and has modest efficacy. The drug is generally safe, although sedation is an issue at higher doses.

[00165] Validation of Cav2.2 as a target for the treatment of neuropathic pain is provided by studies with ziconotide (also known as ω-conotoxin-MVIIA), a selective peptide blocker of this channel (Bowersox, S.S., et al. (1996) J. Pharmacol. Exp. Ther. **279**: 1243-9; Jain, K.K. (2000) Exp. Opin. Invest. Drugs **9**: 2403-10; Vanegas, H. and H. Schaible (2000) Pain **85**: 9-18). In man, intrathecal infusion of Ziconotide is effective for the treatment of intractable pain, cancer pain, opioid resistant pain, and neuropathic pain. The toxin has an 85% success rate for the treatment of pain in humans with a greater potency than morphine. An orally available antagonist of $Ca_V2.2$ should have similar efficacy without the need for intrathecal infusion. $Ca_V2.1$ and $Ca_V2.3$ are also in neurons of nociceptive pathways and antagonists of these channels could be used to treat pain.

[00166] Antagonists of $Ca_V2.1$, $Ca_V2.2$ or $Ca_V2.3$ should also be useful for treating other pathologies of the central nervous system that apparently involve excessive calcium entry. Cerebral

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

[00167] $Ca_V2.2$ also mediates release of neurotransmitters from neurons of the sympathetic nervous system and antagonists could be used to treat cardiovascular diseases such as hypertension, cardiac arrhythmia, angina pectoris, myocardial infarction, and congestive heart failure.

[00168] However, 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.

[00169] SUMMARY OF THE INVENTION

[00170] It has now been found that compounds of this invention, and pharmaceutically acceptable compositions thereof, are useful as inhibitors of voltage-gated sodium and/or calcium channels. These compounds have the general formula I:

$$T\text{——}L_1\text{——}A\text{——}L_2\text{——}Z \qquad (I);$$

or a pharmaceutically acceptable derivative thereof;

wherein:

L_1 is $-(X_1)_p-(X_2)_q-R_y-$;

wherein:

X_1 is O, S, or NR_x

p is 0 or 1;

q is 0 or 1;

R_x is H or R^2;

X_2 is R^2;

R_y is $-C(O)-NR^2-$; or

L_2 and Ry are independently selected from OC(O), C(O)O, S(O), SO_2, $N(R^5)SO_2$, $N(R^6)SO_2$, $SO_2N(R^5)$, $SO_2N(R^6)$, $C(O)N(R^5)$, $C(O)N(R^6)$, $NR^5C(O)$, $NR^6C(O)$, $C(NOR^5)R^6$, $C(NOR^5)R^6$, $C(NOR^6)R^5$, $C(NOR^6)R^6$, $N(R^5)$, $N(R^6)$, $NR^5C(O)O$, $NR^6C(O)O$, $OC(O)NR^5$, $OC(O)NR^6$, $NR^5C(O)N(R^5)$, $NR^5C(O)N(R^6)$, $NR^6C(O)N(R^5)$, $NR^6C(O)N(R^6)$, $NR^5SO_2N(R^5)$, $NR^5SO_2N(R^6)$, $NR^6SO_2N(R^5)$, $NR^6SO_2N(R^6)$, $N(OR^5)$, or $N(OR^6)$;

Z is hydrogen, cycloaliphatic, heterocyclic, aryl, or heteroaryl ring;

T is aliphatic, cycloaliphatic, aryl, heteroaryl, or heterocyclic ring;

A is aryl or heteroaryl ring;

wherein each of T, A, and Z optionally comprises up to 4 suitable substituents independently selected from R^1, R^2, R^3, R^4, or R^5;

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

n is 0, 1 or 2;

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

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

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

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

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

$P(O)(OR^6)N(R^5)_2$, $P(O)(OR^5)N(R^5R^6)$, $P(O)(OR^5)N(R^6)_2$, $P(O)(OR^5)N(R^5)_2$, $P(O)(OR^6)_2$, $P(O)(OR^5)_2$, or $P(O)(OR^6)(OR^5)$;

R^5 is a cycloaliphatic, aryl, heterocyclic, or heteroaryl ring optionally substituted with up to 3 R^1 substituents;

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

R^7 is a cycloaliphatic, aryl, heterocyclic, or heteroaryl ring and each R^7 is optionally substituted with up to 2 substituents independently chosen from H, aliphatic, or $(CH_2)_n$-Z;

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

R^8 is an amino protecting group.

[00171] These compounds and pharmaceutically acceptable compositions thereof are useful for treating or lessening the severity of a variety of diseases, disorders, or conditions, including, but not limited to, acute, chronic, neuropathic, or inflammatory pain, arthritis, migraine, 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.

DESCRIPTION OF THE FIGURES

[00172] **FIGURE 1** (FIGURE 1-1 to FIGURE 1-122) depicts the structures of the compounds of the present invention.

DETAILED DESCRIPTION OF THE INVENTION

[00173] According to one embodiment, the present invention provides compounds of formula (I) useful in inhibiting a sodium and/or calcium channel:

$$T\text{---}L_1\text{---}A\text{---}L_2\text{---}Z \qquad (I);$$

or a pharmaceutically acceptable salt thereof;

wherein:

L_1 is $-(X_1)_p-(X_2)_q-R_y-$;

wherein:

X_1 is O, S, or NR_x

p is 0 or 1;

q is 0 or 1;

R_x is H or R^2;

X_2 is R^2;

R_y is $-C(O)-NR^2-$; or

L_2 and Ry are independently selected from $OC(O)$, $C(O)O$, $S(O)$, SO_2, $N(R^5)SO_2$, $N(R^6)SO_2$, $SO_2N(R^5)$, $SO_2N(R^6)$, $C(O)N(R^5)$, $C(O)N(R^6)$, $NR^5C(O)$, $NR^6C(O)$, $C(NOR^5)R^6$, $C(NOR^5)R^6$, $C(NOR^6)R^5$, $C(NOR^6)R^6$, $N(R^5)$, $N(R^6)$, $NR^5C(O)O$, $NR^6C(O)O$, $OC(O)NR^5$, $OC(O)NR^6$, $NR^5C(O)N(R^5)$, $NR^5C(O)N(R^6)$, $NR^6C(O)N(R^5)$, $NR^6C(O)N(R^6)$, $NR^5SO_2N(R^5)$, $NR^5SO_2N(R^6)$, $NR^6SO_2N(R^5)$, $NR^6SO_2N(R^6)$, $N(OR^5)$, or $N(OR^6)$;

Z is hydrogen, cycloaliphatic, heterocyclic, aryl, or heteroaryl ring;

T is aliphatic, cycloaliphatic, aryl, heteroaryl, or heterocyclic ring;

A is aryl or heteroaryl ring;

wherein each of T, A, and Z is optionally substituted with up to 4 suitable substituents independently selected from R^1, R^2, R^3, R^4, or R^5;

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

n is 0, 1 or 2;

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

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

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

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

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

$NR^6C(O)OR^5$, $NR^5C(O)OR^5$, $NR^6C(O)N(R^6)_2$, $NR^6C(O)NR^5R^6$, $NR^6C(O)N(R^5)_2$, $NR^5C(O)N(R^6)_2$, $NR^5C(O)NR^5R^6$, $NR^5C(O)N(R^5)_2$, $NR^6SO_2R^6$, $NR^6SO_2R^5$, $NR^5SO_2R^5$, $NR^6SO_2N(R^6)_2$, $NR^6SO_2NR^5R^6$, $NR^6SO_2N(R^5)_2$, $NR^5SO_2NR^5R^6$, $NR^5SO_2N(R^5)_2$, $N(OR^6)R^6$, $N(OR^6)R^5$, $N(OR^5)R^5$, $N(OR^5)R^6$, $P(O)(OR^6)N(R^6)_2$, $P(O)(OR^6)N(R^5R^6)$, $P(O)(OR^6)N(R^5)_2$, $P(O)(OR^5)N(R^5R^6)$, $P(O)(OR^5)N(R^6)_2$, $P(O)(OR^5)N(R^5)_2$, $P(O)(OR^6)_2$, $P(O)(OR^5)_2$, or $P(O)(OR^6)(OR^5)$;

R^5 is a cycloaliphatic, aryl, heterocyclic, or heteroaryl ring is optionally substituted with up to 3 R^1 substituents;

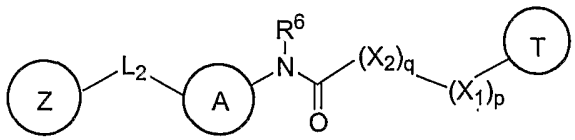
R^6 is H or aliphatic, wherein R^6 is optionally substituted with a R^7 substituent;

R^7 is a cycloaliphatic, aryl, heterocyclic, or heteroaryl ring and each R^7 is optionally substituted with up to 2 substituents independently chosen from H, aliphatic, or $(CH_2)_n$-Z';

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

R^8 is an amino protecting group.

[00174] According to one embodiment, the present invention provides compounds of formula I':



I';

or a pharmaceutically acceptable salt thereof,

wherein:

X_1 is O, S, or NR_x;

p is 0 or 1;

q is 0 or 1;

R_x is H or R^2;

X_2 is a bond R^2;

L_2 is selected from $OC(O)$, $C(O)O$, $S(O)$, SO_2, $N(R^5)SO_2$, $N(R^6)SO_2$, $SO_2N(R^5)$, $SO_2N(R^6)$, $C(O)N(R^5)$, $C(O)N(R^6)$, $NR^5C(O)$, $NR^6C(O)$, $C(NOR^5)R^6$, $C(NOR^5)R^6$, $C(NOR^6)R^5$, $C(NOR^6)R^6$, $N(R^5)$, $N(R^6)$, $NR^5C(O)O$, $NR^6C(O)O$, $OC(O)NR^5$, $OC(O)NR^6$, $NR^5C(O)N(R^5)$, $NR^5C(O)N(R^6)$, $NR^6C(O)N(R^5)$, $NR^6C(O)N(R^6)$, $NR^5SO_2N(R^5)$, $NR^5SO_2N(R^6)$, $NR^6SO_2N(R^5)$, $NR^6SO_2N(R^6)$, $N(OR^5)$, or $N(OR^6)$;

Z is cycloaliphatic, heterocyclic, aryl, or heteroaryl ring;

T is aliphatic, cycloaliphatic, aryl, heteroaryl, or heterocyclic ring;

A is aryl or heteroaryl ring;

wherein each of T, A, and Z is optionally substituted with up to 4 suitable substituents independently selected from R^1, R^2, R^3, R^4, or R^5;

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

n is 0, 1 or 2;

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

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

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

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

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

R^5 is a cycloaliphatic, aryl, heterocyclic, or heteroaryl ring is optionally substituted with up to 3 R^1 substituents;

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

R^7 is a cycloaliphatic, aryl, heterocyclic, or heteroaryl ring and each R^7 is optionally substituted with up to 2 substituents independently chosen from H, aliphatic, or $(CH_2)_n$-Z';

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

R^8 is an amino protecting group.

[00175] 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.

[00176] As described herein, compounds of the invention may optionally be substituted with one or more substituents, such as are illustrated generally above, or as exemplified by particular classes, subclasses, and species of the invention. It will be appreciated that the phrase "optionally substituted" is used interchangeably with the phrase "substituted or unsubstituted." In general, the term "substituted", whether preceded by the term "optionally" or not, refers to the replacement of hydrogen radicals in a given structure with the radical of a specified substituent. Unless otherwise indicated, an optionally substituted group may have a substituent at each substitutable

(i.e., having the requisite valency available for a given substituent) position of the group, and when more than one position in any given structure may be substituted with more than one substituent selected from a specified group, the substituent may be either the same or different at every position. Combinations of substituents envisioned by this invention are preferably those that result in the formation of stable or chemically feasible compounds. The term "stable", as used herein, refers to compounds that are not substantially altered when subjected to conditions to allow for their production, detection, and preferably their recovery, purification, and use for one or more of the purposes disclosed herein. In some embodiments, a stable compound or chemically feasible compound is one that is not substantially altered when kept at a temperature of 40°C or less, in the absence of moisture or other chemically reactive conditions, for at least a week.

[00177] The term "aliphatic" or "aliphatic group", as used herein, means a straight-chain (i.e., unbranched) or branched, substituted or unsubstituted hydrocarbon chain that is completely saturated or that contains one or more units of unsaturation. Unless otherwise specified, aliphatic groups contain 1-20 aliphatic carbon atoms. In some embodiments, aliphatic groups contain 1-10 aliphatic carbon atoms. In other embodiments, aliphatic groups contain 1-8 aliphatic carbon atoms. In still other embodiments, aliphatic groups contain 1-6 aliphatic carbon atoms, and in yet other embodiments aliphatic groups contain 1-4 aliphatic carbon atoms. Suitable aliphatic groups include, but are not limited to, linear or branched, substituted or unsubstituted alkyl, alkenyl, alkynyl groups. The term "cycloaliphatic" means a monocyclic hydrocarbon, bicyclic, or tricyclic hydrocarbon that is completely saturated or

that contains one or more units of unsaturation, but which is not aromatic and has a single point of attachment to the rest of the molecule. In some embodiments, "cycloaliphatic" refers to a monocyclic C_3-C_8 hydrocarbon or bicyclic C_8-C_{12} hydrocarbon that is completely saturated or that contains one or more units of unsaturation, but which is not aromatic, that has a single point of attachment to the rest of the molecule wherein any individual ring in said bicyclic ring system has 3-7 members.

[00178] Unless otherwise specified, the term "heterocycle", "heterocyclyl", "heterocycloaliphatic", or "heterocyclic" as used herein means non-aromatic, monocyclic, bicyclic, or tricyclic ring systems in which one or more ring atoms in one or more ring members is an independently selected heteroatom. Heterocyclic ring can be saturated or can contain one or more unsaturated bonds. In some embodiments, the "heterocycle", "heterocyclyl", or "heterocyclic" group has three to fourteen ring members in which one or more ring members is a heteroatom independently selected from oxygen, sulfur, nitrogen, or phosphorus, and each ring in the ring system contains 3 to 7 ring members.

[00179] The term "heteroatom" means oxygen, sulfur, nitrogen, phosphorus, or silicon (including, any oxidized form of nitrogen, sulfur, phosphorus, or silicon; the quaternized form of any basic nitrogen or; a substitutable nitrogen of a heterocyclic ring, for example N (as in 3,4-dihydro-2*H*-pyrrolyl), NH (as in pyrrolidinyl) or NR^+ (as in N-substituted pyrrolidinyl)).

[00180] The term "unsaturated", as used herein, means that a moiety has one or more units of unsaturation.

[00181] 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.

[00182] The term "aryl" used alone or as part of a larger moiety as in "aralkyl", "aralkoxy", or "aryloxyalkyl", refers to monocyclic, bicyclic, and tricyclic ring systems having a total of five to fourteen ring carbon atoms, wherein at least one ring in the system is aromatic and wherein each ring in the system contains 3 to 7 ring carbon atoms. The term "aryl" may be used interchangeably with the term "aryl ring".

[00183] 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".

[00184] 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.

[00185] 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.

[00186] According to a preferred embodiment, p is 0, and q is 0.

[00187] According to another preferred embodiment, p is 0, and q is 1. Or, p is 1, and q is 0.

[00188] According to yet another preferred embodiment, p is 1 and q is 1.

[00189] According to a preferred embodiment, X_1 is O or NR_X. More preferably, X_1 is O. According to another embodiment, X_1 is NR_X; preferably R_X is H. Or, X_1 is S.

[00190] According to a preferred embodiment, X_2 is a straight or branched (C1-C6)alkyl or (C2-C6)alkenyl or alkynyl, optionally substituted with up to two substituents independently selected from R_1 and R_5. More preferably, X_2 is a straight or branched (C1-C6)alkyl optionally substituted with up to two substituents independently selected from R_1 and R_5. Preferred X_2 include C1-4 alkyl, such as, $-CH_2-$, CH_2CH_2, or $-CH_2CH_2CH_2-$.

[00191] According to a preferred embodiment of formula (I), R_Y is -C(O)-NH- or $-C(O)-NR^2-$. More preferably, R^2 is straight or branched (C1-C6)alkyl or (C2-C6)alkenyl or alkynyl, optionally

substituted with up to two substituents independently selected from R_1 and R_5. More preferably, R_Y is -C(O)-NH-.

[00192] In one embodiment, L_2 is selected from $N(R^5)SO_2$, $N(R^6)SO_2$, $SO_2N(R^5)$, $SO_2N(R^6)$, $C(O)N(R^5)$, $C(O)N(R^6)$, $NR^5C(O)$, $NR^6C(O)$, $NR^5C(O)O$, $NR^6C(O)O$, $OC(O)NR^5$, $OC(O)NR^6$, $NR^5C(O)N(R^5)$, $NR^5C(O)N(R^6)$, $NR^6C(O)N(R^5)$, or $NR^6C(O)N(R^6)$.

[00193] In another embodiment, L_2 is selected from $N(R^6)SO_2$, $SO_2N(R^6)$, $C(O)N(R^6)$, $NR^6C(O)$, $NR^6C(O)O$, $OC(O)NR^6$, or $NR^6C(O)N(R^6)$. Preferably, R^6 is hydrogen.

[00194] In another embodiment, L_2 is selected from $NHSO_2$, SO_2NH, C(O)NH, or NHC(O).

[00195] According to another preferred embodiment, Z is cycloaliphatic, heterocyclic, aryl, or heteroaryl ring.

[00196] According to a preferred embodiment of formula (I), Z is aryl or heteroaryl. More preferably, Z is phenyl or napthyl. According to a more preferred embodiment, Z is heteroaryl. More preferably, Z is selected from thiazole, isothiazole, thiadiazole, thiaphene, furan, oxazole, isooxazole, oxadiazole, triazole, imidazole, pyrazole, pyridine, pyrimidine, pyrazine, pyridazine, triazine, or pyrrolyl.

[00197] According to a preferred embodiment of formula (I), A is aryl. More preferably, A is phenyl or naphthyl. Most preferably, A is phenyl.

[00198] Acccording to another preferred embodiment of formula (I), A is heteroaryl. More preferably, A is a monocyclic aromatic ring containing 1 to 3 heteroatoms. More preferably, A is pyridyl, pyrazyl, triazinyl, furanyl, pyrrolyl, thiophenyl, oxazolyl, isoxazolyl, isothiazolyl, oxadiazolyl, imidazolyl, triazolyl,

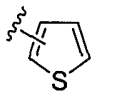
thiadiazolyl, or pyrimidinyl. According to another preferred embodiment of formula (I), A is a bicyclic ring system with at least one aromatic ring, wherein said ring system contains 1-5 heteroatoms. More preferably, A is quinolinyl, isoquinolinyl, benzofuranyl, benzothiophenyl, quinolinyl, isoquinolinyl, benzofuranyl, benzothiophenyl, indolizinyl, indolyl, isoindolyl, indolinyl, indazolyl, benzimidazolyl, benzothiazolyl, purinyl, cinnolinyl, phthalazine, quinazolinyl, quinaoxalinyl, naphthylirinyl, or pteridinyl. According to another preferred embodiment, A is a tricyclic ring system with at least one aromatic ring, wherein said ring system contains 1-5 heteroatoms. More preferably, A is dibenzofuranyl, carbazolyl, acridinyl, phenazinyl, phenothiazinyl, or phenoxazinyl.

[00199] According to a preferred embodiment of formula (I), T is aliphatic or cycloaliphatic. According to a preferred embodiment T is aliphatic; more preferably, (C1-C6) straight or branched alkyl; yet more preferably, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, or t-butyl. According to another preferred embodiment, T is cycloaliphatic; more preferably, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, norbornyl, or adamantyl. Yet more preferably, T is cyclopropyl, cyclohenxyl, norbornyl, or adamantyl.

[00200] According to another preferred embodiment, T is an aryl ring; more preferably, phenyl, napthyl, or anthracenyl. Yet more preferably, T is phenyl or napthyl. According to another preferred embodiment, T is a heteroaryl ring; more preferably, thiophenyl, benzothiophenyl, pyridyl, furanyl, benzofuranyl, oxazolyl, quinolinyl, thiophenyl, benzothiophenyl, pyridiyl, furanyl, benzofuranyl, oxazolyl, quinolinyl, pyrrolyl, thiazolyl,

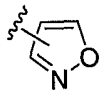
imidazolyl, pyrazolyl, isoxazolyl, isothiazolyl, oxadiazolyl, triazolyl, thiadiazolyl, pyridazinyl, pyrimidinyl, pyrazinyl, triazinyl, indolizinyl, indolyl, isoindolyl, indazolyl, benzimidazolyl, benzthiazolyl, purinyl, isoquinolinyl, cinnolinyl phthalazinyl, quinazolinyl, quinoxalinyl, napthyridinyl, pteridinyl, acridinyl, phenazinyl, phenothiazinyl, phenoxazinyl, carbazolyl.

[00201] In one embodiment, T is selected from:



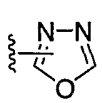
a

b

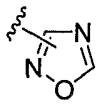


c

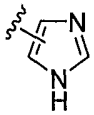
d



e

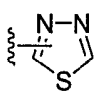


f

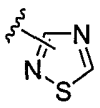


g

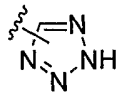
h



i



j

or 

k,

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

[00202] According to another preferred embodiment, T is a heterocyclic ring; preferably, tetrahydrofuranyl, pyrrolidinyl, piperidinyl, morpholinyl, dithianyl, thiomorpholinyl, piperazinyl, quinuclidinyl, tetrahydrofuranyl, pyrrolidinyl, piperidinyl, morpholinyl, dithianyl, thiomorpholinyl, piperazinyl, quinuclidinyl, dioxoianyl, imidazolidinyl, pyrazolidinyl, dioxanyl, piperazinyl, or trithianyl.

[00203] According to another preferred embodiment of formula (I), R^1 is oxo. According to another preferred embodiment, R^1 is R^6 or $(CH_2)_n$-Y; more preferably, R^1 is Y (i.e., n is 0).

[00204] According to another preferred embodiment of formula (I), R^2 is a straight or branched (C1-C6) alkyl or (C2-C6)alkenyl or alkynyl, optionally substituted with up to two R^1 substitutions.

[00205] According to one embodiment, R^1 is $(CH_2)_n$-Y. Or, R^1 is Y. Preferred Y includes halo, CN, NO_2, CF_3, OCF_3, OH, SH, S(C1-4 aliphatic), S(O)(C1-4 aliphatic), SO_2(C1-4 aliphatic), NH_2, NH(C1-4 aliphatic), N(C1-4 aliphatic)$_2$, NR(C1-4 aliphatic)R^8, COOH, COO(C1-4 aliphatic) or O(C1-4 aliphatic). Or two R^1 on adjacent ring atoms, taken together, form 1,2-methylenedioxy or 1,2-ethylenedioxy;

[00206] According to another embodiment, R^1 is selected from halo, cyano, trifluoromethyl, OH, C_{1-4} alkyl, C_{2-4} alkenyl, C_{1-4} alkoxy, trifluoromethoxy, $C(O)NH_2$, NH_2, $NH(C_{1-4}$ alkyl), $N(C_{1-4}$ alkyl)$_2$, $NHC(O)C_{1-4}$ alkyl, 1-pyrrolidinyl, 1-piperidinyl, 1-morpholinyl, or $C(O)C_{1-4}$ alkyl.

[00207] According to another preferred embodiment of formula (I):

Z is thiazol-2-yl;

A is phenyl, pyridyl, pyrazinyl, pyridazinyl, pyrimidinyl, triazinyl, or tetrazinyl;

L_1 is $-(X_1)_p-(X_2)_q-R_y-$;

wherein:

X_1 is O, S, or NR_X

p is 0 or 1;

q is 0 or 1;

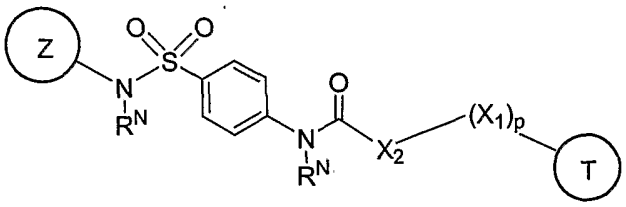
R_X is H or R^2;

X_2 is R^2;

R_Y is -C(O)-NH-; and

L_2 is $SO_2N(R^5)$ or $SO_2N(R^6)$.

[00208] According to one embodiment, the present invention provides a compound of formula I-A:



I-A;

wherein:

X_1 is O, S, or NR^X

p is 0 or 1;

R^X is H or R^2;

R^N is hydrogen or C1-4 aliphatic optionally substituted with up to two substituents selected from R^1, R^4, or R^5;

X_2 is C_{1-3} aliphatic, optionally substituted with up to 2 substituents independently selected from R^1, R^4, or R^5;

Z is a 5-7 membered unsaturated or aromatic ring having 1-4 heteroatoms selected from O, S, SO, SO_2, N, or NH;

T is a 8-14 membered aromatic or non-aromatic bicyclic or tricyclic ring, having 0-5 heteroatoms selected from O, S, N, NH, S(O) or SO_2;

wherein each of Z and T is optionally substituted with up to 4 substituents independently selected from R^1, R^2, R^3, R^4, or R^5;

wherein the phenylene ring attached to the sulfonyl is optionally substituted with up to 3 substituents selected from R^1 and R^2;

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

n is 0, 1 or 2;

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

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

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

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

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

$P(O)(OR^6)N(R^5)_2$, $P(O)(OR^5)N(R^5R^6)$, $P(O)(OR^5)N(R^6)_2$, $P(O)(OR^5)N(R^5)_2$, $P(O)(OR^6)_2$, $P(O)(OR^5)_2$, or $P(O)(OR^6)(OR^5)$;

R^5 is a cycloaliphatic, aryl, heterocyclic, or heteroaryl ring optionally is optionally substituted with up to 3 R^1 substituents;

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

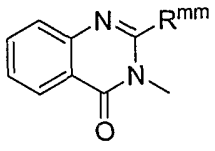
R^7 is a cycloaliphatic, aryl, heterocyclic, or heteroaryl ring and each R^7 is optionally substituted with up to 2 substituents independently chosen from H, aliphatic, or $(CH_2)_n$-Z';

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

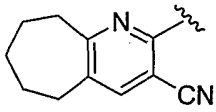
R^8 is an amino protecting group.

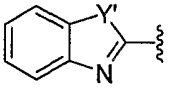
[00209] In certain embodiments, compounds of formula I or formula I-A exclude the following:

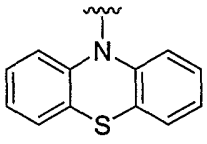
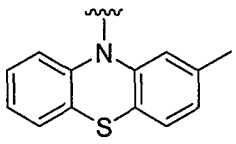
a) when both R^N are hydrogen, and T is isoindol-1,3-dione-2-yl optionally substituted with up to 4 halo atoms, then Z is not pyridyl, thiazol-2-yl, 4-(4-methoxyphenyl)thiazol-2-yl, 2-ethyl-1,3,4-thiadiazol-5-yl, optionally substituted pyrimidin-2-yl, 5-methyl-isoxazolyl, 3,4-dimethyl-isoxazoly, or 2-methyl-isoxazolyl;

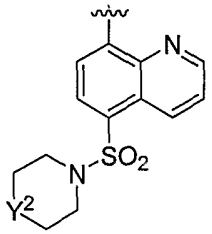
b) when both R^N are hydrogen, and T is  , optionally substituted with up to 4 halo atoms, wherein R^{mm} is phenyl optionally substituted with C_{1-4} alkyl or hydrogen, then Z

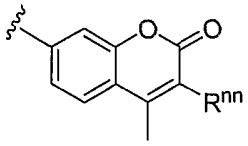
is not optionally substituted pyrimidin-2-yl, 2-pyridyl, or thiazol-2-yl;

c) when both R^N are hydrogen, X_2 is $-CH_2-$, p is 1, X_1 is S, and T is  , then Z is not 3,4-dimethylisoxazolyl, pyrimidin-2-yl, thiazol-2-yl, or 4,6-dimethyl-pyrimidin-2-yl;

c) when both R^N are hydrogen, X_2 is $-CH_2-$ and X_1 is S, or X_2 is CH=CH and X_1 is absent, and T is optionally substituted  , wherein Y' is O, S, or NH, then Z is not pyrimidinyl optionally substituted with up to 2 methyl or methoxy groups, 2-pyridyl, thiazol-2-yl, 2-methoxy-pyrazin-3-yl, 3-chloro-pyridazin-6-yl, 3,4-dimethyl-isoxazolyl, or 2-ethyl-1,3,4-thiadiazol-5-yl;

d) when both R^N are hydrogen, X_2 is $-CH_2-CH_2-$, X_1 is absent, and T is  or  , then Z is not thiazol-2-yl, 2,6-dimethyl-pyrimidin-4-yl, or 3,4-dimethyl-isoxazol-5-yl;

e) when both R^N are hydrogen, X_2 is $-CH_2-$, X_1 is O or S, and T is  , wherein Y^2 is O or CH_2, then Z is not thiazol-2-yl, or 4,6-dimethyl-pyrimidin-2-yl, or pyrimidin-2-yl;

f) when both R^N are hydrogen, X_2 is $-CH_2-$, X_1 is O, T is  , wherein R^{nn} is hydrogen or halo, then Z is not

thiazol-2-yl, 4-methyl-pyrimidin-2-yl, 4,6-dimethylpyrimidin-2-yl, pyrimidin-2-yl, or 5-methyl-isoxazol-3-yl;

g) when both R^N are hydrogen, X_2 is $-CH_2-$, X_1 is absent, T is 1,4-dihydro-quinoxalin-2,3-dione-4-yl, then Z is not 5-methylisoxazol-3-yl, thiazol-2-yl, 4,6-dimethyl-pyrimidin-2-yl, pyrimidin-2-yl, or 2-pyridyl;

h) when both R^N are hydrogen, X_2 is $-CH_2-$, X_1 is absent, and T is 2,3-dihydro-phthalazin-1,4-dione-2-yl, then Z is not pyridyl, thiazol-2-yl, or optionally substituted pyrimidin-2-yl;

i) when both R^N are hydrogen, X_2 is $-CH_2-$, X_1 is absent, and T is adamantyl or haloadamantyl, then Z is not 3,4-dimethylisoxazol-5-yl, thiazol-2-yl, or 4-methyl-pyrimidin-2-yl;

j) the following compounds in Table A, wherein R^N is hydrogen, are excluded:

Table A

ring Z	X_2	X_1	ring T
pyrimidin-2-yl	CH_2	NH	1-naphthyl
4,6-dimethyl-pyrimidin-2-yl	CH_2	NH	1-naphthyl
5-methyl-isoxazol-3-yl	CH_2	-	1-naphthyl
thiazol-2-yl	CH_2	O	1-naphthyl, 2-napthyl, 1,7-dibromo-naphth-2-yl
4,6-dimethyl-pyrimidin-2-yl	CH_2	O	1-naphthyl, 2-napthyl, or 1,7-dibromo-naphth-2-yl
2-methoxy-pyrazin-3-yl	CH_2	O	2-napthyl
5-ethyl-1,3,4-thiadiazol-2-yl	CH_2	-	1-napthyl
thiazol-2-yl	CH_2	-	1-naphtyl
5-ethyl-1,3,4-thiadiazol-2-yl	CH_2	O	2-naphthyl
2,6-dimethoxy-pyrimidin-4-yl	CH_2	O	1-bromo-2-naphthyl
2,6-dimethyl-pyrimidin-4-yl	CH_2	O	2-naphthyl or 1-bromo-2-naphthyl
2,6-dimethoxy-pyrimidin-4-yl	CH_2	O	1-naphthyl or 2-naphthyl

2,4-dimethoxy-pyrimidin-6-yl	CH=CH	-	1-naphthyl
4,6-dimethyl-pyrimidin-2-yl	CH=CH	-	1-naphthyl
5-methyl-isoxazol-3-yl	CH_2	O	1-naphthyl or 2-naphthyl
5-methyl-isoxazol-3-yl	CH_2	O	1-bromo-2-naphthyl or 1,7-dibromo-naphth-2-yl
4,5-dimethyl-isoxazol-3-yl	CH_2	S	4-bromo-7-chloro-naphth-1-yl
thiazol-2-yl	CH_2	S	4-bromo-7-chloro-naphth-1-yl
4,6-dimethyl-pyrimidin-2-yl	CH_2	O or S	2-naphtyl
3,4-dimethyl-isoxazol-2-yl	CH_2	O or S	2-naphthyl
4,6-dimethyl-pyrimidin-2-yl	CH_2	S	quinolin-8-yl
2,6-dimethyl-pyrimidin-2-yl	CH_2	-	1-naphthyl
pyrimidin-2-yl	CH_2	-	1-naphthyl
6-methoxy-pyrimidin-4-yl	CH_2	-	1-naphthyl
2-pyridyl	CH_2	-	1-naphthyl
4-methyl-pyrimidin-2-yl	CH_2	O	2-naphthyl
pyrimidin-2-yl	CH_2	O	2-naphthyl
2,4-dimethoxy-pyrimidin-2-yl	CH_2	O	1,7-dibromo-naphth-2-yl
2,4-dimethoxy-pyrimidin-2-yl or 2,4-dimethyl-pyrimidin-2-yl	CH_2	-	1-naphthyl
thiazol-2-yl or 2,4-dimethyl-pyrimidin-4-yl	CH_2	S	isoquinolin-1-yl or 4-methyl-quinazolin-2-yl

;

k) the following compounds in Table B, wherein R^N is hydrogen, are excluded:

Table B

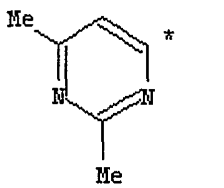
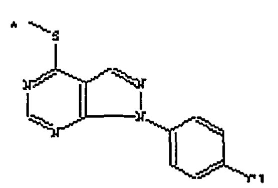
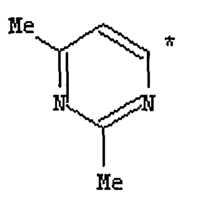
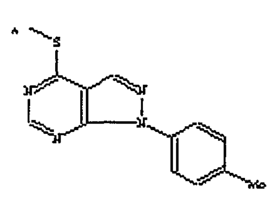
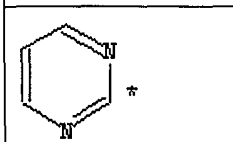
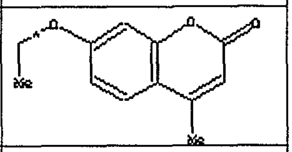
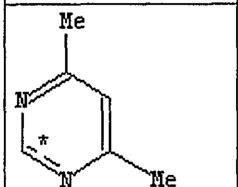
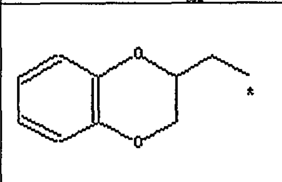
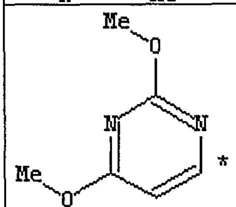
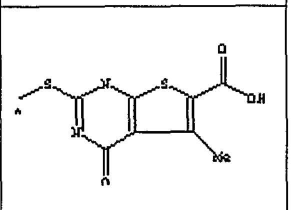
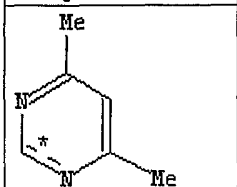
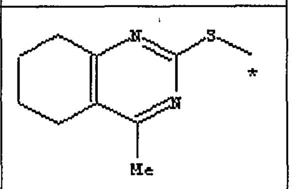
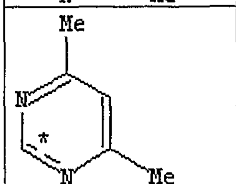
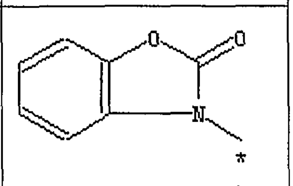
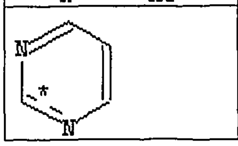
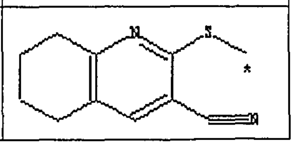
Ring Z	X_2, X_1, and T, together
	
	
	
	
	
	
	
	

Table B

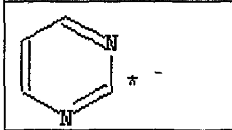
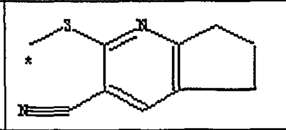
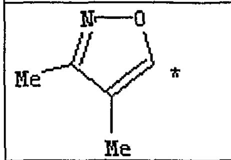
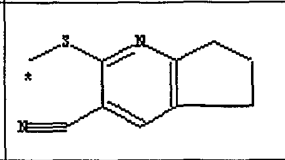
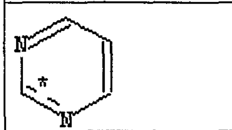
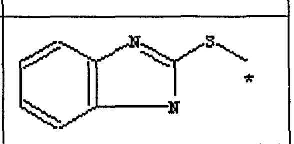
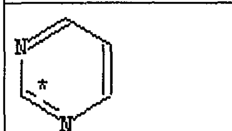
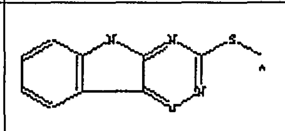
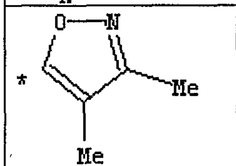
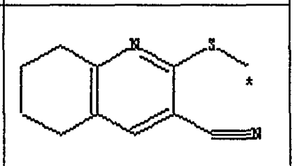
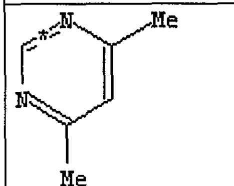
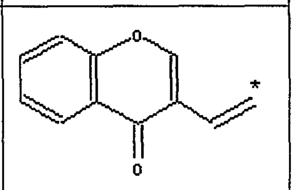
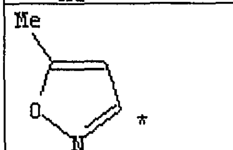
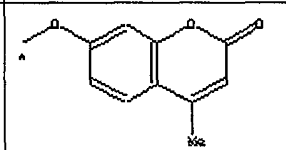
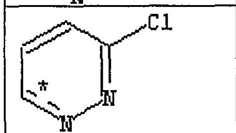
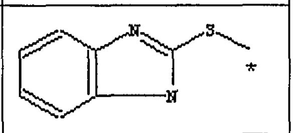
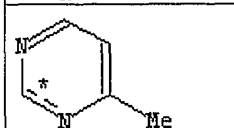
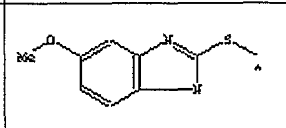
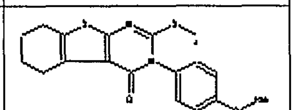
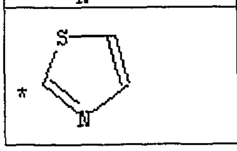
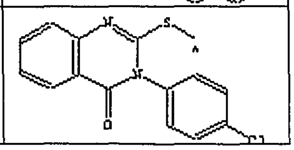
Ring Z	X_2, X_1, and T, together
	
	
	
	
	
	
	
	
	
	
	

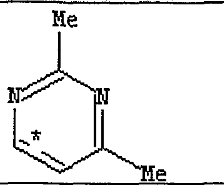
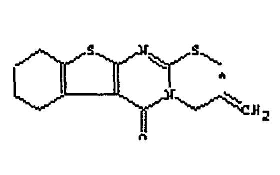
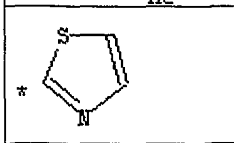
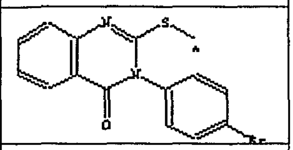
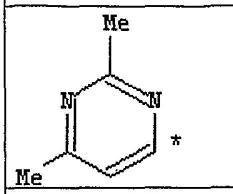
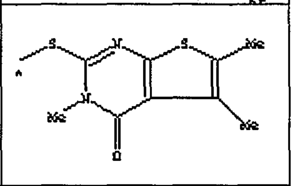
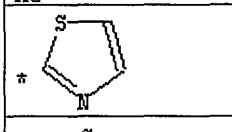
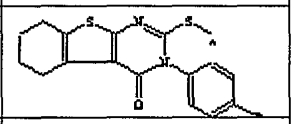
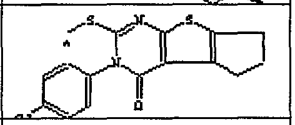
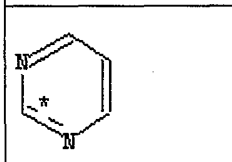
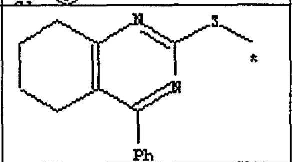
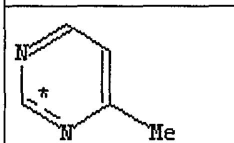
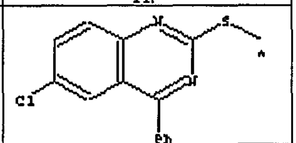
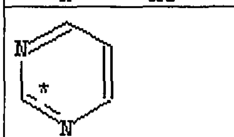
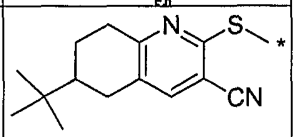
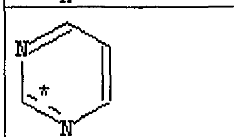
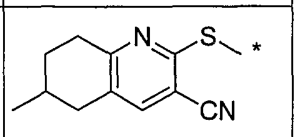
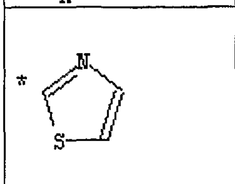
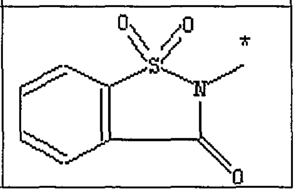
Table B	
Ring Z	X_2, X_1, and T, together
	
	
	
	
	
	
	
	
	
	

Table B	
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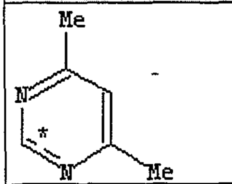
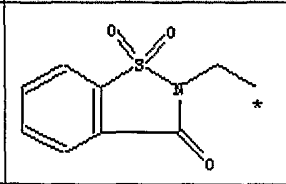
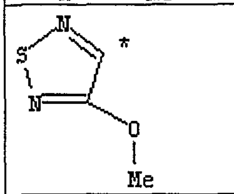
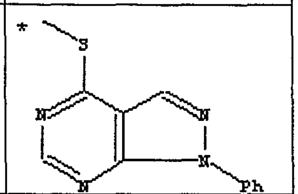
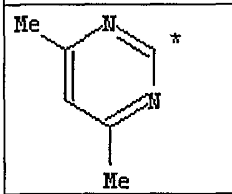
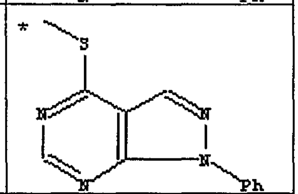
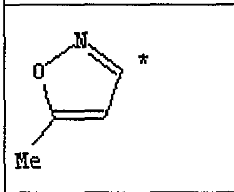
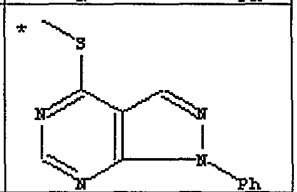
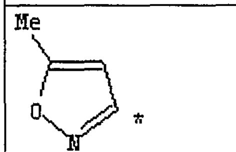
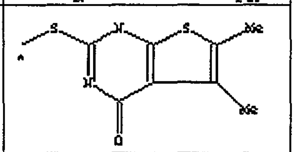
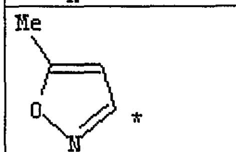
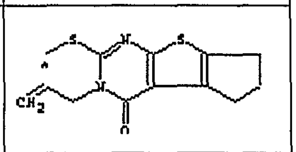
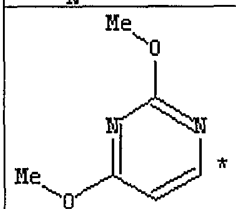
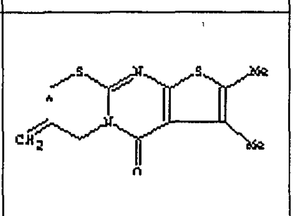
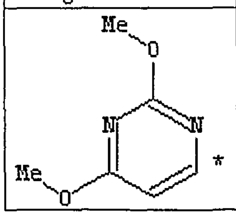
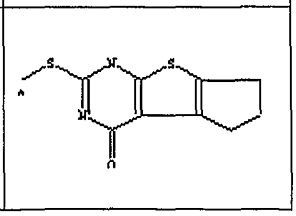
	
	
	
	
	
	
	
	

Table B

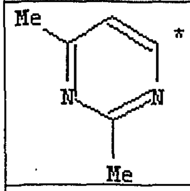
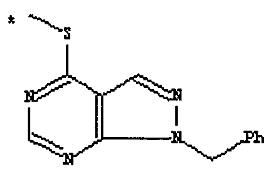
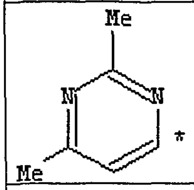
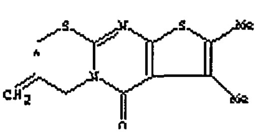
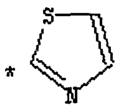
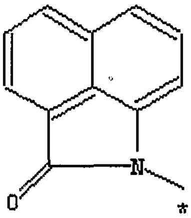
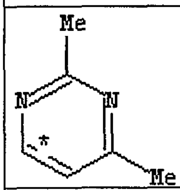
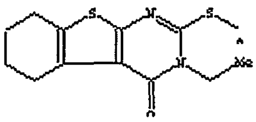
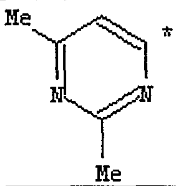
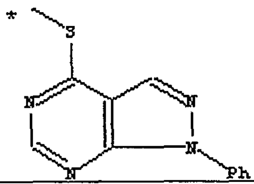
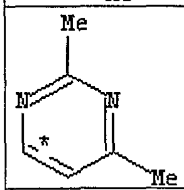
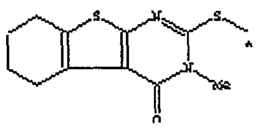
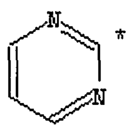
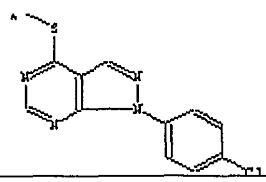
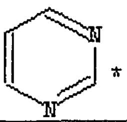
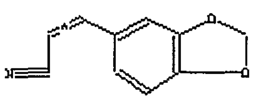
Ring Z	X_2, X_1, and T, together
	
	
	
	
	
	
	
	

Table B

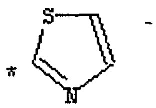
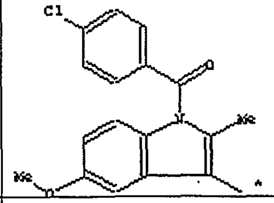
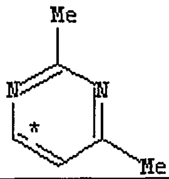
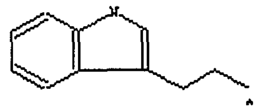
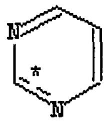
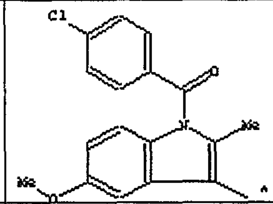
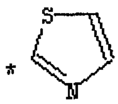
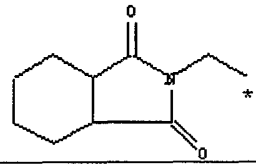
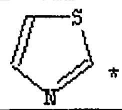
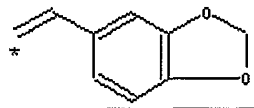
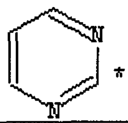
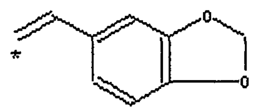
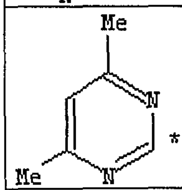
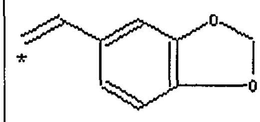
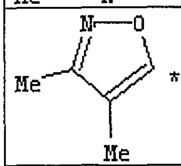
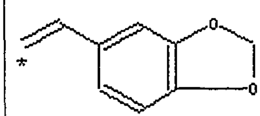
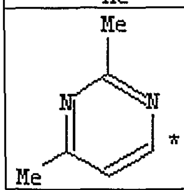
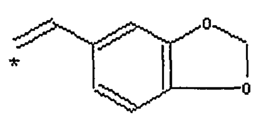
Ring Z	X_2, X_1, and T, together
	
	
	
	
	
	
	
	
	

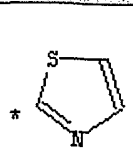
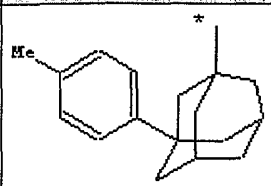
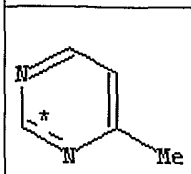
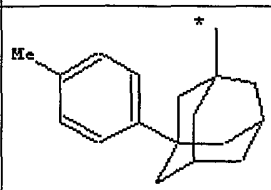
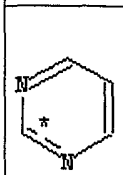
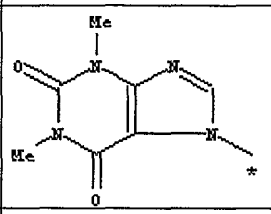
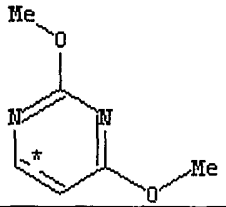
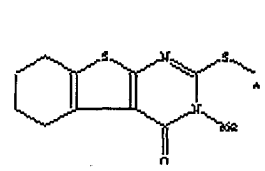
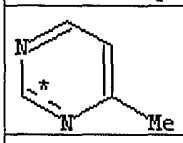
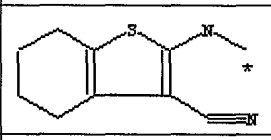
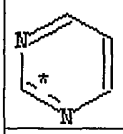
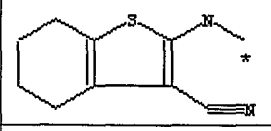
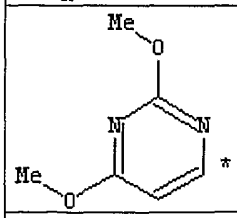
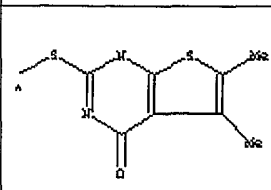
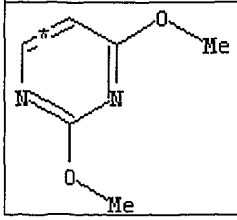
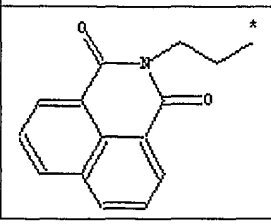
Table B	
Ring Z	X_2, X_1, and T, together
	
	
	
	
	
	
	
	

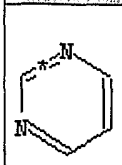
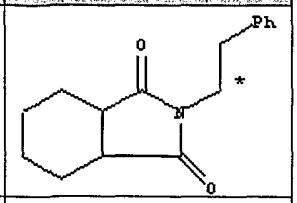
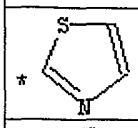
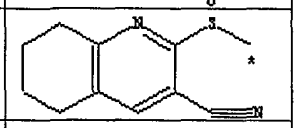
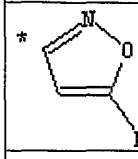
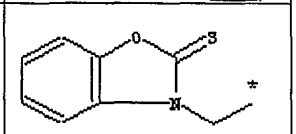
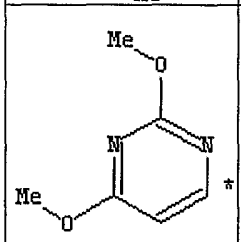
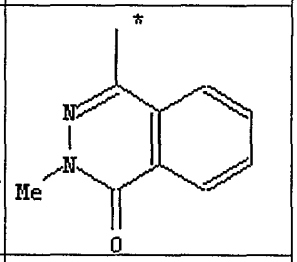
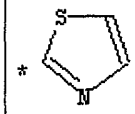
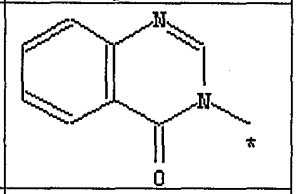
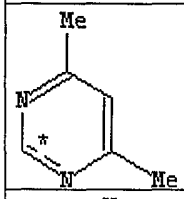
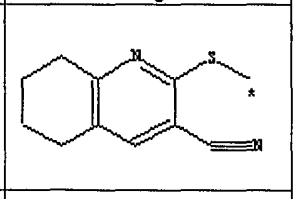
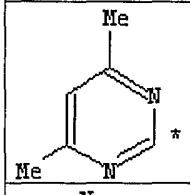
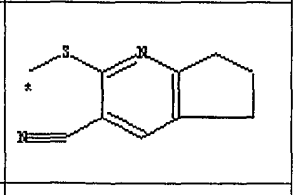
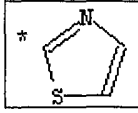
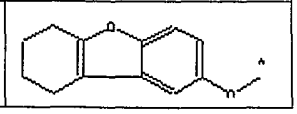
Table B	
Ring Z	X_2, X_1, and T, together
	
	
	
	
	
	
	
	

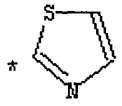
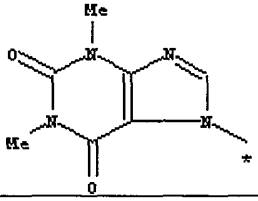
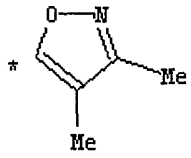
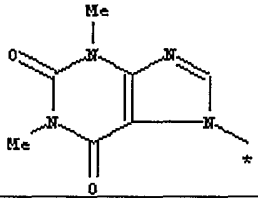
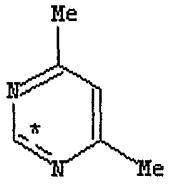
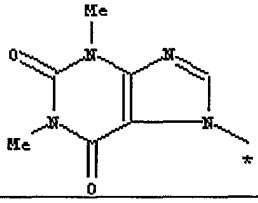
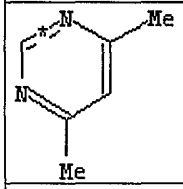
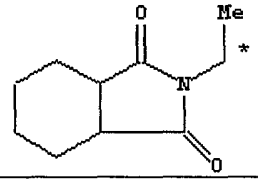
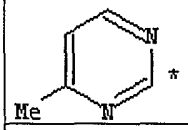
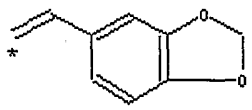
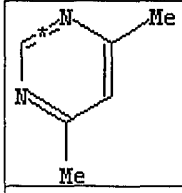
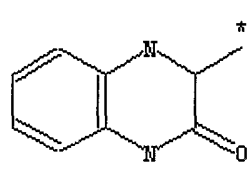
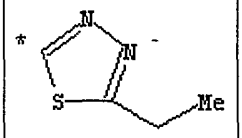
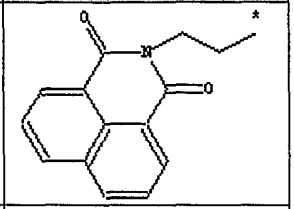
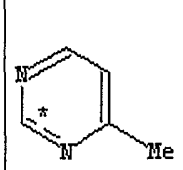
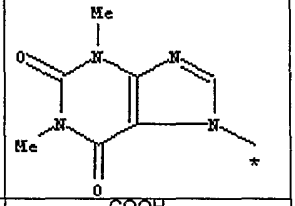
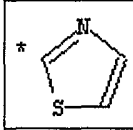
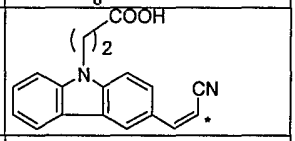
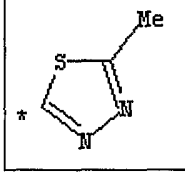
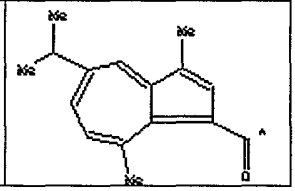
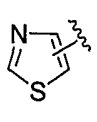
Table B	
Ring Z	X_2, X_1, and T, together
	
	
	
	
	
	

Table B	
Ring Z	X_2, X_1, and T, together
	
	
	
	

wherein the asterisk in each structure fragment denotes the carbon atom attached to the remainder of the molecule; e.g., the fragment —* denotes an ethyl group, wherein the second atom of that ethyl group is attached to the remainder of the molecule.

[00210] In one embodiment, T is attached to X_1 or to X_2 (when X_1 is absent) through a carbon ring atom in T.

[00211] In one embodiment, Z is an optionally substituted ring selected from: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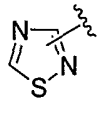
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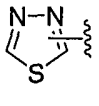
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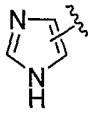
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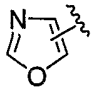
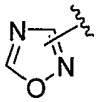

v


vi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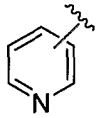
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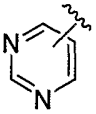
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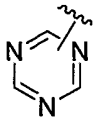
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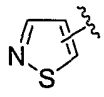
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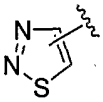
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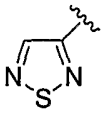
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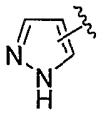
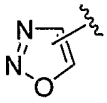

xii


xiii


xiv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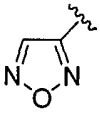
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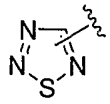
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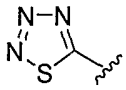
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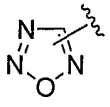
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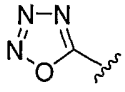
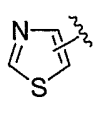
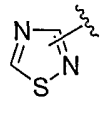
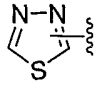
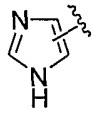

xx.

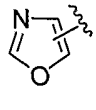
[00212] In certain embodiments of the compounds of the present invention, Z is selected from:





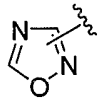




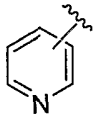


i ii iii iv v

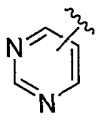
vi



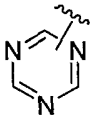
vii



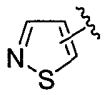
viii



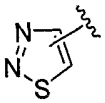
ix



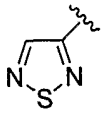
x



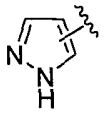
xi



xii

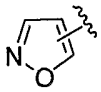


xiii

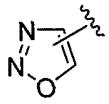


xii

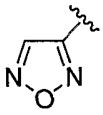
xiii



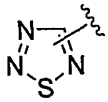
xiv



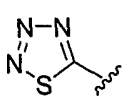
xv



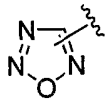
xvi



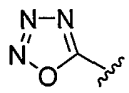
xvii



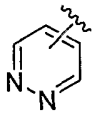
xviii



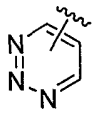
xix



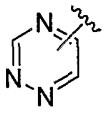
xx



xxi



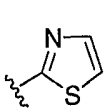
xxii



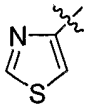
xxiii

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

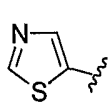
[00213] In other embodiments, Z is selected from:



i-a



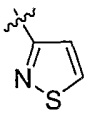
i-b or



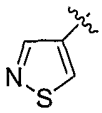
i-c.

[00214] Or, Z is formula i-a.

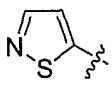
[00215] In other embodiments, Z is selected from:



xi-a

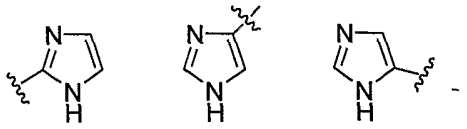


xi-b or



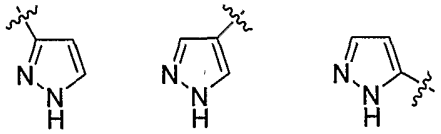
xi-c.

[00216] In certain embodiments of the present invention, Z is selected from:



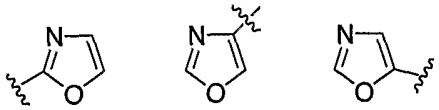
iv-a **iv-b** or **iv-c.**

[00217] Or, Z is selected from:



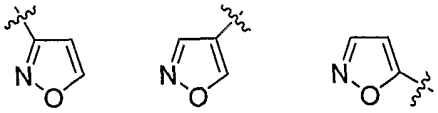
xii-a **xii-b or** **xii-c.**

[00218] Or, Z is selected from:



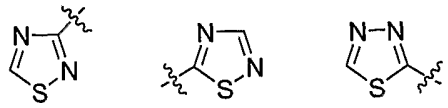
v-a **v-b** or **v-c.**

[00219] In certain embodiments, Z is selected from:



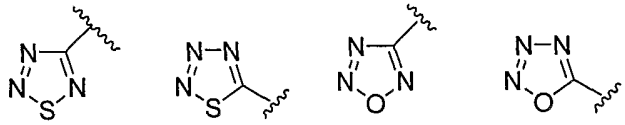
xiv-a **xiv-b or** **xiv-c.**

[00220] In certain embodiments, Z is selected from:



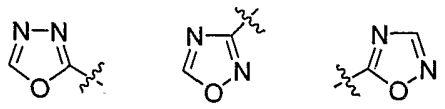
ii-a **ii-b** or **iii-a.**

[00221] In certain embodiments, Z is selected from:



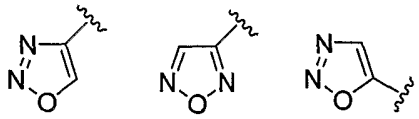
xvii **xviii** **xix** **or xx.**

[00222] In other embodiments, Z is selected from:



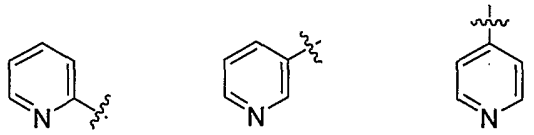
vi-a **vii-a** or **vii-b.**

[00223] In other embodiments, Z is selected from:



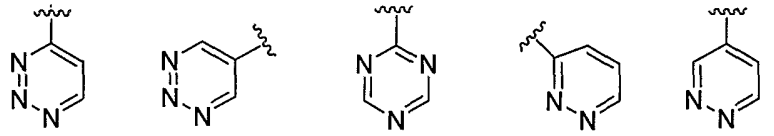
xv-a **xvi-a** **or xv-b**

[00224] In certain embodiments, Z is selected from:

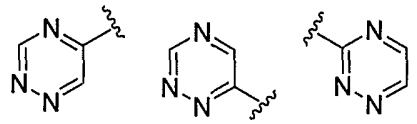


viii-a **viii-b** or **viii-c.**

[00225] In certain embodiments, Z is selected from:

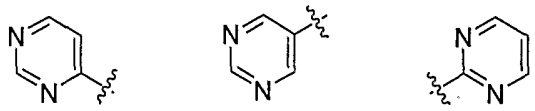


xxii-a **xxii-b** **x-a** **xxi-a** **xxi-b**



xxii-a **xxii-b** **xxii-c.**

[00226] In other embodiments, Z is selected from:



ix-a **ix-b** or **ix-c.**

[00227] In certain embodiments, R^N is hydrogen. Or, R^N is unsubstituted C1-4 alkyl.

[00228] In one embodiment, X^2 is selected from $-CH_2-$, $-CH_2-CH_2-$, $-(CH_2)_3-$, $-C(Me)_2-$, $-CH(Me)-$, $-C(Me)=CH-$, $-CH=CH-$,

-CH(Ph)-, -CH_2-CH(Me)-, -CH(Et)-, -CH(i-Pr)-, or cyclopropylene.

[00229] In another embodiment, p is 1 and X_1 is O.

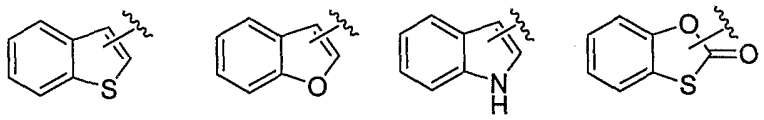
[00230] In another embodiment, p is 1, and X_1 is S.

[00231] In another embodiment, p is 1, and X_1 is NR^N. Preferably, R^N is hydrogen.

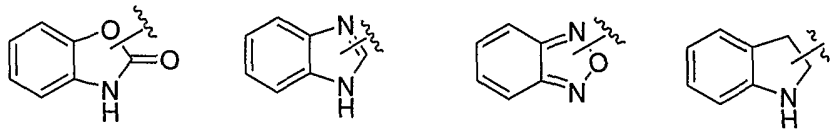
[00232] In certain embodiments of the present invention, T is naphthyl, tetralinyl, decalinyl, or 6,7,8,9-tetrahydro-5H-benzo[7]annulenyl, optionally substituted with up to 3 substituents independently selected from halo, cyano, trifluoromethyl, OH, C_{1-4} alkyl, C_{2-4} alkenyl, C_{1-4} alkoxy, trifluoromethoxy, $C(O)NH_2$, NH_2, $NH(C_{1-4}$ alkyl), $N(C_{1-4}$ alkyl)$_2$, $NHC(O)C_{1-4}$ alkyl, 1-pyrrolidinyl, 1-piperidinyl, 1-morpholinyl, or $C(O)C_{1-4}$ alkyl.

[00233] Or, T is optionally substituted napthyl.

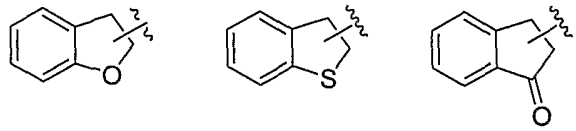
[00234] In another embodiment, T is selected from:



p **q** **r** **s**



s **t** **u** **v**



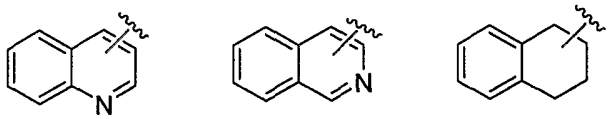
w **x** or **af,**

wherein T is optionally substituted with up to three substituents independently selected from halo, cyano,

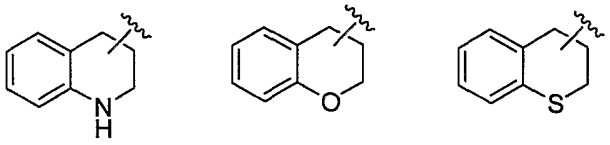
trifluoromethyl, OH, C_{1-4} alkyl, C_{2-4} alkenyl, C_{1-4} alkoxy, trifluoromethoxy, $C(O)NH_2$, NH_2, $NH(C_{1-4}$ alkyl), $N(C_{1-4}$ alkyl)$_2$, $NHC(O)C_{1-4}$ alkyl, or $C(O)C_{1-4}$ alkyl.

[00235] In another embodiment, T is a 5-membered ring having up to 4 heteroatoms selected from O, S, N, or NH, optinally fused to a phenyl ring, wherein said phenyl ring is unsubstituted or substituted with up to 4 substituents selected from R^1 or R^2. Preferred 5-membered rings in such embodiments of T include formula **i** through **xxiii** defined above for ring Z that are capable of being fused to a phenyl ring.

[00236] In other embodiments, T is selected from:



y **z** **aa**



ac **ad** or **ae**,

wherein T is optionally substituted with up to three substituents independently selected from halo, cyano, trifluoromethyl, OH, C_{1-4} alkyl, C_{2-4} alkenyl, C_{1-4} alkoxy, trifluoromethoxy, $C(O)NH_2$, NH_2, $NH(C_{1-4}$ alkyl), $N(C_{1-4}$ alkyl)$_2$, $NHC(O)C_{1-4}$ alkyl, or $C(O)C_{1-4}$ alkyl.

[00237] In one embodiment, the phenylene ring attached to the sulfonyl group is optionally substituted with up two substituents selected from halo, cyano, trifluoromethyl, OH, C_{1-4} alkyl, C_{2-4} alkenyl, C_{1-4} alkoxy, trifluoromethoxy, $C(O)NH_2$, NH_2, $NH(C_{1-4}$ alkyl), $N(C_{1-4}$ alkyl)$_2$, $NHC(O)C_{1-4}$ alkyl, or $C(O)C_{1-4}$ alkyl.

[00238] In one embodiment, the present invention provides compounds wherein:

a. Z is thiazol-2-yl;

b. R^N is hydrogen;

c. X_2 is absent or is C1-4 alkylene optionally substituted with phenyl;

d. X_1 is absent or is O or S;

e. T is selected from quinolin-4-yl, benzofuran-2-yl, benzothiophen-3-yl, phenyl, tetralin-2-yl, tetralin-6-yl, phenyl, indol-2-yl, chroman-3-yl, quinolin-3-yl, benzo[1,3]oxathiol-2-one-6-yl, benzothiophen-2-yl, 1,2,3,4-tetrazol-5-yl, furan-5-yl, quinolin-5-yl, benzothiazol-5-yl, or 5,6,7,8-tetrahydroquinolin-2-yl, optionally substituted with up to three substituents selected from trifluoromethyl, halo, cyano, C1-4 alkoxy, piperidinylsulfonyl, C1-4 alkyl, phenyl optionally substituted with up to three halo, cyano, C1-4 alkyl, or C1-4 alkoxy.

[00239] In one embodiment, the present invention provides compounds wherein:

a. Z is thiazol-2-yl;

b. R^N is hydrogen;

c. X_2 is absent or is C1-4 alkylene optionally substituted with phenyl;

d. X_1 is absent or is O or S;

e. T is selected from 8-trifluoromethyl-quinolin-4-yl, benzofuran-2-yl, benzothiophen-3-yl, 3-fluoro-4-chloro-phenyl, 8-methoxy-tetralin-2-yl, tetralin-6-yl, 4-piperidinylsulfonylphenyl, 2,4-dichlorophenyl, 5-fluoroindol-2-yl, 4,6-dichloroindol-2-yl, chroman-3-yl, 2-methyl-6-fluoro-quinolin-4-yl, 2,7-dimethyl-

quinolin-3-yl, 4-trifluoromethylphenyl, 2-fluoro-4-chloro-phenyl, benzo[1,3]oxathiol-2-one-6-yl, 5-chloro-benzothiophen-2-yl, 1-phenyl-1,2,3,4-tetrazol-5-yl, 2-(3',5'-dichlorophenyloxy)-furan-5-yl, 5-fluoro-benzothiophen-2-yl, quinolin-5-yl, 2-methyl-quinolin-4-yl, 2-methyl-benzothiazol-5-yl, or 4-cyano-5,6,7,8-tetrahydroquinolin-2-yl.

[00240] In one embodiment, the present invention provides compounds wherein:

a. Z is thiazol-2-yl or 1,2,4-thiadiazol-5-yl;

b. R^N is hydrogen;

c. X_2 is absent or C1-4 alkylene;

d. X_1 is absent or O;

e. T is selected from phenyl, benzo[1,3]oxathiol-2-one-5-yl, benzothiophen-2-yl, benzofuran-2-yl, quinolin-4-yl, indolin-2-yl, 1,2,3,4-tetrazol-5-yl, 5,6,7,8-tetrahydroquinolin-2-yl, indol-2-yl, norbornyl, furan-2-yl, 2-naphthyl, benzothiophen-3-yl, phenyl, quinolin-7-yl, tetralin-6-yl, benzothiophen-3-yl, tetralin-2-yl, chroman-3-yl, benzo[1,2,5]oxadiazol-5-yl, quinolin-5-yl, benzothiazol-5-yl, indol-5-yl, quinolin-3-yl, 1,2,3,4-tetrahydroisoquinolin-3-yl, quinolin-2-yl, benzo-[1,3]-dioxolan-5-yl, or benzo-[1,3]dixolan-4-yl, wherein T is optionally substituted with up to three substituents independently selected from trifluoromethyl, trifluoromethoxy, halo, cyano, C1-4 alkoxy, C1-4 alkyl, acyl, N(C1-4alkyl)2, phenyloxy or phenyl optionally substituted with up to three halo, cyano, C1-4 alkyl, or C1-4 alkoxy.

[00241] In one embodiment, the present invention provides compounds wherein:

a. Z is thiazol-2-yl or 1,2,4-thiadiazol-5-yl;

b. R^N is hydrogen;

c. X_2 is absent or C1-4 alkylene;

d. X_1 is absent or O;

e. T is selected from 4-trifluoromethylphenyl, 3-fluoro-4-chlorophenyl, 2-chloro-4-cyanophenyl, 2,3-dichlorophenyl, benzo[1,3]oxathiol-2-one-5-yl, 5-fluorobenzothiophen-2-yl, 3,4-dichlorophenyl, benzofuran-2-yl, 8-trifluoromethyl-quinolin-4-yl, 2-chloro-4-cyanophenyl, 1-acyl-indolin-2-yl, 1-phenyl-1,2,3,4-tetrazol-5-yl, 2-fluoro-3-chlorophenyl, 2-methyl-4-fluorophenyl, 2,3-difluorophenyl, 3-cyano-5,6,7,8-tetrahydroquinolin-2-yl, 2-chlorophenyl, 5-fluoro-indol-2-yl, 2,4-dichlorophenyl, 3,5-dichlorophenyl, 3-chlorophenyl, 5-bromo-indol-2-yl, 4-chlorophenyl, 1-norbornyl, 2-methoxy-4-chlorophenyl, 5-(3',5'-dichlorophenyloxy)-furan-2-yl, 2-naphthyl, benzothiophen-3-yl, 2-fluoro-3-trifluoromethylphenyl, 2-methyl-4-chlorophenyl, quinolin-7-yl, 2-fluoro-6-chlorophenyl, 2-methyl-6-fluoro-quinolin-4-yl, 5-methoxy-benzofuran-2-yl, phenyl, 3,4-difluorophenyl, 4,6-dichloroindol-2-yl, 2-trifluoromethoxyphenyl, 4-fluorophenyl, 5-chlorobenzothiophen-2-yl, 2-methyl-quinolin-4-yl, tetralin-6-yl, 2,6-dimethylphenyl, benzothiophen-3-yl, 8-methoxy-tetralin-2-yl, 2-methoxy-4-methylphenyl, chroman-3-yl, 3,4-dicyanophenyl, 2,6-dimethyl-4-cyanophenyl, benzo[1,2,5]oxadiazol-5-yl, 3-diethylaminophenyl, quinolin-5-yl, 2-methyl-benzothiazol-5-yl, 8-fluoro-quinolin-4-yl, 3-trifluoromethoxyphenyl, 2-chloro-3-

trifluoromethylphenyl, 2-aminocarbonyl-phnyl, 2,3-dimethyl-indol-5-yl, 3-cyanophenyl, 7-dimethyl-quinolin-3-yl, 1-acyl-1,2,3,4-tetrahydroisoquinolin-3-yl, 4-methyl-quinolin-2-yl, benzo-[1,3]-dioxolan-5-yl, or 2,2-difluoro-benzo-[1,3]dixolan-4-yl.

[00242] In one embodiment, the present invention provides compounds wherein:

a. Z is thiazol-2-yl, oxazol-2-yl, 1,3,4-thiadiazol-2-yl, 1,2,4-thiadiazol-5-yl, wherein Z is optionally substituted with CF_3, C1-4 alkyl, or C1-4 alkyl substituted with phenyl having 0-3 halo substituents. Preferably, Z is thiazol-2-yl, 5-benzyl-thiazol-2-yl, 5-(4'-chlorobenzyl)-oxazol-2-yl, 5-trifluoromethyl-1,3,4-thiadiazol-2-yl, 5-(2'-chlorobenzyl)-1,3,4-thiadiazol-2-yl, 5-cyclopropyl-1,3,4-thiadiazol-2-yl, 3-ethyl-1,2,4-thiadiazol-2-yl, or 5-(2',3'-dichlorobenzyl)-thiazol-2-yl;

b. R^N is hydrogen;

c. X_2 is C1-3 alkylene;

d. X_1 is O or is absent; and

e. T is phenyl or 3-methyl-1,2,3,4-tetrahydro-isoquinolin-2-yl, wherein T has up to 2 substituents selected from halo, cyano, trifluoromethyl, OH, C_{1-4} alkyl, C_{2-4} alkenyl, C_{1-4} alkoxy, trifluoromethoxy, $C(O)NH_2$, NH_2, $NH(C_{1-4}$ alkyl), $N(C_{1-4}$ alkyl$)_2$, $NHC(O)C_{1-4}$ alkyl, or $C(O)C_{1-4}$ alkyl. Preferably, T is 2,4-dichlorophenyl or 3-methyl-1,2,3,4-tetrahydro-isoquinolin-2-yl.

[00243] In one embodiment, the present invention provides compounds wherein:

a. Z is selected from thiazol-2-yl, 1,2,4-thiadiazol-5-yl, 2-pyrazol-3-yl, 1,3,4-thiadiazol-2-yl, 1,2,5-thiadiazol-4-yl, or 1,2,3,4-thiatriazol-5-yl, optionally substituted with up to two substituents selected from C1-4 alkyl, phenyl, or halo. Preferred Z includes 3-isopropyl-1,2,4-thiadiazol-5-yl, thiazol-2-yl, 2,5-dimethyl-1,2-pyrazol-3-yl, 5-phenyl-1,3,4-thiadiazol-2-yl, 1,2,5-thiadiazol-4-yl, 5-ethyl-1,3,4-thiadiazol-2-yl, 2-methyl-1,2-pyrazol-3-yl, 1,2,3,4-thiatriazol-5-yl;

b. R^N is hydrogen;

c. X_2 is absent or is C1-3 alkylene;

d. X_1 is absent or is O; and

e. T is selected from quinolinyl, preferably, quinolin-7-yl, dihalo-substituted phenyl, preferably dichlorophenyl, or naphthyl, preferably, 1-naphthyl.

[00244] In one embodiment, the present invention provides compounds wherein:

a. Z is selected from thiazol-2-yl, 1,3,4-thiadiazol-2-yl, pyrimidin-2-yl, pyrimidin-2-yl, 1,2,4-triazol-3-yl, or 3-t-butyl-1,2-pyrazol-5-yl, optionally substituted with C1-4 alkyl, or benzyl;

b. R^N is hydrogen;

c. X_2 is absent or C1-4 alkylene or alkenylene;

d. X_1 is absent or O;

e. T is selected from phenyl, naphthyl, 2,2,-difluoro-benzo[1,3]dioxol-5-yl, norbornyl, indol-2-yl, benzothiophen-3-yl, benzo[1,3]oxathiol-2-one-5-yl, benzo[1,2,5]oxadiazol-5-yl, quinolinyl, or 1,2,3,4-tetralin-5-yl, optionally substituted with up to 3 substituents selected from halo, cyano,

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

[00245] In one embodiment, the present invention provides compounds wherein:

a. Z is selected from thiazol-2-yl, 5-methyl-1,3,4-thiadiazol-2-yl, pyrimidin-2-yl, 4-methyl-pyrimidin-2-yl, 1,2,4-triazol-3-yl, or 1-benzyl-3-t-butyl-1,2-pyrazol-5-yl;

b. R^N is hydrogen;

c. X_2 is absent or is C1-4 straight or branched alkylene or alkenylene, optionally substituted with phenyl;

d. X_1 is absent or is O; and

e. T is selected from phenyl, 2,2,-difluoro-benzo[1,3]dioxol-5-yl, norbornyl, indol-2-yl, benzothiophen-3-yl, benzo[1,3]oxathiol-2-one-5-yl, benzo[1,2,5]oxadiazol-5-yl, quinolinyl, or 1,2,3,4-tetralin-5-yl, optionally substituted with up to 3 substituents selected from halo, cyano, trifluoromethyl, C_{1-4} alkyl, C_{2-4} alkenyl, C_{1-4} alkoxy, trifluoromethoxy, $C(O)NH_2$, $NH(C_{1-4}$ alkyl), $N(C_{1-4}$ alkyl$)_2$, $NHC(O)C_{1-4}$ alkyl, or $C(O)C_{1-4}$ alkyl.

[00246] In one embodiment, the present invention provides compounds wherein:

a. Z is selected from thiazol-2-yl, 5-methyl-1,3,4-thiadiazol-2-yl, pyrimidin-2-yl, 4-methyl-pyrimidin-2-yl, or 1,2,4-triazol-3-yl;

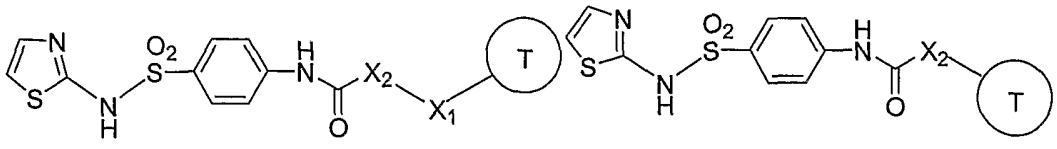
b. R^N is hydrogen;

c. X_2 is absent; or X_2 is C1-4 straight or branched alkyl;

d. X_1 is absent; or X_1 is O;

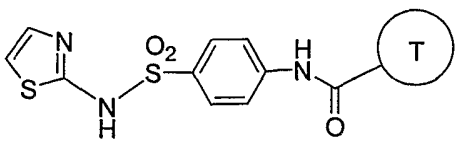
e. T is 2,6-dichlorophenyl, 3-diethyaminophenyl, 2-methyl,4-fluorophenyl, 2-cyanophenyl, 2-ethoxyphenyl, 2-chlorophenyl, 4-cyanophenyl, 1-naphthyl, 5-methoxybenzofuran-2-yl, 6-chlorobenzofuran-2-yl, 2-methyl-5,7-dichloro-quinolin-8-yl, 2-piperidinyl-phenyl, 1,2,3,4-tetralin-6-yl, 2-dimethyl-4,7-dimethyl-1,2,3,4-tetrahydroquinolin-1-yl, 2,6-difluorophenyl, 3-fluorophenyl, 2-fluoro-3-chlorophenyl, 2,5-dimethylphenyl, 2,4-dichlorophenyl, 4-chlorophenyl, 2-fluoro-6-chlorophenyl, 3,5,-dimethyl-4-chlorophenyl, 3,5-difluorophenyl, 2,3-dichlorophenyl, 2-fluoro-3-methyl-6-chlorophenyl, isoquinolin-5-yl, 2,6-dimethoxyphenyl, 4-ethoxyphenyl, 5-fluoro-indol-2-yl, 2-methoxy-4-methylphenyl, 3-fluoro-5-trifluoromethylphenyl, 3-fluorophenyl, 1-methyl-5-chloro-indol-2-yl, 2,3-difluorophenyl, 8-methyl-1,2,3,4-tetrahydroquinolin-1-yl, 1,2,3,4-tetrahydroquinolin-1-yl, 2-trifluoromethoxyphenyl, 7-trifluoromethyl-1,2,3,4-tetrahydroquinolin-1-yl, or 2-chloro-3,5-difluorophenyl.

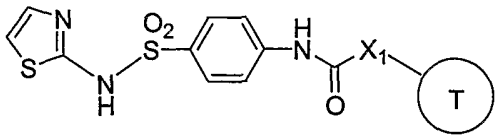
[00247] In certain embodiments, the present invention provides compounds of formula IIA-i, formula IIB-i, formula IIC-i, and formula IID-i:



(IIA-i)

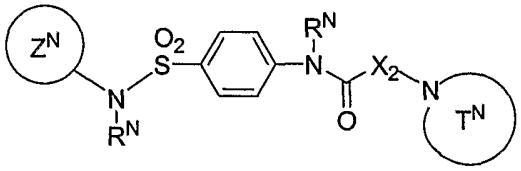
(IIB-i)



(IIC-i) or  (IID-i);

wherein T is X_2, X_1, and T are as defined above.

[00248] According to another embodiment, the present invention provides a compound of formula III:



III;

or a pharmaceutically acceptable salt thereof, wherein:

Z^N is a 5-7 membered monocyclic, unsaturated or aromatic, heterocyclic ring, having up to 4 heteroatoms independently selected from O, N, NH, S, SO, or SO_2;

each R^N is is independently hydrogen or C1-4 aliphatic optionally substituted with up to two substituents selected from R1, R4, or R5;

X_2 is C_{1-3} aliphatic, optionally substituted with up to 2 substituents independently selected from R^1, R^4, or R^5;

T^N is a 3-14 membered monocyclic, bicyclic, or tricyclic, saturated, unsaturated, or aromatic ring system having up to 5 heteroatoms independently selected from O, N, NH, S, SO, or SO_2;

wherein Z^N and T^N each is independently and optionally substituted with up to 4 substituents independently selected from R^1, R^2, R^3, R^4, or R^5;

wherein the phenylene ring attached to the sulfonyl is optionally substituted with up to 3 substituents selected from R^1 and R^2;

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

n is 0, 1 or 2;

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

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

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

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

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

$P(O)(OR^5)N(R^5R^6)$, $P(O)(OR^5)N(R^6)_2$, $P(O)(OR^5)N(R^5)_2$, $P(O)(OR^6)_2$, $P(O)(OR^5)_2$, or $P(O)(OR^6)(OR^5)$;

R^5 is a cycloaliphatic, aryl, heterocyclic, or heteroaryl ring optionally is optionally substituted with up to 3 R^1 substituents;

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

R^7 is a cycloaliphatic, aryl, heterocyclic, or heteroaryl ring and each R^7 is optionally substituted with up to 2 substituents independently chosen from H, aliphatic, or $(CH_2)_n$-Z';

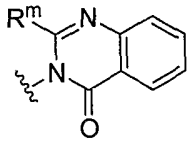
Z' is selected from halo, CN, NO_2, $C(halo)_3$, $CH(halo)_2$, $CH_2(halo)$, $-OC(halo)_3$, $-OCH(halo)_2$, $-OCH_2(halo)$,OH, S-aliphatic, S(O)-aliphatic, SO_2-aliphatic, NH_2, NH-aliphatic, $N(aliphatic)_2$, $N(aliphatic)R^8$, COOH, C(O)O(-aliphatic), or O-aliphatic; and

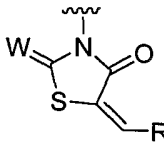
R^8 is an amino protecting group.

[00249] In certain embodiments of formula III, the following compounds are excluded:

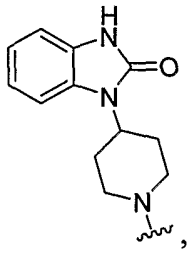
a) when both R^N are hydrogen, then T^N is not:

(i) 1,3-dione-isoindol-2-yl, 1,3-dione-isoindol-2-yl substituted with up to 4 halo substituents;

(ii)  , wherein R^m is methyl or phenyl optionally substitued with up to 4 halo;

(iii)  , wherein W is O or S, and R^o is phenyl or substituted phenyl,

(iv) 4-methyl-1,4-dihydro-quinoxalin-1-yl,

(v)  ,

(b) when both R^N are hydrogen, then the following compounds in Table C are excluded:

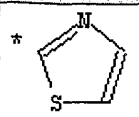
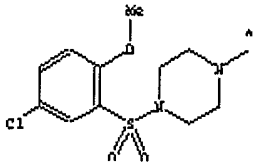
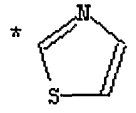
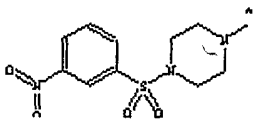
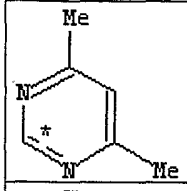
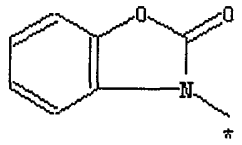
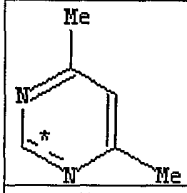
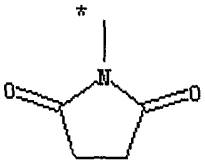
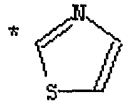
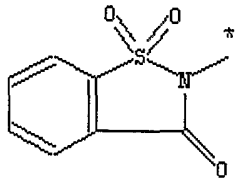
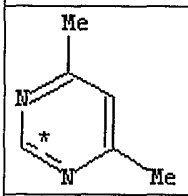
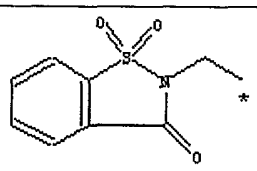
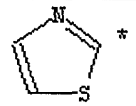
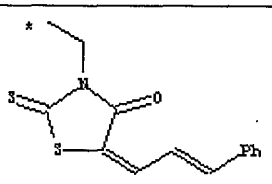
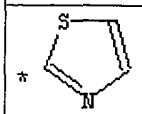
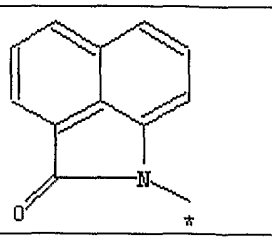
Table C	
Z^N	X_2, together with T^N
	
	
	
	
	
	
	
	

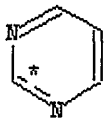
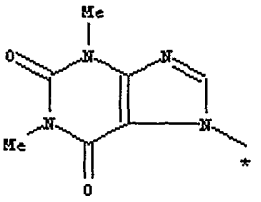
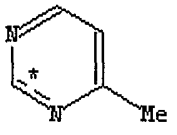
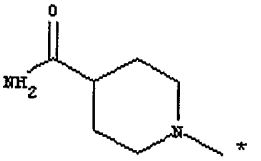
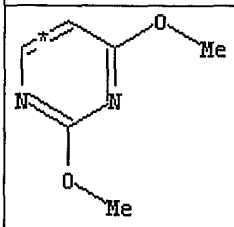
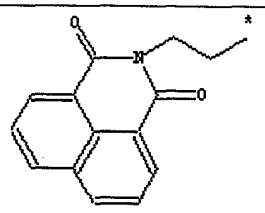
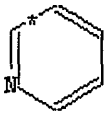
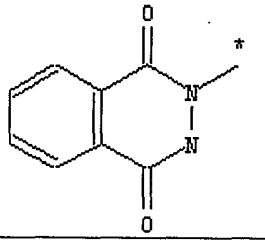
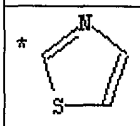
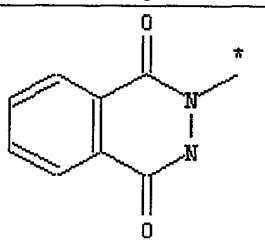
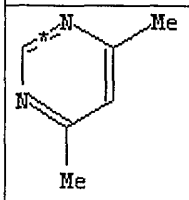
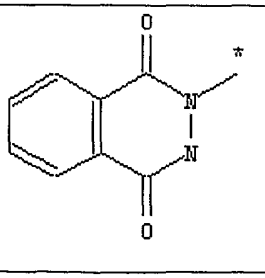
Table C	
Z^N	X_2, together with T^N
	
	
	
	
	
	

Table C

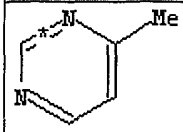
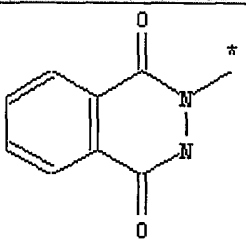
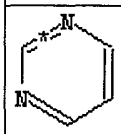
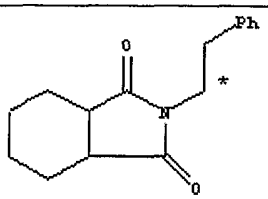
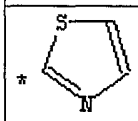
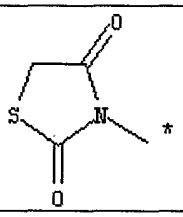
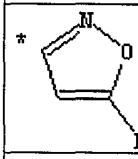
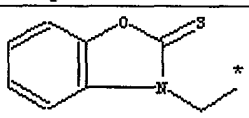
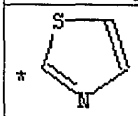
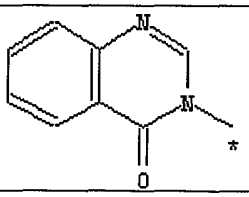
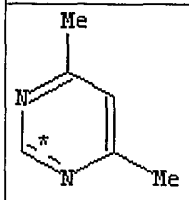
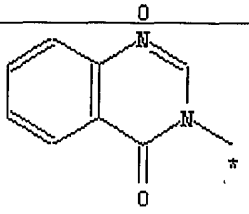
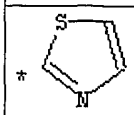
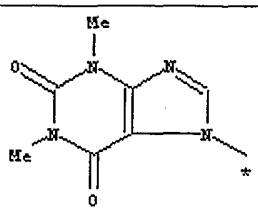
Z^N	X_2, together with T^N
	
	
	
	
	
	
	

Table C

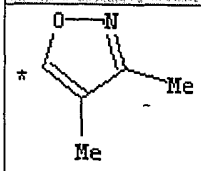
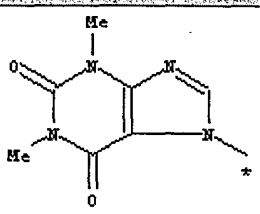
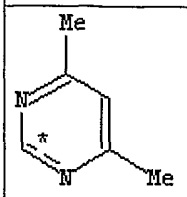
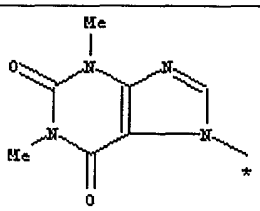
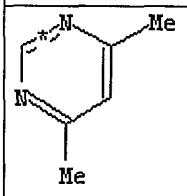
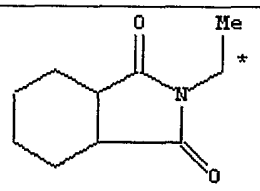
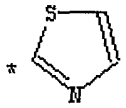
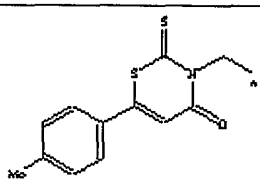
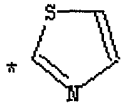
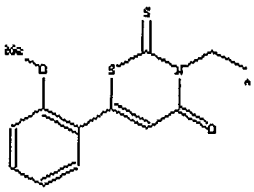
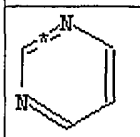
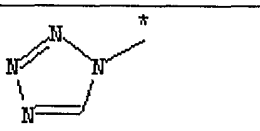
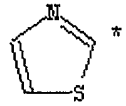
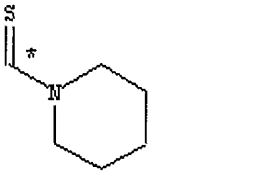
Z^N	X_2, together with T^N
	
	
	
	
	
	
	

Table C	
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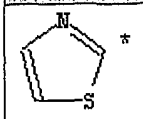
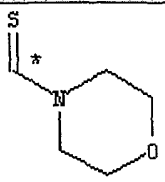
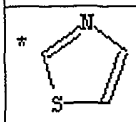
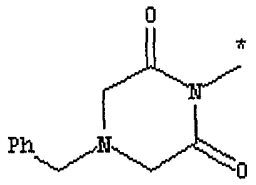
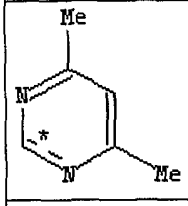
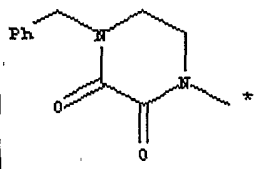
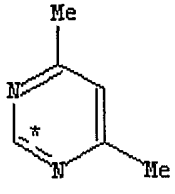
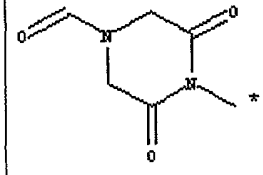
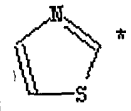
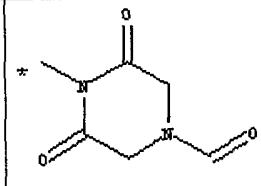
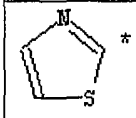
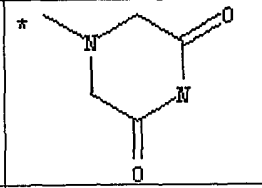
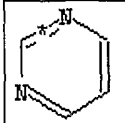
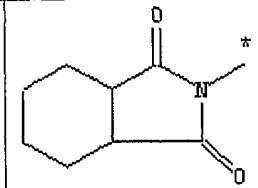
	
	
	
	
	
	
	

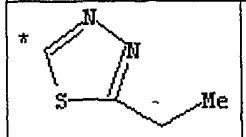
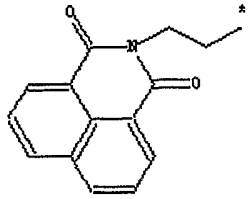
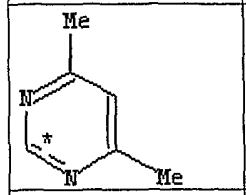
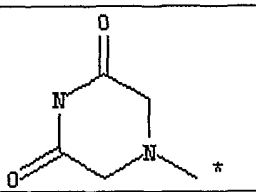
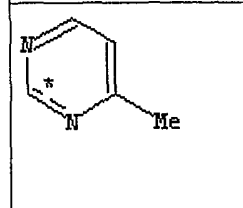
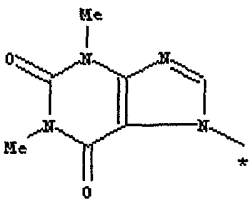
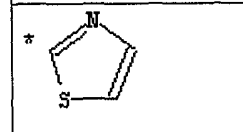
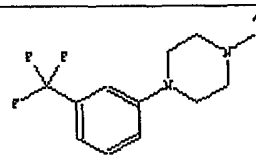
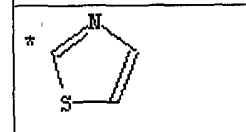
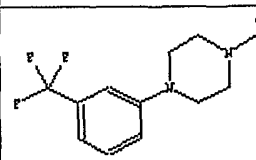
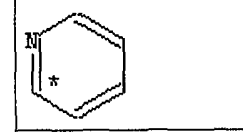
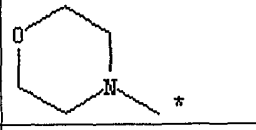
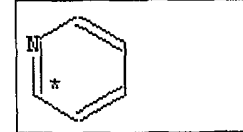
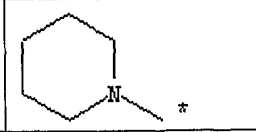
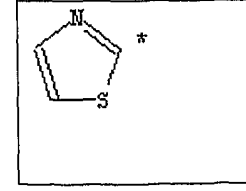
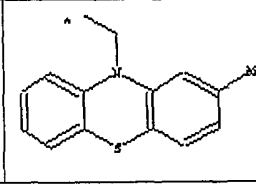
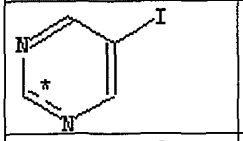
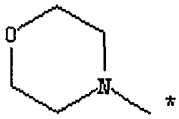
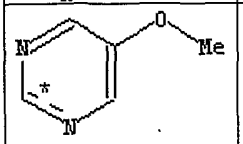
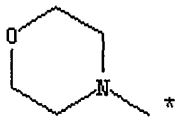
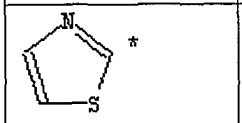
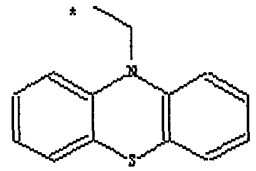
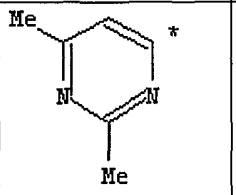
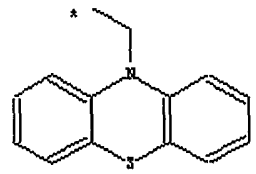
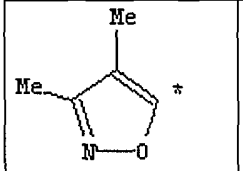
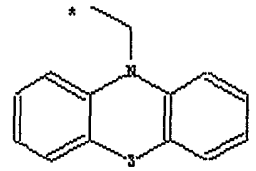
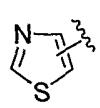
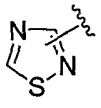
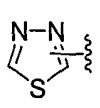
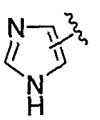
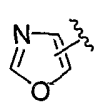
Table C	
Z^N	X_2, together with T^N
	
	
	
	
	
	
	
	

Table C

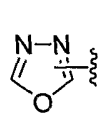
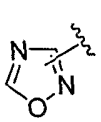
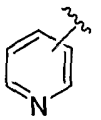
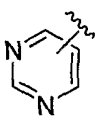
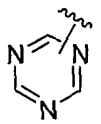
Z^N	X_2, together with T^N
	
	
	
	
	

wherein the asterisk denotes the point of attachment of a carbon atom to the rest of the molecule.

[00250] In certain embodiments, Z^N is selected from:

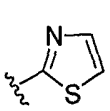
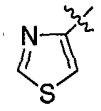
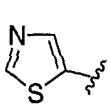






i **ii** **iii** **iv** **v**

vi **vii** **viii** **ix** or **x.**

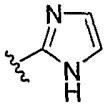
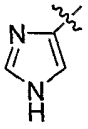
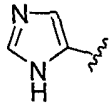
[00251] In other embodiments, Z^N is selected from:

i-a **i-b** *or* **i-c.**

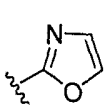
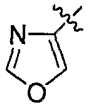
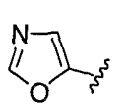
[00252] Preferably, Z^N is formula **i-a.**

[00253] In certain embodiments, Z^N is selected from:

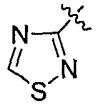
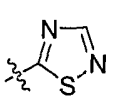
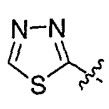
iv-a **iv-b** or **iv-c.**

[00254] In certain other embodiments, Z^N is selected from:

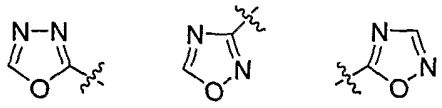
v-a **v-b** or **v-c.**

[00255] In yet other embodiments, Z^N is selected from:

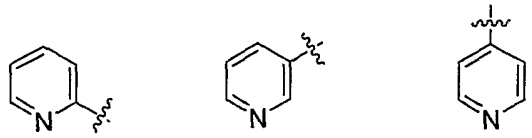
ii-a **ii-b** or **iii-a.**

[00256] Or, Z^N is selected from:



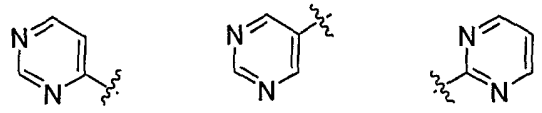
vi-a **vii-a** or **vii-b.**

[00257] In certain embodiments, Z^N is selected from:



viii-a **viii-b** or **viii-c.**

[00258] In other embodiments, Z^N is selected from:



ix-a **ix-b** or **ix-c.**

[00259] In one embodiment, Z^N is as defined above for Z.

[00260] In certain embodiments, R^N is hydrogen. Or, R^N is unsubstituted C1-4 alkyl.

[00261] In some embodiments, X_2 is selected from $-CH_2-$, $-CH_2-CH_2-$, $-(CH_2)_3-$, -CH(Me)-, -C(Me)=CH-, -CH=CH-, -CH(Ph)-, $-CH_2-$CH(Me)-, -CH(Et)-, -CH(i-Pr)-, or cyclopropylene.

[00262] Preferably, X_2 is selected from $-CH_2-$, -CH(Me)-, $-CH_2-CH_2-$, or $-(CH_2)_3-$. Or, X_2 is $-CH_2-$.

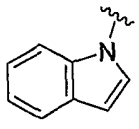
[00263] In certain embodiments, T^N is an optionally substituted, saturated, unsaturated, or aromatic 5-6 membered monocyclic ring. Preferably T^N is a 5-membered ring with up to 3 heteroatoms, preferably two heteroatoms. Or, T^N is a 6-membered ring with up to 2 heteroatoms, preferably 1 heteroatom. In

certain preferred embodiments, T^N has a second heteroatom selected from O, S, N, or NH.

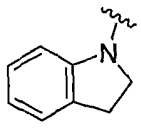
[00264] In other embodiments, T^N is an optionally substituted, saturated, unsaturated, or aromatic 8-12 membered bicyclic ring.

[00265] In other embodiments, T^N is selected from 1-pyrrolyl, 2,3-dihydro-1H-pyrrol-1-yl, 1-pyrazolyl, 1-imidazolyl, 1-pyrrolidinyl, 1,2,3,4-tetrahydropyrid-1-yl, 1,2,3,6-tetrahydropyrid-1-yl, 1-piperidinyl, 1-piperazinyl, 1-morpholinyl, 1-azepinyl, 1-azepanyl, 1-indolyl, 1-indolinyl, 1,2,3,4-tetrahydroquinolin-1-yl, 1,2,3,4-tetrahydroisoquinolin-2-yl, wherein said ring is optionally substituted with up to 3 substituents. Preferably, T^N is fused to a phenyl ring, wherein said phenyl ring is optionally substituted with up to three substituents.

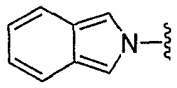
[00266] According to another embodiment, T^N is an optionally substituted ring selected from:



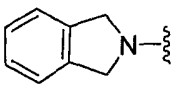
i



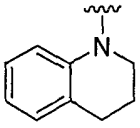
ii



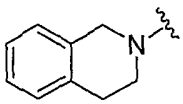
iii



iv

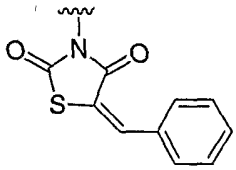


v



vi

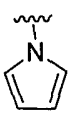
or



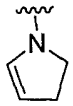
vii.

[00267] According to one embodiment, T^N is formula **i** or **ii** above, optionally substituted as provided above. Or, T^N is formula **v** or **vi** above, optionally substituted as provided above. Or, T^N is formula **vii**, optionally substituted as provided above.

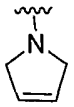
[00268] According to another embodiment, T^N is an optionally substituted ring selected from:



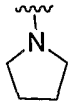
viii



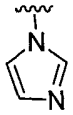
ix



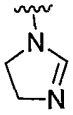
x



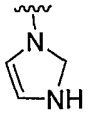
xi



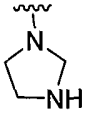
xii



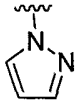
xiii



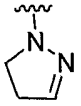
xiv



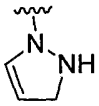
xv



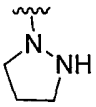
xvi



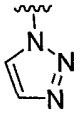
xvii



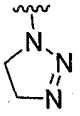
xviii



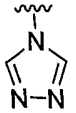
xix



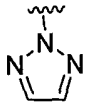
xx



xxi



xxii

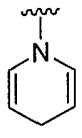
or 

xxiii.

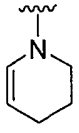
[00269] According to another embodiment, T^N is any of the above rings **viii** to **xxiii**, optionally fused to an optionally substituted phenyl ring.

[00270] According to another embodiment, T^N is any of the above rings **viii** to **xxiii**, optionally fused to an optionally substituted 6-membered aromatic heterocyclic ring having up to 3 nitrogen atoms. Preferred such 6-membered rings include pyridyl, pyrimidinyl, pyrazyl, or pyridazinyl.

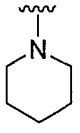
[00271] According to another embodiment, T^N is an optionally substituted ring selected from:



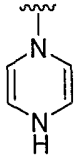
xxiii



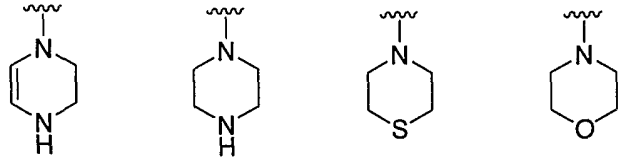
xxiv



xxv



xxvi



xxvii **xxviii** **xxix** or **xxx.**

[00272] According to another embodiment, T^N is any of the above rings **xxiii** to **xxx**, optionally fused to an optionally substituted phenyl ring.

[00273] According to another embodiment, T^N is any of the above rings **xxiii** to **xxx**, optionally fused to an optionally substituted 6-membered aromatic heterocyclic ring having up to 3 nitrogen atoms. Preferred such 6-membered rings include pyridyl, pyrimidinyl, pyrazyl, or pyridazinyl.

[00274] Preferred substituents on T^N are independently selected from halo, cyano, trifluoromethyl, OH, C_{1-4} alkyl, C_{2-4} alkenyl, C_{1-4} alkoxy, trifluoromethoxy, $C(O)NH_2$, NH_2, $NH(C_{1-4}$ alkyl), $N(C_{1-4}$ alkyl)$_2$, $NHC(O)C_{1-4}$ alkyl, or $C(O)C_{1-4}$ alkyl.

[00275] In one embodiment, the phenylene ring attached to the sulfonyl group is optionally substituted with up two substituents selected from halo, cyano, trifluoromethyl, OH, C_{1-4} alkyl, C_{2-4} alkenyl, C_{1-4} alkoxy, trifluoromethoxy, $C(O)NH_2$, NH_2, $NH(C_{1-4}$ alkyl), $N(C_{1-4}$ alkyl)$_2$, $NHC(O)C_{1-4}$ alkyl, or $C(O)C_{1-4}$ alkyl.

[00276] In one embodiment, the present invention provides compounds wherein:

a. Z^N is thiazol-2-yl;

b. R^N is hydrogen;

c. X_2 is C1-4 alkylene, preferably, $-CH_2-$ or $-CH_2-CH_2-$; and

d. T^N is selected from indol-1-yl, 1,2,3,4-tetrahydroquinolin-1-yl, indolin-1-yl, 1,2,3,4-tetrahydroisoquinolin-2-yl, or 5-benzylidene-thiazolidin-2,4-dione-3-yl, optionally substituted with up to three

substituents independently selected from C1-4 alkyl, C1-4 alkoxy, halo, trifluoromethyl, or cyano.

[00277] In one embodiment, the present invention provides compounds wherein:

a. Z^N is thiazol-2-yl;

b. R^N is hydrogen;

c. X_2 is C1-4 alkylene, preferably, $-CH_2-$ or $-CH_2-CH_2-$; and

d. T^N is selected from 4-fluoro-indol-1-yl, 6-chloro-indol-1-yl, 6-chloro-1,2,3,4-tetrahydroquinolin-1-yl, 5-ethyl-indol-1-yl, 4-fluoro-indol-1-yl, indol-1-yl, 5-methyl-indol-1-yl, 5-fluoro-indolin-1-yl, 7-chloro-indol-1-yl, 1,2,3,4-tetrahydroquinolin-1-yl, 1,2,3,4-tetrahydroisoquinolin-2-yl, 6,7-dimethoxy-1,2,3,4-tetrahydroisoquinolin-2-yl, 2-methyl-indolin-1-yl, 5-chloro-indolin-1-yl, 6-methyl-1,2,3,4-tetrahydroquinolin-1-yl, 5,6-dimethoxy-indol-1-yl, 1-methyl-1,2,3,4-tetrahydroisoquinolin-2-yl, 6-methoxy-1,2,3,4-tetrahydroquinolin-1-yl, 5-fluoro-6-chloro-indol-1-yl, 4-methyl-indol-1-yl, 4-chloro-6-methoxy-indol-1-yl, 2-methyl-indol-1-yl, 2,3-dimethyl-indol-1-yl, or 5-(4'-fluoro-benzylidene)-3-methyl-thiazolidin-2,4-dione-3-yl.

[00278] In one embodiment, the present invention provides compounds wherein:

a. Z^N is thiazol-2-yl;

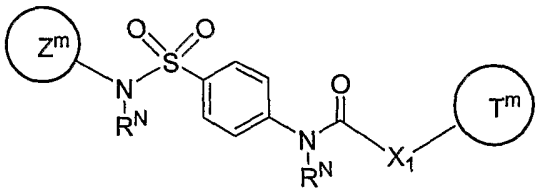
b. R^N is hydrogen;

c. X_2 is C1-3 alkylene, preferably $-CH_2-$;

d. T^N is selected from indol-1-yl, 1,2,3,4-tetrahydroisoquinolin-2-yl, 5-methyl-indol-1-yl, 6-chloroindolin-1-yl, 6-chloro-indol-1-yl, 6-fluoro-indol-1-yl, 6-chloro-1,2,3,4-tetrahydroquinolin-1-yl, 4-fluoro-

indol-1-yl, 5-fluoro-indol-1-yl, 4,4-difluoropiperidinyl, 5-cyano-indol-1-yl, 5-ethyl-indol-1-yl, 1,2,3,4-tetrahydroquinolin-1-yl, 6-trifluoromethyl-indol-1-yl, 5,6-dimethoxy-indol-1-yl, 6-fluoro-1,2,3,4-tetrahydroquinolin-1-yl, 5-chloroindolin-1-yl, 1-methyl-1,2,3,4-tetrahydroisoquinolin-2-yl, 3-cyano-indol-1-yl, 3-methyl-indol-1-yl, 2-methyl-6-fluoro-quinolin-4-yl, 5-methoxy-benzofuran-2-yl, 4-methyl-indol-1-yl, 5,6-dichloro-indol-1-yl, 6-methylindol-1-yl, 4,6-dichloroindol-1-yl, 4-methoxy-indol-1-yl, 5-methoxy-indol-1-yl, 7-fluoro-indol-1-yl, 5-fluoro-indolin-1-yl, 5-(4'-fluoro-benzylidene)-1,3-thiolan-2,4-dione-3-yl, 2,3-dimethyl-indol-1-yl, 7-trifluoromethyl-1,2,3,4-tetrahydroquinolin-1-yl, 6-methoxy-1,2,3,4-tetrahydroquinolin-1-yl, 7-ethyl-indol-1-yl, or 2,7-dimethyl-1,2,3,4-tetrahydroquinolin-1-yl.

[00279] According to another embodiment, the present invention provides a compound of formula **IV**:



(IV);

or a pharmaceutically acceptable salt thereof;

wherein:

Z^M is a 5-7 membered monocyclic, unsaturated or aromatic, heterocyclic ring, having up to 4 heteroatoms independently selected from O, N, NH, S, SO, or SO_2;

each R^N is is independently hydrogen or C1-4 aliphatic optionally substituted with up to two substituents selected from R1, R4, or R5;

X_1 is O, S, or NR^N;

X_2 is C_{1-3} aliphatic, optionally substituted with up to 2 substituents independently selected from R^1, R^4, or R^5;

T^M is a 8-14 membered aromatic or non-aromatic bicyclic or tricyclic ring, having 0-5 heteroatoms selected from O, S, N, NH, S(O) or SO_2;

wherein the phenylene ring attached to the sulfonyl is optionally substituted with up to 3 substituents selected from R^1 and R^2;

wherein Z^M and T^M each is independently and optionally substituted with up to 4 substituents independently selected from R^1, R^2, R^3, R^4, or R^5;

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

n is 0, 1 or 2;

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

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

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

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

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

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

R^5 is a cycloaliphatic, aryl, heterocyclic, or heteroaryl ring is optionally substituted with up to 3 R^1 substituents;

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

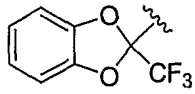
R^7 is a cycloaliphatic, aryl, heterocyclic, or heteroaryl ring and each R^7 is optionally substituted with up to 2 substituents independently chosen from H, aliphatic, or $(CH_2)_n$-Z';

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

R^8 is an amino protecting group.

[00280] In one embodiment of formula IV, the following compounds are excluded:

(a) when Z is optionally substituted pyrimidinyl or thiazolyl, both R^6 are hydrogen, and X1 is NH, then T is not optionally substituted adamantyl;

(b) when Z is optionally substituted pyridyl, pyrimidinyl, isoxazolyl, or thiazolyl, both R_6 are hydrogen, and X_1 is NH, then T is not  , optionally substituted with up to two halo atoms;

(c) when both R_6 are hydrogen, and X_1 is NH, then T is not 1-naphthyl, 2-naphthyl, or 7-hydroxynaphth-1-yl;

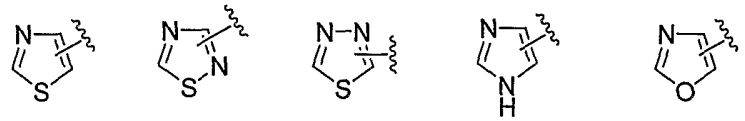
(d) when Z is pyrimidinyl, 5-methylisoxazolyl, or pyridyl, both R_6 are hydrogen, and X_1 is NH, then T is not subtituted purinyl; and

(e) when Z is thiazol-2-yl, both R_6 are hydrogen, and X_1 is NH, then T is not substituted 3*H*-isobenzofuran-1-one-7-yl.

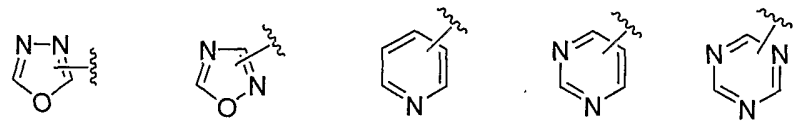
[00281] In one embodiment, X^1 is O. Or, X^1 is S. Or X1 is NR^N.

[00282] In one embodiment, each R^N is independently hydrogen. Or, each R^N is independently C1-4 alkyl.

[00283] In certain embodiments, Z^M is selected from:

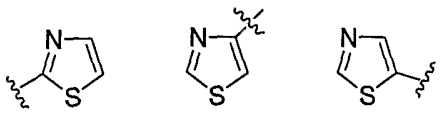


i **ii** **iii** **iv** **v**



vi **vii** **viii** **ix** or **x.**

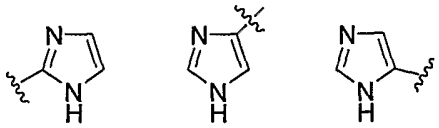
[00284] In other embodiments, Z^M is selected from:



i-a **i-b** or **i-c.**

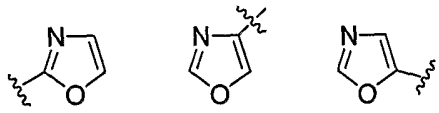
[00285] Preferably, Z^M is formula **i-a.**

[00286] In other embodiments, Z^M is selected from:



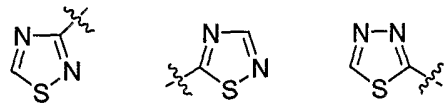
iv-a **iv-b** or **iv-c.**

[00287] In yet other embodiments, Z^M is selected from:



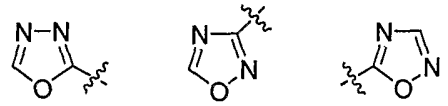
v-a **v-b** or **v-c.**

[00288] Or, Z^M is selected from:



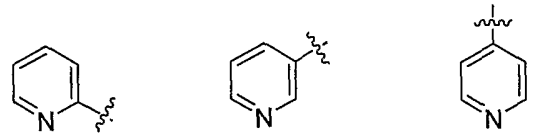
ii-a **ii-b** or **iii-a.**

[00289] In certain embodiments, Z^M is selected from:



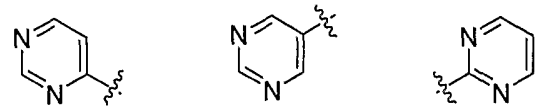
vi-a **vii-a** or **vii-b.**

[00290] In certain other embodiments, Z^M is selected from:



viii-a **viii-b** or **viii-c.**

[00291] Or, Z^M is selected from:



ix-a **ix-b** or **ix-c.**

[00292] In one embodiments, Z^M is as defined above for Z.

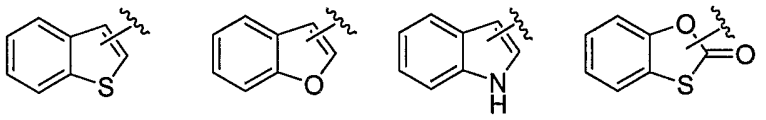
[00293] In certain embodiments, R^N is hydrogen. Or, R^N is unsubstituted C1-4 alkyl.

[00294] In another embodiment, Z^M is an optionally substituted 5-6 membered monocyclic ring.

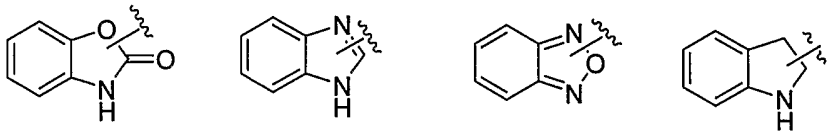
[00295] In one embodiment, X_1 is NH. Or, X_1 is O.

[00296] In certain embodiments, T^M is phenyl or naphthyl, optionally substituted with up to 3 substituents independently selected from halo, cyano, trifluoromethyl, OH, C_{1-4} alkyl, C_{2-4} alkenyl, C_{1-4} alkoxy, trifluoromethoxy, $C(O)NH_2$, NH_2, $NH(C_{1-4}$ alkyl), $N(C_{1-4}$ alkyl)$_2$, $NHC(O)C_{1-4}$ alkyl, 1-pyrrolidinyl, 1-piperidinyl, 1-morpholinyl, or $C(O)C_{1-4}$ alkyl.

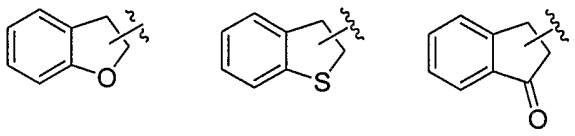
[00297] In other embodiments, T^M is selected from:



p **q** **r** **s**



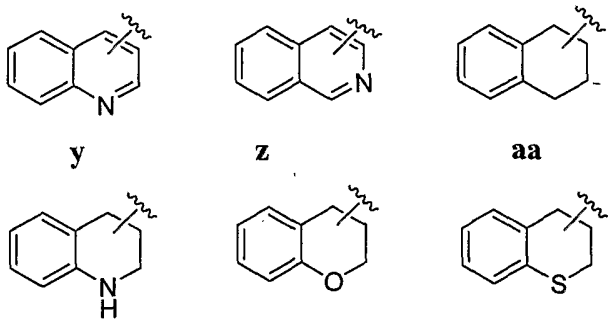
s **t** **u** **v**



w **x** or **af,**

wherein T^M is optionally substituted with up to three substituents independently selected from halo, cyano, trifluoromethyl, OH, C_{1-4} alkyl, C_{2-4} alkenyl, C_{1-4} alkoxy, trifluoromethoxy, $C(O)NH_2$, NH_2, $NH(C_{1-4}$ alkyl), $N(C_{1-4}$ alkyl)$_2$, $NHC(O)C_{1-4}$ alkyl, or $C(O)C_{1-4}$ alkyl.

[00298] Or, T^M is selected from:



y **z** **aa**

ac **ad** or **ae**,

wherein T^M is optionally substituted with up to three substituents independently selected from halo, cyano, trifluoromethyl, OH, C_{1-4} alkyl, C_{2-4} alkenyl, C_{1-4} alkoxy, trifluoromethoxy, $C(O)NH_2$, NH_2, $NH(C_{1-4}$ alkyl), $N(C_{1-4}$ alkyl)$_2$, $NHC(O)C_{1-4}$ alkyl, or $C(O)C_{1-4}$ alkyl.

[00299] Or, T^M is a tricyclic ring selected from: dibenzofuranyl, carbazolyl, acridinyl, phenazinyl, phenothiazinyl, or phenoxazinyl, fluorenyl, anthracenyl, or phenoxazinyl.

[00300] In certain embodiments, the substituents are independently selected from oxo, halo, cyano, trifluoromethyl, OH, C_{1-4} alkyl, C_{2-4} alkenyl, C_{1-4} alkoxy, trifluoromethoxy, $C(O)NH_2$, NH_2, $NH(C_{1-4}$ alkyl), $N(C_{1-4}$ alkyl)$_2$, $NHC(O)C_{1-4}$ alkyl, or $C(O)C_{1-4}$ alkyl.

[00301] In one embodiment of formula (IIA-i):

a. X_2 is $-CH_2-$; $-CH_2-CH_2-$ or $-CH_2CH_2CH_2-$;

b. X_1 is O or S; and

c. T is selected from 8-trifluoromethylquinolin-4-yl, 3-chloro-4-fluorophenyl, 1-naphthyl, 4-chloro-3-fluorophenyl, 6-fluoro-2-methyl-quinolin-4-yl, 2,4-dichlorophenyl, 4-chlorophenyl, 2,3-difluorophenyl, 2-chloro-4-methoxyphenyl, 4-trifluoromethylpehnyl, 4-chloro-2-fluorophenyl,

benzo[1,3]oxathiol-2-one-6-yl, 1-phenyl-tetrazol-5-yl, benzo[1,2,5]oxadiazol-5-yl, 3-cyano-5,6,7,8-tetrahydroquinolin-2-yl, quinolin-2-yl, isoquinolin-5-yl, quinolin-7-yl, or 3,5-dimethyl-4-cyanophenyl.

[00302] In one embodiment of formula (IIB-i):

a. X_2 is $-CH_2-$, $-CH_2-CH_2-$, $-CH_2CH_2CH_2-$, or $-CH=CH-$;

b. T is selected from benzo[b]thiophen-3-yl, 5-chloro-benzo[b]thiophen-2-yl, 5-chloro-2,3-dihydro-1H-indol-1-yl, 5-fluoro-2,3-dihydro-1H-indol-1-yl, 8-methoxy-1,2,3,4-tetrahydronaphth-2-yl, 1,2,3,4-tetrahydroquinolin-1-yl, 6,7-dimethoxy-1,2,3,4-tetrahydroisoquinolin-2-yl, 2,3-dihydro-1H-indol-1-yl, 1,2,3,4-tetrahydroisoquinolin-2-yl, 2-methyl-2,3-dihydro-1H-indol-1-yl, 6-methoxy-1,2,3,4-tetrahydroquinolin-1-yl, or 3-(t-butylamino carbonyl)-1,2,3,4-tetrahydro isoquinolin-2-yl.

[00303] In one embodiment of formula (IIC-i), T is selected from 4,6-dichloroindol-2-yl, benzofuran-2-yl, 1-naphthyl, 2-methyl-6-fluoroquinolin-4-yl, 5-fluoro-indol-2-yl, 5-chlorothiophen-2-yl, benzopyran-3-yl, 3-bromo-4-methylphenyl, 2-(furan-2-yl)-quinolin-4-yl, N-methyl-5-trifluoromethoxy-indol-2-yl, benzothiophen-3-yl, 5-fluoro-benzothiophen-2-yl, 2-methyl-quinolin-4-yl, 6-chloro-indol-2-yl, 6-bromo-indol-2-yl, 2-phenyl-5-methyl-1,2-oxazol-3-yl, N,6-dimethyl-indol-2-yl, or 5-3,5,dichlorophenoxy-furan-2-yl.

[00304] In one embodiment of formula (IIA-i):

a. X_2 is CH_2, $-CH_2CH_2$, or $CH_2CH_2CH_2$;

b. X_1 is O, S, or NH; and

c. T is phenyl optionally substituted with up to three substituents selected from halo, cyano, trifluoromethyl,

OH, C_{1-4} alkyl, C_{1-4} alkoxy, trifluoromethoxy, $C(O)NH_2$, NH2, NH(C1-4 alkyl), N(C1-4 alkyl)2, NHC(O)C1-4 alkyl, 1-pyrrolidinyl, 1-piperidinyl, 1-morpholinyl, or $C(O)C_{1-4}$ alkyl.

[00305] In one embodiment, X_1 is O. Or, X_1 is S. Or, X_1 is NH.

[00306] In one embodiment of formula (IIIA-i):

a. X_2 is CH_2, $-CH_2CH_2$, or $CH_2CH_2CH_2$;

b. X_1 is O, S, or NH; and

c. T is quinolin-4-yl, quinolin-5-yl, quinolin-6-yl, quinolin-7-yl, quinolin-8-yl, isoquinolin-1-yl, 1-naphthyl, 2-naphthyl, 5a,6,7,8,9,9a-hexahydro-dibenzofuran-2-yl, benzo[1,3]dioxol-6-yl, benzothiazol-5-yl, indan-1-one-4-yl, benzo[1,2,5]oxadiazol-4-yl, indol-4-yl, 4-methyl-chromen-2-one-7-yl, indol-5-yl, benzo-[1,2,3]-triazin-4-yl, or benzimidazol-2-yl, wherein T is optionally substituted with up to three substituents selected from halo, cyano, trifluoromethyl, OH, C1-4 alkyl, C1-4 alkoxy, trifluoromethoxy, $C(O)NH_2$, NH2, NH(C1-4 alkyl), N(C1-4 alkyl)2, NHC(O)C1-4 alkyl, 1-pyrrolidinyl, 1-piperidinyl, 1-morpholinyl, or C(O)C1-4 alkyl.

[00307] In another embodiment of formula (IIIA-i):

a. X_2 is CH_2, $-CH_2CH_2$, or $CH_2CH_2CH_2$;

b. X_1 is O, S, or NH; and

c. T is quinolin-5-yl, 2-naphthyl, 5a,6,7,8,9,9a-hexahydro-dibenzofuran-2-yl, benzo[1,3]dioxol-6-yl, 8-fluoroquinolin-4-yl, 2-methyl-benzothiazol-5-yl, 7-trifluoromethyl-quinolin-4-yl, indan-1-one-4-yl, benzo[1,2,5]oxadiazol-4-yl, isoquinolin-1-yl, indol-4-yl, 5,7-dichloro-2-methylquinolin-8-yl, 7-chloro-quinolin-4-yl, 4-methyl-chromen-2-one-7-yl, quinolin-8-yl, 5-chloro-

quinolin-8-yl, indol-5-yl, quinolin-6-yl, benzo-[1,2,3]-triazin-4-yl, 7-fluoro-quinolin-4-yl, benzimidazol-2-yl, or 2-methyl-quinolin-8-yl.

[00308] According to an alternate embodiment, the present invention provides a compound having formula (V):

$$T_1\text{--}L_{11}\text{—}A\text{--}L_{22}\text{—}Z;$$

wherein:

T_1 is a 8-14 membered aromatic or non-aromatic bicyclic or tricyclic ring, having 0-5 heteroatoms selected from O, S, N, NH, S(O) or SO_2;

L_{11} is $-(X_1)_p-(CHR^1)_r-(X_2)-Ry$;

wherein:

p is 0 or 1;

r is 0 or 1;

X_1 is O, S, or NRx, wherein R_x is H or R_2;

X_2 is R^2;

Ry is $-C(O)-NR^2-$;

L_{22} is $OC(O)$, $C(O)O$, $S(O)$, SO_2, $N(R^5)SO_2$, $N(R^6)SO_2$, $SO_2N(R^5)$, $SO_2N(R^6)$, $C(O)N(R^5)$, $C(O)N(R^6)$, $NR^5C(O)$, $NR^6C(O)$, $C(NOR^5)R^6$, $C(NOR^5)R^6$, $C(NOR^6)R^5$, $C(NOR^6)R^6$, $N(R^5)$, $N(R^6)$, $NR^5C(O)O$, $NR^6C(O)O$, $OC(O)NR^5$, $OC(O)NR^6$, $NR^5C(O)N(R^5)$, $NR^5C(O)N(R^6)$, $NR^6C(O)N(R^5)$, $NR^6C(O)N(R^6)$, $NR^5SO_2N(R^5)$, $NR^5SO_2N(R^6)$, $NR^6SO_2N(R^5)$, $NR^6SO_2N(R^6)$, $N(OR^5)$, or $N(OR^6)$;

A is a 5-7 membered monocyclic aromatic ring, having 0-4 heteroatoms;

Z is 2-thiazolyl;

wherein each of T_1, A, and Z is optionally substituted with up to 4 suitable substituents independently selected from R^1, R^2, R^3, R^4, or R^5;

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

n is 0, 1 or 2;

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

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

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

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

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

$NR^6SO_2N(R^5)_2$, $NR^5SO_2NR^5R^6$, $NR^5SO_2N(R^5)_2$, $N(OR^6)R^6$, $N(OR^6)R^5$, $N(OR^5)R^5$, $N(OR^5)R^6$, $P(O)(OR^6)N(R^6)_2$, $P(O)(OR^6)N(R^5R^6)$, $P(O)(OR^6)N(R^5)_2$, $P(O)(OR^5)N(R^5R^6)$, $P(O)(OR^5)N(R^6)_2$, $P(O)(OR^5)N(R^5)_2$, $P(O)(OR^6)_2$, $P(O)(OR^5)_2$, or $P(O)(OR^6)(OR^5)$;

R^5 is a cycloaliphatic, aryl, heterocyclic, or heteroaryl ring is optionally substituted with up to 3 R^1 substituents;

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

R^7 is a cycloaliphatic, aryl, heterocyclic, or heteroaryl ring and each R^7 is optionally substituted with up to 2 substituents independently chosen from H, aliphatic, or $(CH_2)_n$-Z;

Z is selected from halo, CN, NO_2, CF_3, OCF_3, OH, S-aliphatic, S(O)-aliphatic, SO_2-aliphatic, NH_2, N-aliphatic, $N(aliphatic)_2$, $N(aliphatic)R^8$, COOH, C(O)O(-aliphatic, or O-aliphatic; and

R^8 is an amino protecting group.

[00309] In one embodiment of formula V:

(i) when:

L_{22} is SO_2, $N(R^5)SO_2$, $N(R^6)SO_2$, $SO_2N(R^5)$, $SO_2N(R^6)$, $C(O)N(R^5)$, $C(O)N(R^6)$, $NR^5C(O)$, or $NR^6C(O)$;

A is optionally substituted 5-6 membered monocyclic aromatic ring with 0-4 heteroatoms independently selected from N, S, or O;

X_2 is optionally substituted methylene or ethylene;

T_1 is an optionally substituted fused aromatic bicyclic ring system containing 0-4 heteroatoms independently selected from N, O, or S;

then:

r is 1;

(ii) when:

L_{22} is SO_2, $N(R^5)SO_2$, $N(R^6)SO_2$, $SO_2N(R^5)$, $SO_2N(R^6)$, $C(O)N(R^5)$, $C(O)N(R^6)$, $NR^5C(O)$, or $NR^6C(O)$;

A is optionally substituted 5-6 membered monocyclic aromatic ring with 0-4 heteroatoms independently selected from N, S, or O;

p is 1;

X_2 is optionally substituted methylene, ethylene, or propylene;

T_1 is an optionally substituted fused aromatic bicyclic ring system containing 0-4 heteroatoms independently selected from N, O, or S;

then:

X_1 is not O or S;

(iii) when:

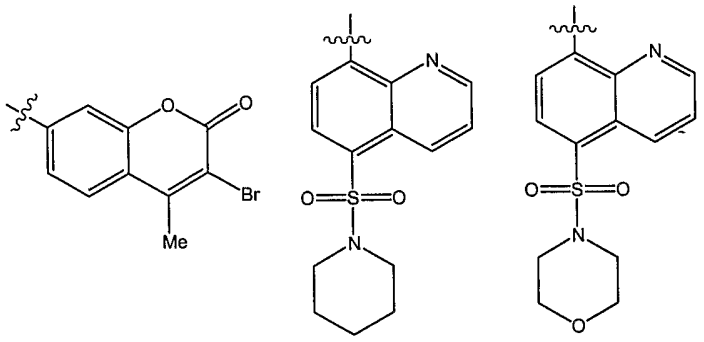
L_{11} is $-O-CH_2-C(O)-NH-$;

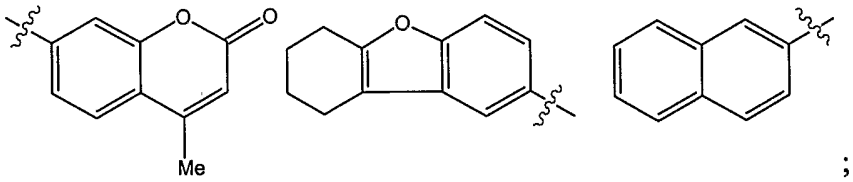
A is phenylene;

L_{22} is $-S(O)_2-NH-$;

then:

T_1 is not any of the following:





;

(iv) when:

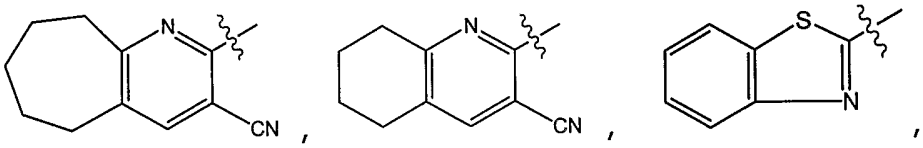
L_{11} is $-S-CH_2-C(O)-NH-$;

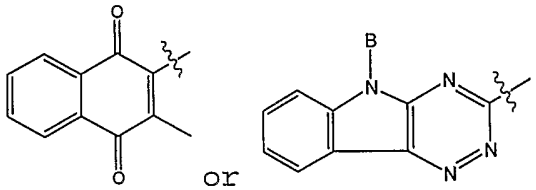
A is phenylene;

L_{22} is $-S(O)_2-NH-$;

then:

T_1 is not any of the following:





, wherein B is hydrogen, methyl, n-propyl, isopropyl, allyl, benzyl, or phenylethyl.

[00310] Preferred embodiments of L_{11}, L_{22}, R^1, R^2, R^3, R^4, R^5, R^6, R^7, and R^8 in formula (V) are as described above for formula (I).

[00311] According to a preferred embodiment, Ry is $-C(O)-NR^2-$.

[00312] According to a preferred embodiment, T_1 is a 8-14 membered aromatic or non-aromatic bicyclic or tricyclic ring, having 0 heteroatoms. More preferably, T_1 is naphthyl. Or, T_1 is anthracenyl. According to an alternate more preferred embodiment, T_1 is tetralinyl or decalinyl.

[00313] According to a preferred embodiment, T_1 is a 8-14 membered aromatic or non-aromatic bicyclic or tricyclic ring, having up to 5 heteroatoms, preferably 1 or 2 heteroatoms. More preferably, T_1 is a 8-14 membered aromatic bicyclic ring, having up to 5 heteroatoms. Or, T_1 is a 8-14 membered non-aromatic bicyclic ring, having up to 5 heteroatoms. Exemplary bicyclic rings include quinolinyl, isoquinolinyl, benzofuranyl, benzothiophenyl, quinolinyl, isoquinolinyl, benzofuranyl, benzothiophenyl, indolizinyl, indolyl, isoindolyl, indolinyl, indazolyl, benzimidazolyl, benzothiazolyl, purinyl, cinnolinyl, phthalazine, quinazolinyl, quinaoxalinyl, naphthylirinyl, or pteridinyl.

[00314] According to another preferred embodiment, T_1 is a 8-14 membered non-aromatic tricyclic ring, having up to 5 heteroatoms. Or, T_1 is a 8-14 membered aromatic tricyclic ring, having up to 5 heteroatoms. Exemplary tricyclic rings include dibenzofuranyl, carbazolyl, acridinyl, phenazinyl, phenothiazinyl, phenoxazinyl, acridinyl, phenazinyl, phenothiazinyl, phenoxainyl, or carbazolyl.

[00315] According to a preferred embodiment of formula (II), A is phenyl.

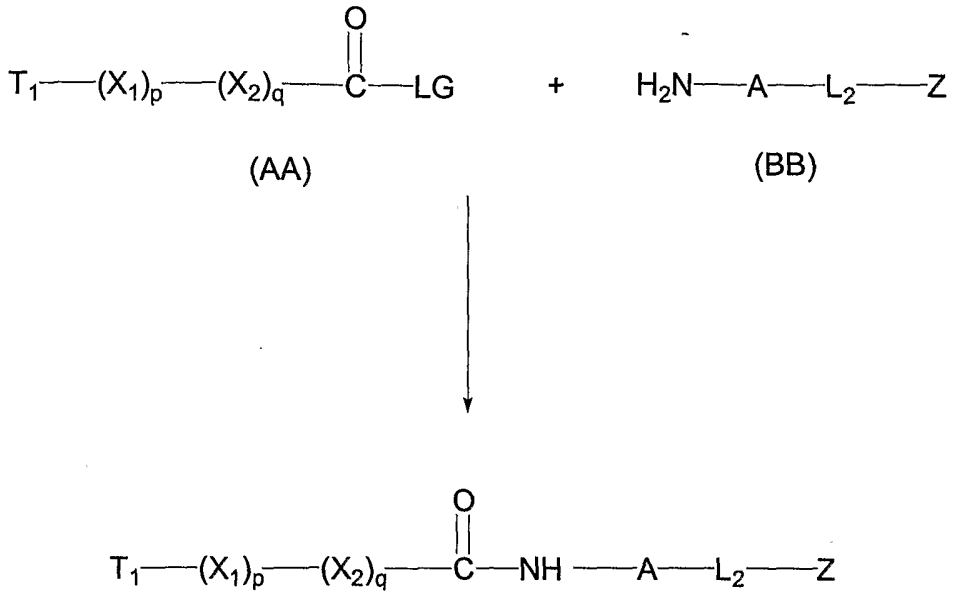
[00316] According to another preferred embodiment of formula (II), A is a 5-6 membered monocyclic aromatic ring having 1-4

heteroatoms. More preferably, A is 5-6 membered monocyclic aromatic ring having 1-3 heteroatoms. Exemplary rings include thiazolyl, isothiazolyl, thiadiazolyl, thiaphenyl, furanyl, oxazolyl, isooxazolyl, oxadiazolyl, triazolyl, imidazolyl, pyrazolyl, pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, triazinyl, or pyrrolyl.

[00317] **FIGURE 1** recites exemplary compounds of the present invention.

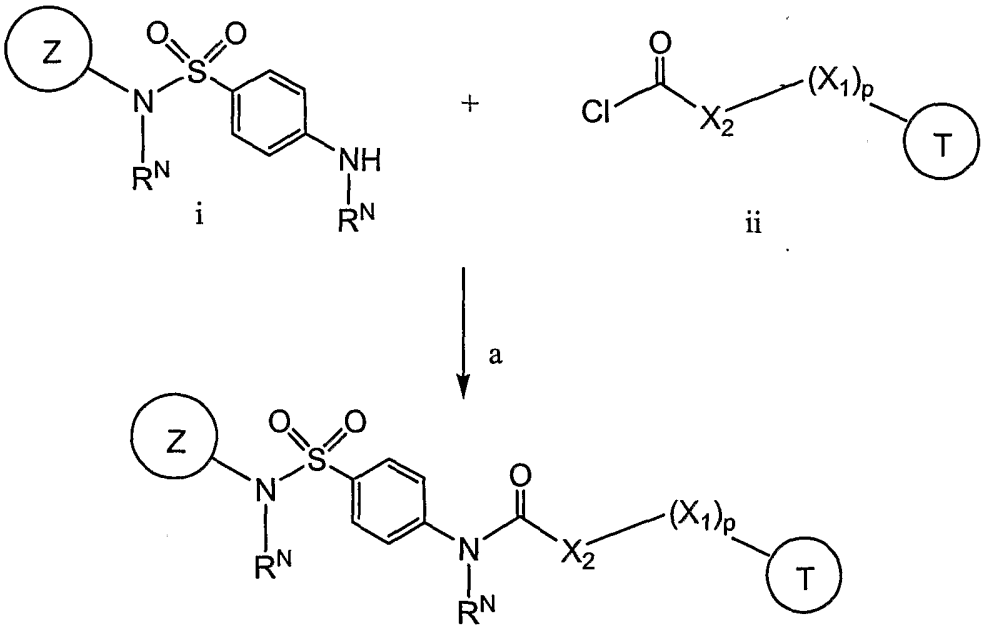
[00318] The compounds of the present invention may be readily prepared by methods well known in the art. An exemplary method for synthesizing certain compounds of formula (I) is illustrated below in the schemes.

Scheme 1:



[00319] In Scheme 1 above, the synthesis of compounds of formula (I), wherein Ry is an amide (-C(O)-NH-) is illustrated. Compound of formula (AA) is coupled with an amine of formula (BB), wherein T_1, X_1, X_2, p, q, A, L_2, and Z have the meaning as defined in formula (I). LG is any suitable leaving group. Suitable leaving groups useful in the method of Scheme 1 are well known in the art. See, e.g., "March's Advanced Organic Chemistry", 5th Ed., Ed.: Smith, M.B. and March, J., John Wiley & Sons, New York: 2001.

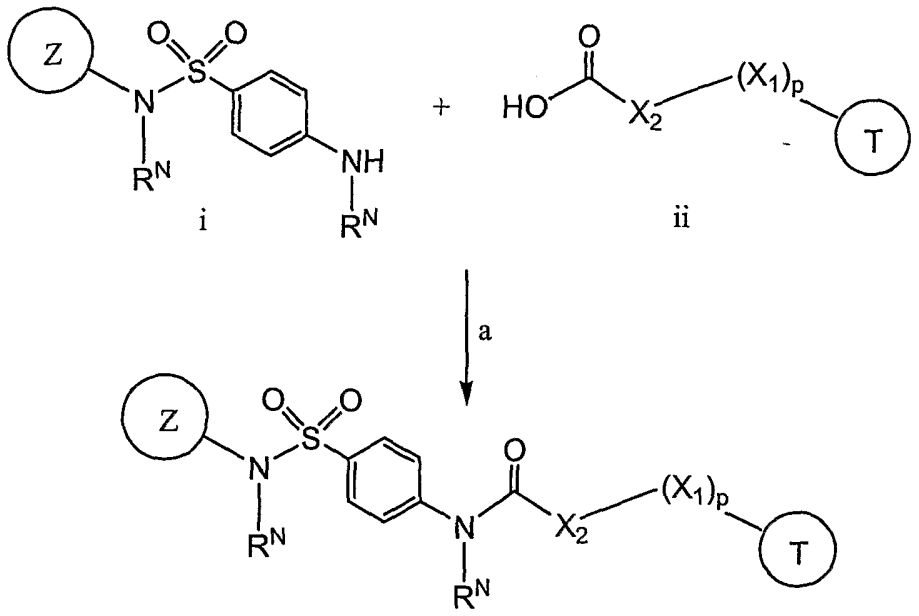
[00320] Scheme A:



IA

Reaction of i and ii (step a) in pyridine and DCM at room temperature (rt) yields **IA**.

[00321] Scheme B:

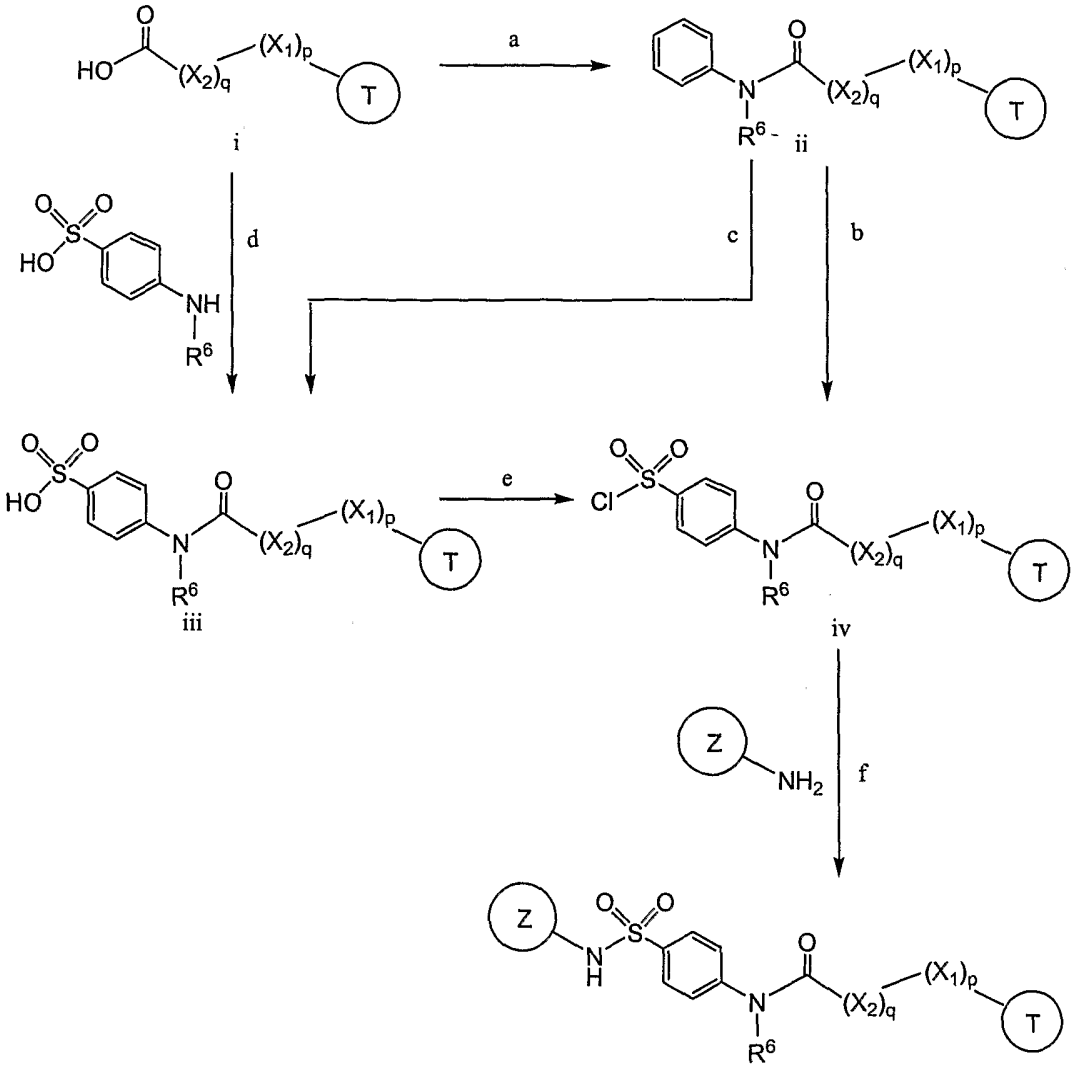


IA

The coupling of i and ii (step a) using CDI and DMA under refluxing conditions, or HATU and TEA in pyridine under mircrowave conditions at 200°C, or BOP and TEA in CH_3CN at rt yields **IA.**

In the schemes below, R^6 is as defined for R^N.

Scheme C: Scheme C provides an alternative synthesis for compounds of formula **IA.**

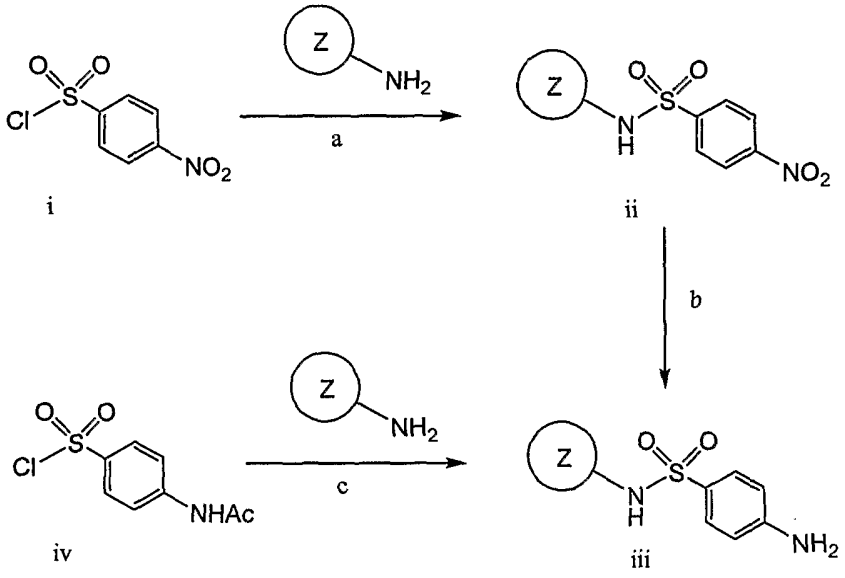


IA

The coupling of i with anilines (step a) using CDI and DMA under refluxing conditions, or HATU and TEA in pyridine under mircrowave conditions at 200°C, or isobutyl chlorocarbonate and TEA in DCM yields ii. Reaction of intermediate ii with $ClSO_3H$ (step b) under refluxing conditions gives iv. Reaction of ii $ClSO_3H$ at 0°C (step c) gives intermediate iii. Coupling of intermediate i with aminosulfonic acids (step d) using HATU and TEA in pyridine under mircrowave conditions at 200°C, or BOP and

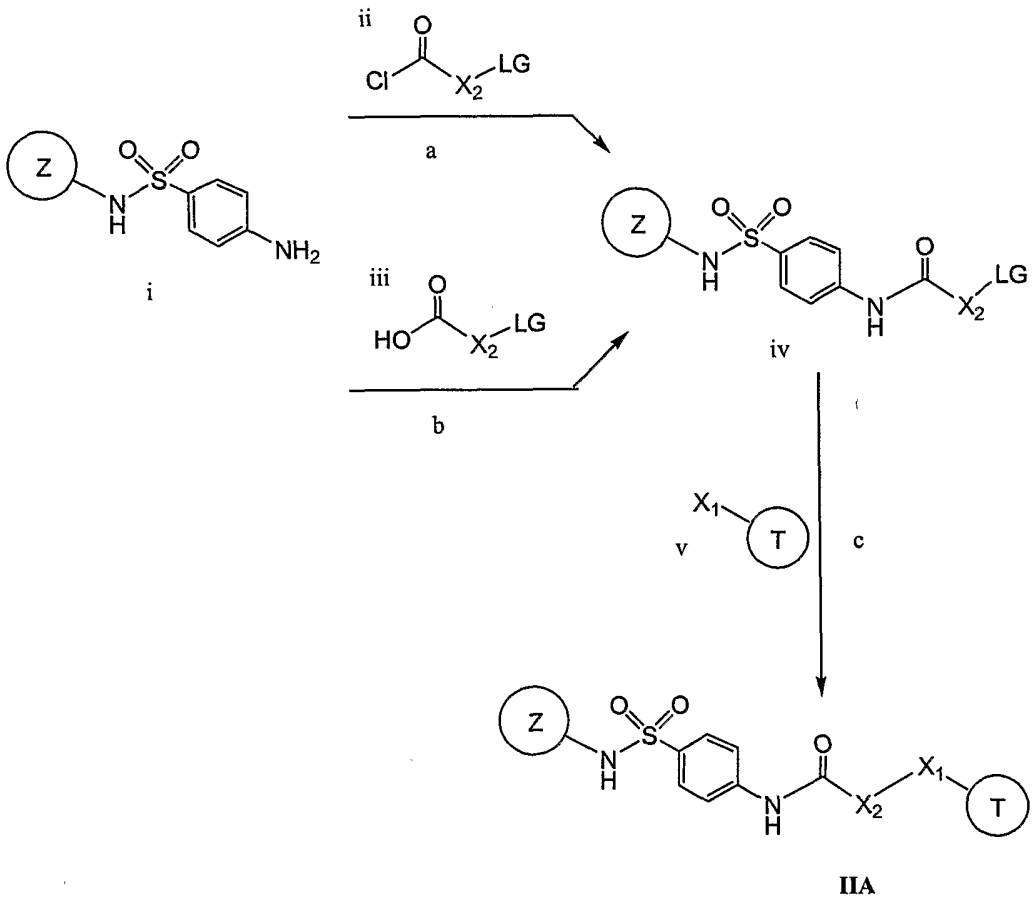
TEA in CH_3CN at rt yields iii. Reaction of intermediate iii with SO_2Cl (step e) yields iv. Alternatively, reaction of intermediate iii with cyanuric chloride and TEA in acetone under microwave conditions at 120°C (step e) provides iv. Reaction of iv with various amines (step f) in pyridine at room temperature yields **IA.**

Scheme D: Scheme D provides useful intermediates for Schemes A and B.



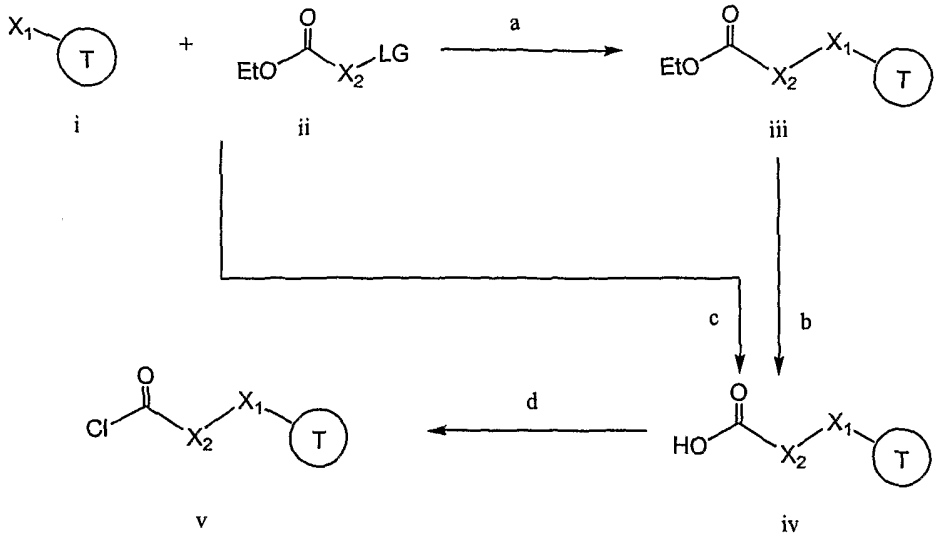
The reaction of intermediate i with amines (step a) in pyridine at rt yields ii. Reaction of intermediate ii with tin in 10% HCl (step b) under refluxing conditions gives iii. Reaction of iv with amines (step c) in pyridine, followed by treatment with 10% NaOH provides iii.

Scheme E: Scheme E provides a synthesis for compounds of Formula **IIA**.



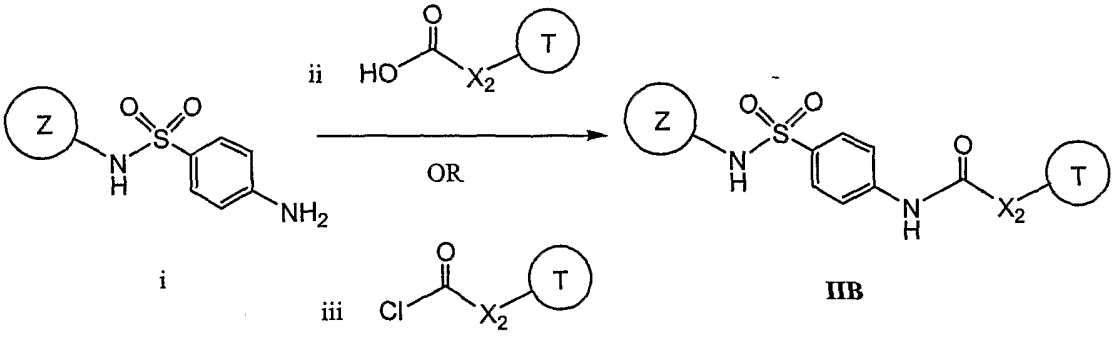
Reaction of i and ii (step a) in pyridine and DCM at rt yields iv. The coupling of i and iii (step b) using CDI and DMA under refluxing conditions, or HATU and TEA in pyridine under mircrowave conditions at 200°C, or BOP and TEA in CH_3CN at rt yields iv. The reaction of iv and v (step c) under alkylation conditions provides **IIA**. These alkylation conditions include NaH and K_2CO_3 as bases, DMF, DMSO, and THF as solvents, under rt, microwave, and reflux conditions.

Scheme F: Scheme F provides useful intermediates for Scheme A-C, E.



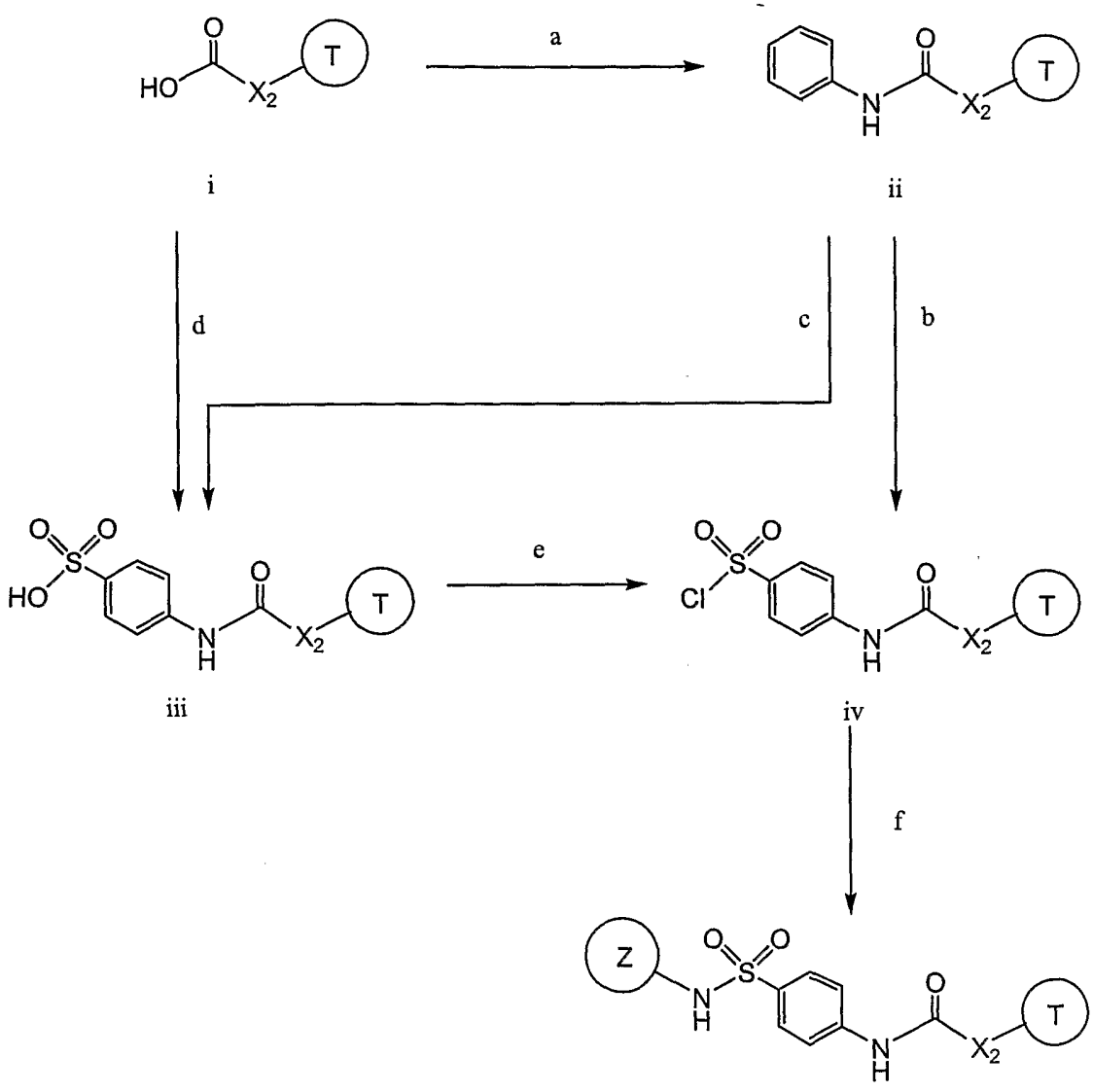
The reaction of i and ii (step a) under alkylation conditions provides intermediate iii. These alkylation conditions include NaH and K_2CO_3 as bases, and NaI can be added. Solvents include DMF, DMSO, and THF, and reaction conditions include rt, microwave, and refluxing conditions. The reaction of i and ii (step c) in H_2O and NaOH provides intermediate iv. The reaction of intermediate iii (step b) using 2N NaOH, or H_2O in DMA under microwave conditions yields iv. Treatment of iv with oxalyl chloride or thionyl chloride provides v.

Scheme G: Scheme G provides a synthesis to compounds of Formula IIB.



The coupling of i and ii (step a) using CDI and DMA under refluxing conditions, or HATU and TEA in pyridine under mircrowave conditions at 200°C, or BOP and TEA in CH_3CN at rt yields **IIB**. Reaction of i and iii (step a) in pyridine and DCM at rt yields **IIB**.

Scheme H: Scheme H provides an alternative synthesis to compounds of Formula **IIB**.

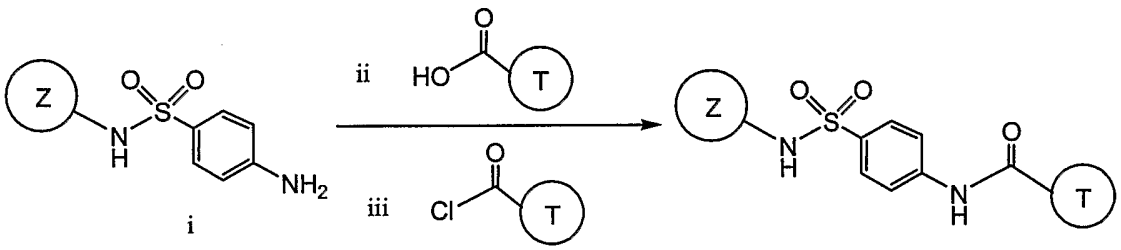


IIB

The coupling of i with anilines (step a) using CDI and DMA under refluxing conditions, or HATU and TEA in pyridine under mircrowave conditions at 200°C, or isobutyl chlorocarbonate and TEA in DCM yields ii. Reaction of intermediate ii with $ClSO_3H$ (step b) under refluxing conditions gives iv. Reaction of ii

$ClSO_3H$ at 0°C (step c) gives intermediate iii. Coupling of intermediate i with aminosulfonic acids (step d) using HATU and TEA in pyridine under mircrowave conditions at 200°C, or BOP and TEA in CH_3CN at rt yields iii. Reaction of intermediate iii with SO_2Cl (step e) yields iv. Alternatively, reaction of intermediate iii with cyanuric chloride and TEA in acetone under microwave conditions at 120°C (step e) provides iv. Reaction of iv with various amines (step f) in pyridine at room temperature yields **IIB**.

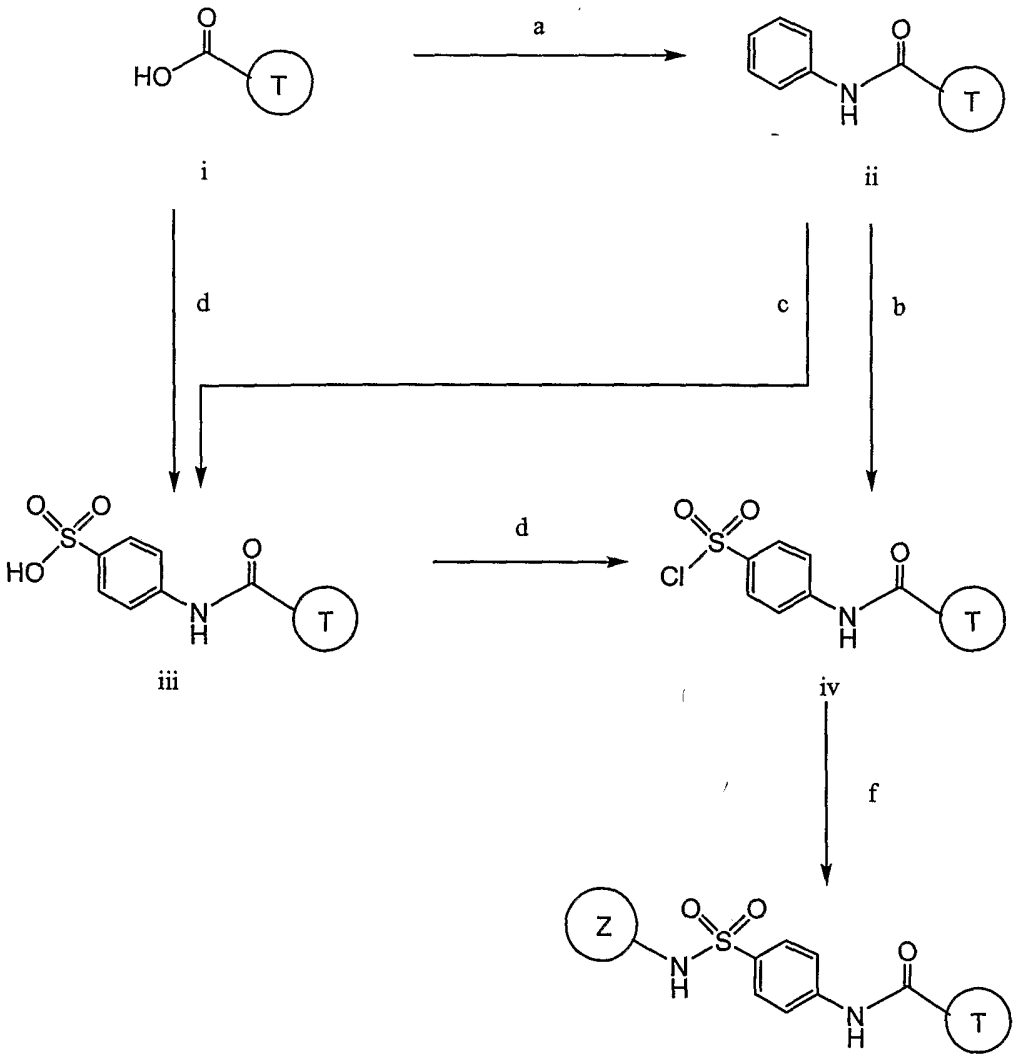
Scheme I: Scheme I provides a synthesis for compounds of Formula **IIC**.



IIC

The coupling of i and ii (step a) using CDI and DMA under refluxing conditions, or HATU and TEA in pyridine under mircrowave conditions at 200°C, or BOP and TEA in CH_3CN at rt yields **IIC**. Reaction of i and iii (step a) in pyridine and DCM at rt yields **IIC**.

Scheme J: Scheme J provides an alternative synthesis for compounds of Formula **IIC**.

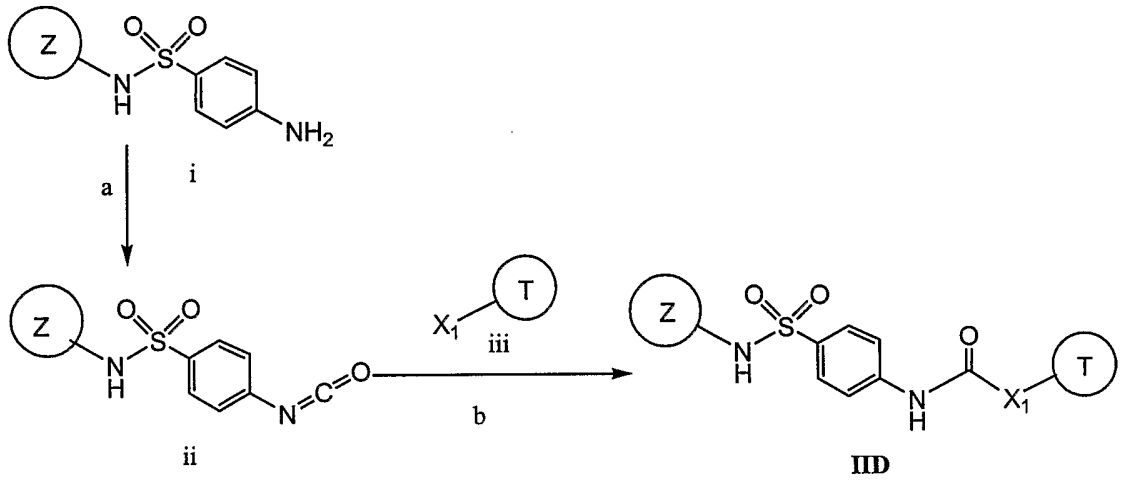


IIC

The coupling of i with anilines (step a) using CDI and DMA under refluxing conditions, or HATU and TEA in pyridine under mircrowave conditions at 200°C, or isobutyl chlorocarbonate and TEA in DCM yields ii. Reaction of intermediate ii with $ClSO_3H$ (step b) under refluxing conditions gives iv. Reaction of ii $ClSO_3H$ at 0°C (step c) gives intermediate iii. Coupling of intermediate i with aminosulfonic acids (step d) using HATU and TEA in pyridine under mircrowave conditions at 200°C, or BOP and TEA in CH_3CN at rt yields iii. Reaction of intermediate iii with

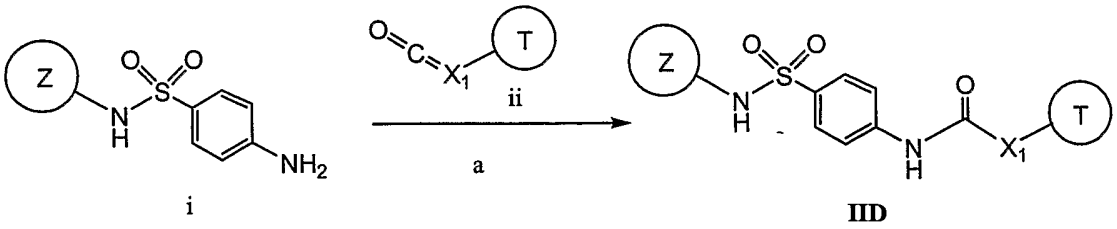
SO_2Cl (step e) yields iv. Alternatively, reaction of intermediate iii with cyanuric chloride and TEA in acetone under microwave conditions at 120°C (step e) provides iv. Reaction of iv with various amines (step f) in pyridine at room temperature yields **IIB**.

Scheme K: Scheme K provides a synthesis for compounds of Formula **IID**.



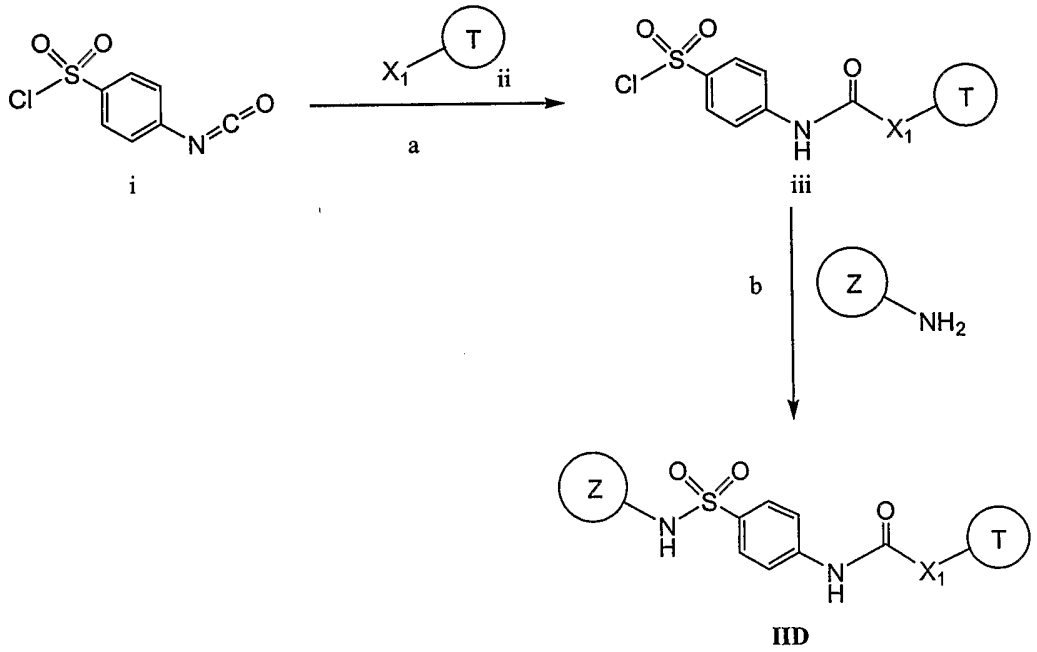
The reaction of intermediate i with 20% diphosgene and TEA (step a) in $PhCH_3$ with heating provides ii. The treatment of ii with iii (step b) yields **IID**.

Scheme L: Scheme L provides an alternative synthesis for compounds of Formula **IID**.



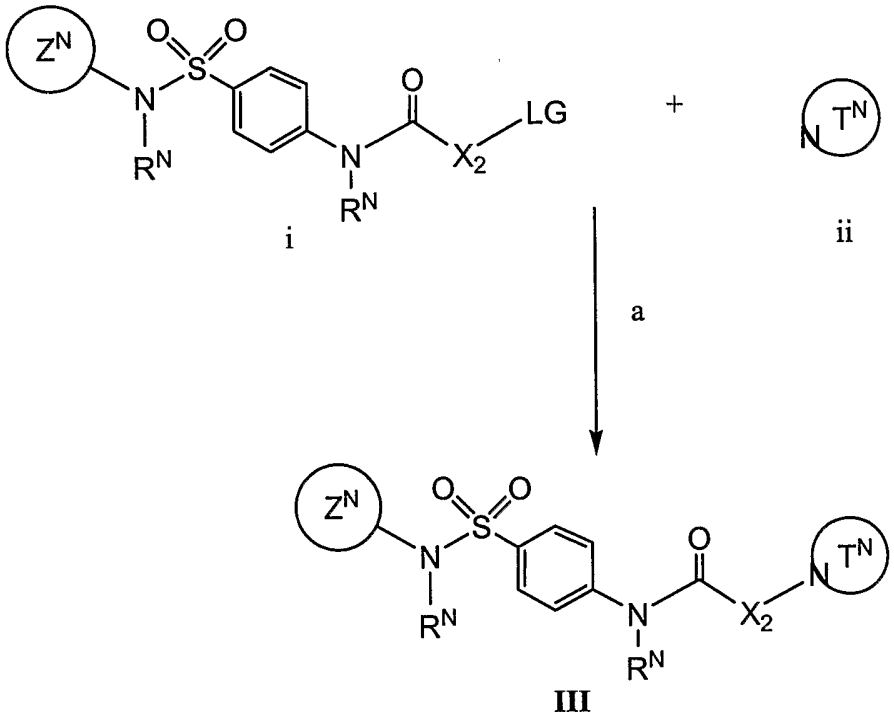
The reaction of intermediate i with ii in TEA/CH_3CN (step a) provides compounds **IID**.

Scheme M: Scheme M provides an alternative synthesis for compounds of Formula **IID**.



The reactions of intermediate i and ii (step a) in THF at rt provides intermediate iii. The treatment of intermediate iii with various amines (step b) in yridines at rt provides **IID**.

Scheme N: Scheme N provides a synthesis for compounds of Formula **III**.



The reaction of i and ii (step a) under alkylation conditions provides **III**. These alkylation conditions include NaH and K_2CO_3 as bases, and NaI can be added. Solvents include DMF, DMSO, and THF, and reaction conditions include rt, microwave, and refluxing conditions.

[00146]

[00147] One of skill in the art will appreciate that in addition to the above schemes, analogous methods known in the art may be readily used to synthesize other compounds of the present invention.

[00148] 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, migraine, 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.

[00149] 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.

[00150] 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.

[00151] 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.

[00152] 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.

[00153] In yet another aspect, a method for the treatment or lessening the severity of acute, chronic, neuropathic, or inflammatory pain, arthritis, migraine, cluster headaches, trigeminal neuralgia, herpetic neuralgia, general neuralgias, epilepsy or epilepsy conditions, neurodegenerative disorders, psychiatric disorders such as 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.

[00154] 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.

[00155] 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.

[00156] 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.

[00157] 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.

[00158] 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.

[00159] 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.

[00160] 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.

[00161] 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.

[00162] 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.

[00163] 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.

[00164] 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 a 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.

[00322] 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.

[00323] 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.

[00324] 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.

[00165] 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".

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

[00167] Examples of additional agents opiois, COX-2 inhibitors, local anesthestics, tricyclic antidepressants, NMDA modulators, cannibaloid receptor agonists, P2X family modulators, VR1 antagonists, and substance P antagonists.

[00168] 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.

[00169] 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

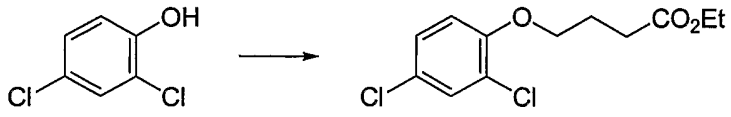
mammal or extracts thereof; and blood, saliva, urine, feces, semen, tears, or other body fluids or extracts thereof.

[00170] Inhibition of NaV1.1, NaV1.2, NaV1.3, NaV1.4, NaV1.5, NaV1.6, NaV1.7, NaV1.8, NaV1.9, or 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.

[00171] 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.

[00172] EXAMPLES

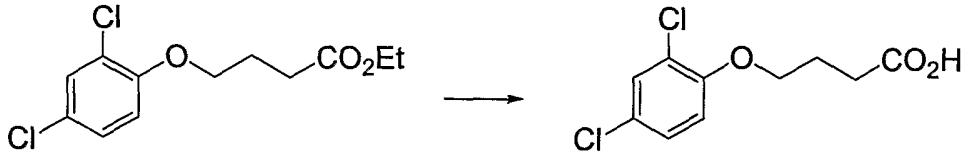
[00173] **4-(2,4-Dichloro-phenoxy)-butyric acid ethyl ester**



To a mixture of 2,4-dichlorophenol (32.6 g, 0.2 mol), NaI (3 g) and K_2CO_3 (69 g, 0.5 mol) in DMF (500 mL) was added dropwise ethyl 4-bromobutyrate (39 g, 0.2 mol) at 80 °C. The reaction mixture was stirred at 80 °C for 2 h until the reaction mixture turned to colorless. The cooled mixture was filtered and the filtrate was diluted with EtOAc (1000 mL), washed with water (3 x 500 mL), dried, and concentrated to give the crude butyrate (57

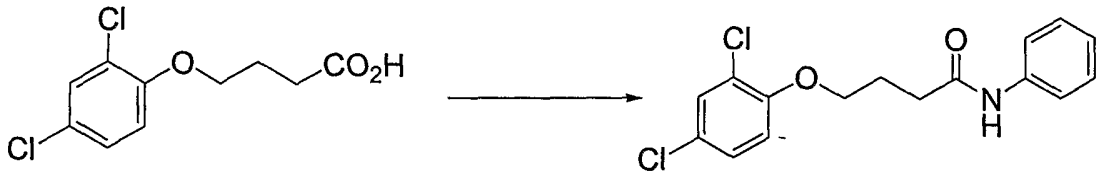
g) as colorless oil. ^{1}H-NMR ($CDCl_3$): δ 7.34 (d, 1 H, J = 8.8 Hz), 7.16 (dd, 1 H, J_1 = 8.8 Hz, J_2 = 2.4 Hz), 6.84(d, 1 H, J = 8.8 Hz), 4.15 (q, 2 H, J = 7.2 Hz), 4.06 (t, 2 H, J = 7.2 Hz), 2.54 (t, 2 H, J = 7.2 Hz), 2.17 (p. 2 H, 6.4), 1.25 (t, 3 H, J = 7.2 Hz).

[00174] 4-(2,4-Dichloro-phenoxy)-butyric acid



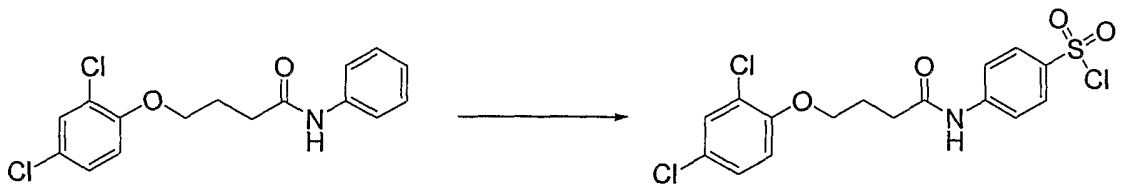
To a solution of ethyl 4-(2,4-dichlorophenoxy)-butyrate (57 g, crude from last step, about 0.2 mol) in THF (500 mL) and water (500 mL) was added $LiOH \cdot H_2O$ (12.6 g, 0.3 mol), and the reaction mixture was stirred for 5 h at RT. The mixture was washed with Et_2O (3 x 200 mL), and the aqueous layer was acidified by addition of HCl (20%) to pH ~ 2. The mixture was extracted with EtOAc (3 x 400 mL), the combined organic extracts were washed with water and brine, dried over Na_2SO_4 and concentrated *in vacuo* to give the butyric acid (37 g, 74.3% from 2,4-dichlorophenol) as a white solid. ^{1}H-NMR ($CDCl_3$): δ 7.36 (d, 1 H, J = 8.8 Hz), 7.18 (dd, 1 H, J_1 = 8.8 Hz, J_2 = 2.4 Hz), 6.84 (d, 1 H, J = 8.8 Hz), 4.07 t, 2 H, J = 7.2 Hz), 2.64 (t, 2 H, J = 7.2 Hz), 2.17 (p, 2 H, J = 6.4 Hz).

[00175] 4-(2,4-dichlorophenoxy)-*N*-phenylbutyramide



To a solution of the 4-(2,4-dichloro-phenoxy)-butyric acid (9.8 g, 40 mmol) and triethylamine (6.0 ml, 40 mmol) in dichloromethane (150 mL) was added dropwise isobutyl chlorocarbonate (6 mL, 40 mol) at -30 °C. After stirring at -30 °C for 3 h, aniline (4 mL 40 mol) was added dropwise. The reaction mixture was stirred for 3 h at -30 °C and then allowed to warm up to RT. Aqueous HCl (5%, 100 mL) was added and stirring was continued for 0.5 h. The phases were separated, the aqueous layer was extracted with dichloromethane (2 × 200 mL). The combined organic extracts were washed with water and brine, dried over Na_2SO_4 and concentrated *in vacuo* to give the product (10 g, 77.5%). ^{1}H-NMR ($CDCl_3$): δ 7.49 (d, 2 H, J = 8.0 Hz), 7.38 (d, 1 H, J = 2.4 Hz), 7.31 (t, 2 H, J = 8.0 Hz), 7.18 (dd, 1 H, J_1 = 8.8 Hz, J_2 = 2.4 Hz) 7.12 (t, 1 H, J = 8.0), 6.87 (d, 1 H, J = 8.8 Hz), 4.12 (t, 2 H, J = 6.4 Hz), 2.64 (t, 2 H, J = 6.4 Hz), 2.25(p, 2 H, J = 6.4 Hz).

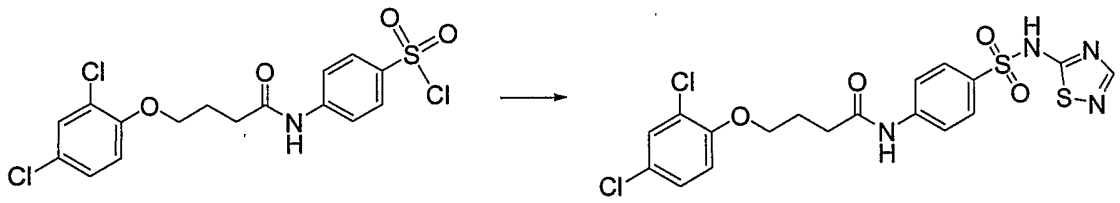
[00176] 4-[4-(2,4-Dichlorophenoxy)-butyrylamino]-benzenesulfonyl chloride



To a solution of 4-(2,4-dichlorophenoxy)-N-phenyl- butyramide (9.8 g, 30 mmol) in chloroform (100 mL) was added chlorosulfonic

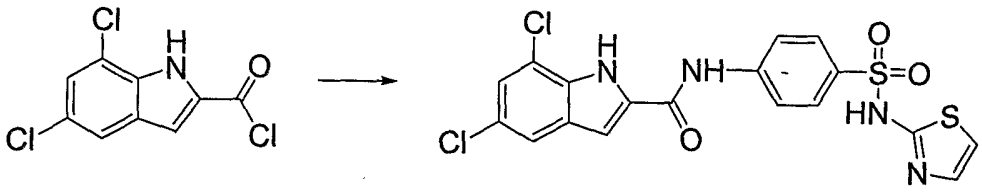
acid (11.6 g, 100 mmol). The reaction mixture was stirred at RT for 36 h, then water (200 mL) was added to quench the reaction. The mixture was extracted with EtOAc (3 × 200 mL), the combined organic extracts were washed with water and brine, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by chromatography over silica to give the sulfonyl chloride (3.5 g, 32%) as a white solid: ^{1}H-NMR ($CDCl_3$): δ 7.97 (d, 2 H, J = 8.8 Hz), 7.75 (d, 2 H, J = 8.8 Hz), 7.63 (br, s, 1 H), 7.37 (d, 1 H, J = 2.4 Hz), 7.21 (dd, 1 H, J_1 = 8.8 Hz, J_2 = 2.4 Hz), 6.87 (d, 1 H, J = 8.8 Hz), 4.12 (t, 2 H, J = 5.6 Hz), 2.72 (t, 2 H, J = 6.8 Hz), 2.31 (p, 2 H, J = 6.4 Hz).

[00177] 4-(2,4-Dichloro-phenoxy)- *N*- [(4-[1,2,4]thiadiazol-5-ylsulfamoyl)-phenyl] butyramide



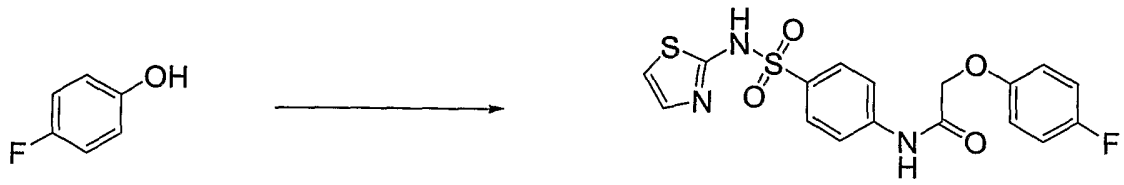
To a solution of the sulfonyl chloride (84 mg, 0.2 mmol) in pyridine (1 mL) was added 5-amino-1,2,4-thiazole (40 mg, 0.4 mmol) and the reaction mixture stirred at rt for 24 h. The reaction mixture was quenched with 50% DMSO and MeOH (3 mL) and purified by HPLC (gradient 10-99% CH_3CN/water). LC/MS (10-99%) M/Z: M^+1 obs = 487.0; t_R = 3.23 min.

[00178] 5,7-Dichloro-1*H*-indol-2-carboxylic acid [4-(thiazol-2-ylsulfamoyl)-phenyl]-amide



To a solution of 5,7-dichloro-indole-2-carbonylchloride (186 mg, 0.75 mmol) in pyridine (0.8 mL, 1 mmol) and DCM (5.2 mL) was added N'-(2-thiazolyl)sulfanilamide (128 mg, 0.5 mmol) and the reaction mixture stired at rt for 16 h. The resulting solid was filtered, washed with DCM (3 x 5 mL), and dried under vacuum overnight to provide the product (0.21 g; yield = 90%)as a white-green solid. ^{1}H-NMR (DMSO-d_6) 12.78 (s, 1H), 12.33 (s, 1H), 10.67 (s, 1H), 7.97 (d, J = 7.0 Hz, 2H), 7.82 (d, J = 7.0 Hz, 2H), 7.62 (d, J = 1.5 Hz, 1H), 7.47 (s, 1H), 7.30 (d, J = 1.7 Hz, 1H), 7.27 (d, J = 4.6 Hz, 1H), 6.84 (d, J = 4.6 Hz, 1H). LC/MS (10-99%) M/Z: M^+1 obs = 467.0; t_R = 3.12 min.

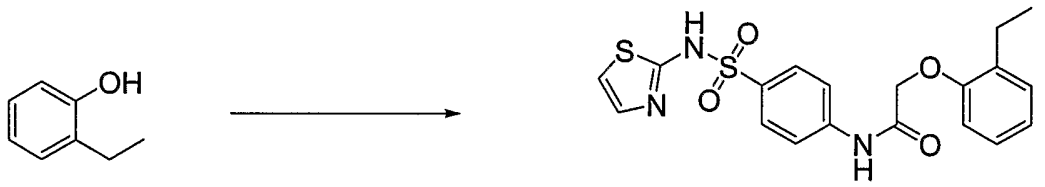
[00179] 2-(4-Fluoro-phenoxy)-*N*-[4-thiazol-2-ylsulfamoyl)-phenyl]-acetamide



4-Fluorophenol (0.050 g, 0.45 mmol) was dissolved in 1.0 mL dimethylacetamide containing K_2CO_3 (0.15 g, 2.5 equiv). *tert*-Butyl chloroacetate (0.081 g, 85 µL, 1.2 equiv) was added neat and the mixture was microwave irradiated at 150 °C for 30 min. After cooling, the contents of the tube were filtered through

Celite into a clean microwave tube, the bed was rinsed with 1.0 mL dimethylacetamide, 1.0 mL H_2O was added to the tube and this mixture was irradiated for 3 min at 190 °C. Volatiles were evaporated. To the crude residue was added carbonyldiimidazole (0.68 mL of 1.0 M in DMA). The solution was placed on the shaker for 1.0 h at rt, after which N'-(2-thiazolyl)sulfanilamide (1.8 mL of 1.0 M in DMA) was added and shaking continued overnight at rt. Volatiles were again evaporated, and the product isolated by HPLC purification.

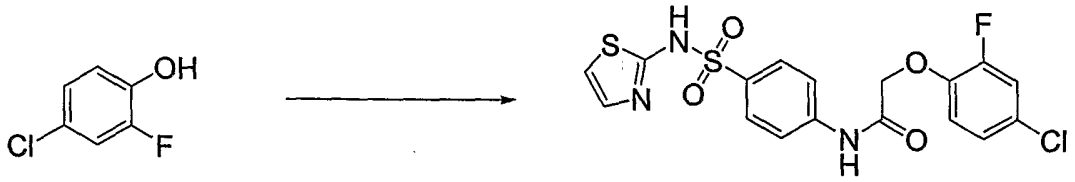
[00180] 2-(2-Ethyl-phenoxy)-*N*-[4-thiazol-2-ylsulfamoyl)-phenyl]-acetamide



2-Ethylphenol (0.061 g, 0.50 mmol) was dissolved in DMSO (0.5 mL) and powdered K_2CO_3 (0.070 g, 0.50 mmol) was added followed by ethyl bromoacetate (0.12 g, 86 µL neat, 1.2 equiv). The mixture was shaken at rt for 16 h. NaOH (1.0 mL of 2 N) was added and shaking continued for 4 h. Aryloxybutanoic acid was precipitated by adding HCl (2.0 mL of 2 N) and collected by centrifugation and decantation of supernatant. A water wash was similarly employed prior to evaporation of volatiles. The dry crude product was weighed and assumed to be pure as it was treated with carbonyldiimidazole (1.0 equiv of 0.50 M in DMA) for 1 h at 45 °C, then N'-(2-thiazolyl)sulfanilamide (1.0 equiv of 1.0 M in DMA) was added and shaking continued overnight overnight at

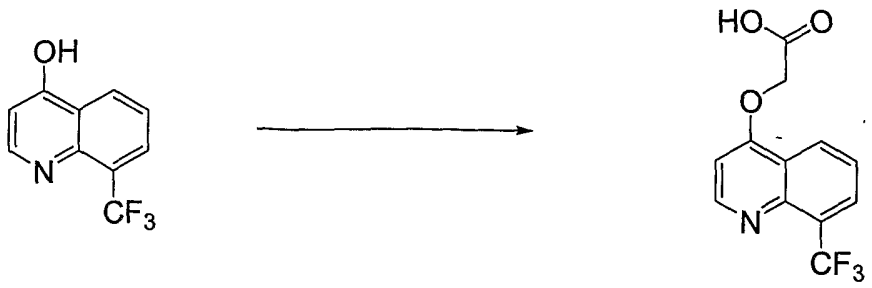
rt. Volatiles were again evaporated, and the product isolated by HPLC purification.

[00181] 2-(4-Chloro-2-fluoro-phenoxy)-*N*-[4-thiazol-2-ylsulfamoyl)-phenyl]-acetamide



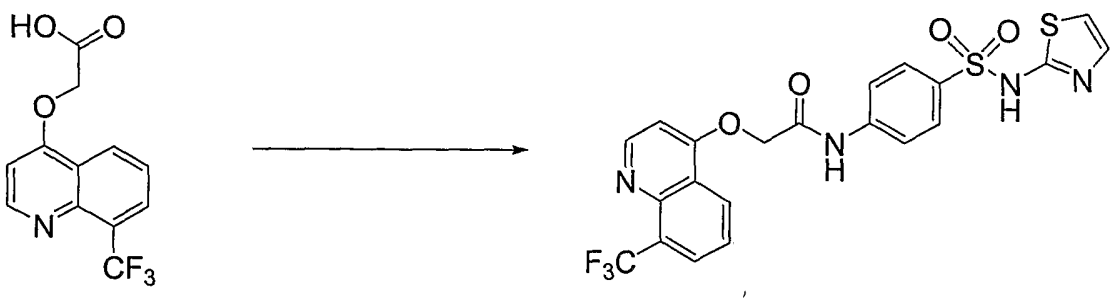
4-Chloro-2-fluorophenol (0.073 g, 0.50 mmol) was suspended in 0.62 mL H_2O and NaOH (0.10 mL, 10 N) was added. The mixture was shaken until homogenous, chloroacetic acid (0.50 mL of 1.0 M) was added and the solution was heated to 110 °C in a test tube equipped with a rubber cap punctured by a syringe needle. Water was allowed to distill out. After 4-5 h, the temperature was increased to about 120 °C and most of the rest of the water was distilled off. When the volume reduction was about 75%, the tube was cooled and 1.0 mL of 6 N HCl was added to precipitate product which was collected by centrifugation and decantation of supernatant. Water washes (2 x 2 mL) were similarly employed prior to evaporation of volatiles. The dry crude product was weighed and assumed to be pure as it was treated with carbonyldiimidazole (1.0 equiv of 0.50 M in dimethylamine) for 1 h at 45 °C, then N'-(2-thiazolyl)sulfanilamide (1.0 equiv of 1.0 M in dimethylamine) was added and shaking continued overnight overnight at rt. Volatiles were again evaporated, and the product isolated by HPLC purification.

[00182] (8-Trifluoromethyl-quinolin-4-yloxy)-acetic acid



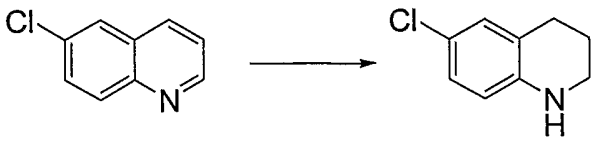
4-Hydroxy-8-trifluoromethylquinoline (0.50 g, 2.35 mmol) was dissolved in DMSO (2 mL). Potassium carbonate was added (0.32 g, 2.35 mmol) and the mixture was stirred vigorously for 2 h. Ethyl bromoacetate (0.32 mL, 1.2 equiv) was added dropwise and heat was applied at 50°C for 6 h. At 50 °C, 2N NaOH (2 mL) was added and stirring continued for 4 h. The mixture was cooled and quenched with water (4 mL). Glacial acetic acid (1.4 mL) was added to ~pH 4 resulting in precipitation of product. After stirring the suspension for 6 h, the solid was collected by vacuum filtration, rinsed with water, and dryed in a vacuum dessicator over CaCl. The yield of white solid was 0.56 g (87%). ^{1}H-NMR (DMSO-d_6) 5.04 (s, 2H), 7.11 (d, J = 5.2 Hz, 1H), 7.69 (t, J = 8.0 Hz, 1H), 8.15 (d, J = 8.0 Hz, 1H), 8.47 (d, J = 8.0 Hz, 1H), 8.83 (d, J = 5.2 Hz, 1H), 13.3 (br s, 1H); LC/MS (10-99%) M/Z: M^+1 *obs* = 333.5; t_R = 2.63 min.

[00183] N-[4-(Thiazol-2-ylsulfamoyl)-phenyl]-2-(8-trifluoromethyl-quinolin-4-yloxy)-acetamide



(8-Trifluoromethylquinolin-4-yloxy)-acetic acid (0.50 g, 1.84 mmol) was suspended in 20 mL DCM with rapid stirring. At rt, oxalyl chloride (0.19 mL, 1.2 equiv) was added dropwise and stirring continued for 4 h. Solvent and excess oxalyl chloride were removed *in vacuo*, the white residue was re-suspended in DCM, and the mixture cooled to 0°C. N'-(2-thiazolyl)sulfanilamide (0.47 g, 1.0 equiv) was added followed by pyridine (0.30 mL, 2.0 equiv).The mixture was allowed to warm to rt overnight. The solid was collected and rinsed with fresh DCM. Further purification was effected by suspending the solid in 20 mL methanol, stirring vigorously for 4 h, and filtration. After drying under vacuum, white solid 0.65 g (69%) was obtained. ^{1}H-NMR (DMSO-d_6) 5.11 (s, 2H), 6.79 (d, J = 4.8 Hz, 1H), 7.12 (d, J = 5.2 Hz, 1H), 7.22 (d, J = 4.8 Hz, 1H), 7.71 (t, J = 8.0 Hz, 1H), 8.17 (d, J = 8.0 Hz, 1H), 8.55 (d, J = 8.0 Hz, 1H), 8.85 (d, J = 5.2 Hz, 1H),; ^{13}C-NMR (DMSO-d_6) 68.0, 103.6, 108.8, 120.0, 122.0, 124.8 (q, J = 270 Hz), 125.1, 125.4, 126.4 (q, J = 33 Hz), 127.7, 127.8, 129.2, 137.7, 142.1, 145.6, 153.2, 161.2, 166.5, 169.4 LC/MS (10-99%) M/Z: M^+1 *obs* = 509.5; t_R = 3.13 min.

[00184] 6-Chloro-1,2,3,4-tetrahydroquinoline



Method A: To a solution of 6-chloroquinoline (2.0 g, 12.2 mmol) in anhydrous MeOH (500 mL) under nitrogen was added PtO_2 (0.2 g,

1.6 mmol). Hydrogen gas was then passed through the reaction mixture and the mixture stirred for 45 min. The reaction mixture was filtered and the filtrate evaporated. The product was taken up in DCM, filtered through celite and chromatographed (gradient of 0-10% EtOAc/Hex) to afford 0.9 g (41 %) as clear colorless oil. HNMR ($CDCl_3$): δ 6.85-6.83 (m, 2 H), 6.42-6.39 (m, 1 H), 5.82 (s, 1 H), 3.17-3.13 (m, 2 H), 2.63 (t, , J = 6.3 Hz, 2 H), 1.75 (q, , J = 5.9 Hz, 2 H),LC/MS (10-99%) M/Z: M^+1 *obs* = 168.3; t_R = 1.74 min.

Method B: A mixture of 6-chloroquinoline (0.82 g, 0.5 mmol), indium powder (0.53 g, 4.6 mmol), and saturated aq. NH_4Cl (789 µL) in absolute EtOH (2.5 mL) was microwaved at 160 °C for 8h. The mixture was then filtered and the filtrate concentrated to give a crude yield of 0.10 g. The product was taken up in DCM, filtered through celite and chromatographed (gradient of 0-10% EtOAc/Hex) to afford 0.01 g (12 %) as clear colorless oil. LC/MS (10-99%) M/Z: M^+1 *obs* = 168.3; t_R = 1.74 min.

[00185] 1-Methyl-1,2,3,4-tetrahydro-isoquinoline

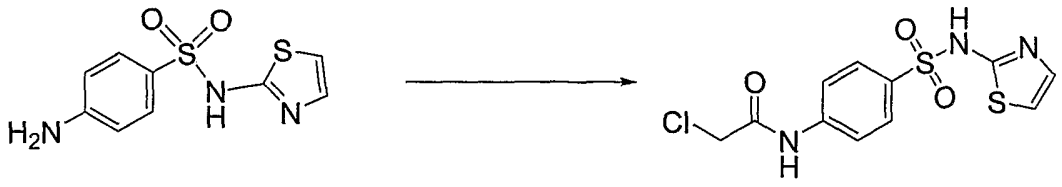
To a solution of 1-methylisoquinoline (133 µL, 1.0 mmol) in THF under nitrogen was added dropwise a solution of $LiBEt_3H$ in THF (1.0M, 2.2 mL, 2.2 mmol) to give a yellow solution. After stirring 1.5 h, MeOH (1.2 mL) was added dropwise to produce a clear colorless solution, which was then diluted with 1M aq. HCl and ether. The aqueous layer was extracted three times with

ether, then made basic (pH 14) by addition of 1M aq. NaOH. The aqueous layer was extracted five times with DCM, dried over $MgSO_4$, filtered and concentrated to give the desired product in 77 % yield, which was used without further purification. LC/MS (10-99%) M/Z: M^+1 *obs* = 148.3; t_R = 0.62 min.

[00186] 6-Methoxy-1,2,3,4-tetrahydro-quinoline

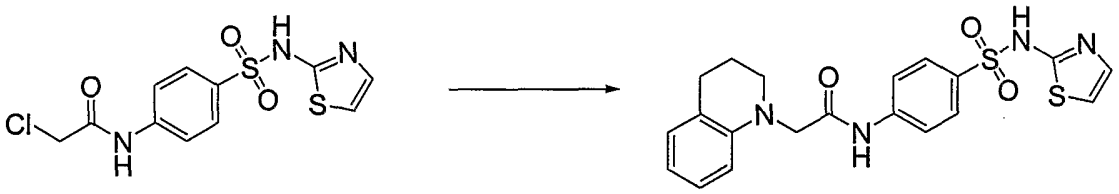
A mixture of 6-methoxyquinoline (69 µL, 0.5 mmol), ammonium formate (0.32 g, 5.0 mmol), and 10% Pd/C (0.05 g) in anhydrous MeOH (5 mL) was microwaved for 900 s at 100 °C. The mixture was filtered and 2M HCl in Et_2O (1.5 mL) was added. The product was redissolved in H_20/DCM and the aqueous layer basified with 0.1M aq. NaOH (pH 8). After extracting three times with DCM, the organic layer was concentrated to give the product in 89% yield. The product was used without further purification. LC/MS (10-99%) M/Z: M^+1 *obs* = 164.0; t_R = 0.40 min.

[00187] 2-Chloro-*N*-[4-(thiazol-2-ylsulfamoyl)-phenyl]-acetamide



General procedure 1: *N'*-(2-thiazolyl)sulfanilamide (10.0 g, 39.2 mmol) was suspended in DCM containing pyridine (3.80 mL, 1.2 equiv) and chilled in an ice bath. Chloroacetyl chloride (5.3 g, 3.74 mL, 1.2 equiv) was added dropwise with vigorous stirring. The mixture was allowed to warm to rt overnight. The solid was filtered, rinsed with fresh DCM, and air dried to give 11.6 g (89%) white solid. ^{1}H-NMR (DMSO-d_6) 4.56 (s, 2H), 6.78 (d, J = 4.8 Hz, 1H), 7.21 (d, J = 4.8 Hz, 1H), 7.70 (d, J = 9.0 Hz, 2H), 7.75 (d, J = 9.0 Hz, 2H), 10.61 (s, 1H); ^{13}C-NMR (DMSO-d_6)44.2, 108.8, 119.7, 125.1, 127.7, 137.7, 142.3, 165.8, 169.4; LC/MS (10-99%) M/Z: M^+1 *obs* = 333.6; t_R = 2.63 min.

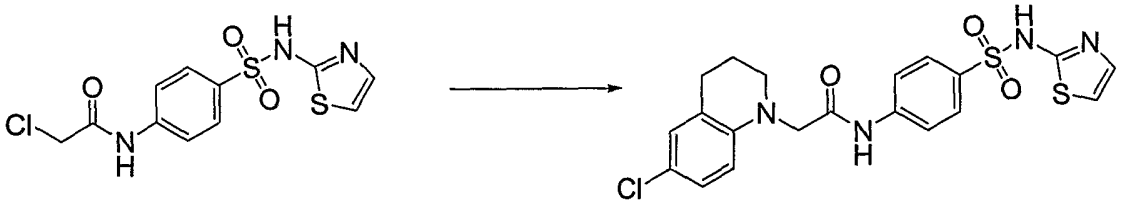
[00188] 2-(3,4-Dihydro-2*H*-quinolin-1-yl)-*N*-[4-(thiazol-2-ylsulfamoyl)-phenyl]-acetamide



General procedure 2: To the 2-chloroacetamide (2.00 g, 6.03 mmol) in DMF (15 mL) was added tetrahydroquinoline (2.27 mL, 18.09 mmol) and the reaction mixture was microwaved at 200 °C for 300 s. The reaction mixture was taken up in DCM, filtered through celite and chromatographed (gradient of 0-10% MeOH/DCM) to provide 1.53 g (59%) of a white solid. ^{1}H-NMR (DMSO-d_6) 12.70 (s, 1H), 10.37 (s, 1H), 7.74 (s, 4H), 7.25 (d, J = 5.6 Hz, 1H), 6.87-6.95 (m, 2H), 6.82 (d, J = 4.6 Hz, 1H), 6.50 (t, J = 7.3 Hz, 1H), 6.42 (d, J = 7.9 Hz, 1H), 3.41 (t, J = 5.6 Hz, 2H),

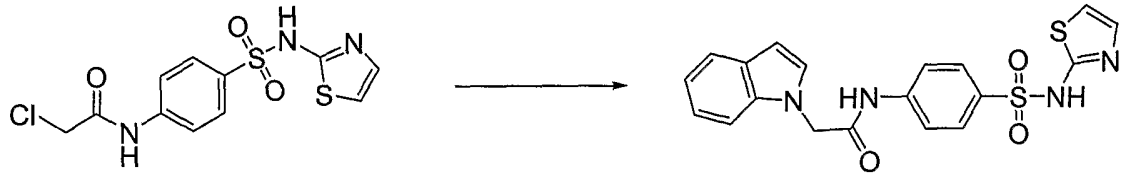
2.73 (t, J = 6.3 Hz, 2H), 1.86-1.95 (m, 2H). LC/MS (10-99%) M/Z: M^+1 *obs* = 429.0; t_R = 2.79 min.

[00189] 2-(6-Chloro-3,4-dihydro-2*H*-quinoline-1-yl)-N-[4-(thiazol-2-ylsulfamoyl)-phenyl]-acetamide



Synthesized according to **general procedure 2**: 2-chloroacetamide (1.0 g, 3.0 mmol), 6-chloro-tetrahydro-quinoline (0.85 g, 5.0 mmol) in DMF (15 mL). Purified by column chromatography (5-10% MeOH/DCM), followed by HPLC purification (1-99% CH_3CN/H_2O). LC/MS (10-99%) M/Z: M^+1 *obs* = 463.3; t_R = 2.93 min.

[00190] 2-Indol-1-yl-*N*-[4-(thiazol-2-ylsulfamoyl)-phenyl]-acetamide



General procedure 3: A dry, 10 mL borosilicate glass reaction vessel was put under an inert atmosphere of argon and loaded with sodium hydride (60% wt. dispersion in mineral oil, 5 equiv) to which dry DMF (1 mL) was added. The resulting suspension was cooled to 0 °C. Subsequently, a solution of the indole in dry

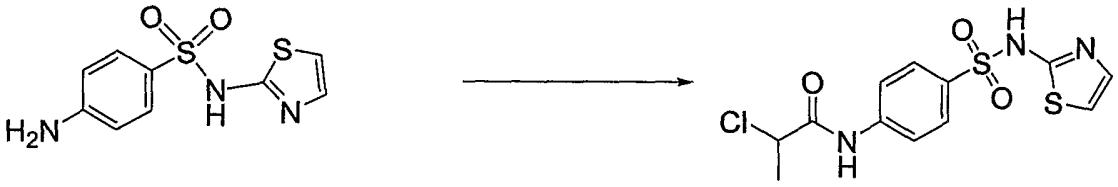
DMF (0.1M, 1 mL, 0.1 mmol) was added to the vessel and the reaction mixture was stirred for 30 min. at 0°C. Next, a solution of the 2-chloro-*N*-[4-(thiazol-2-ylsulfamoyl)-phenyl]-acetamide in dry DMF (0.1M, 1 mL, 1 equiv) was added. The reaction mixture was allowed to warm to room temperature and stirred for 72 h, after which the reaction was quenched by the addition of water (5 mL). The work-up consisted of washing the aqueous phase with heptane (2 x 5 mL), addition of aqueous HCl (1M, 1 mL) and extraction with DCM (2 x 4 mL). Finally, removal of the DCM under reduced pressure and stripping the resulting solid with CH_3CN (5 times), afforded the final product. ^{1}H-NMR (DMSO-d_6): δ 10.73 (s, 1H), 7.78-7.71 (m, 4 H), 7.55 (d, J = 7.7 Hz, 1H), 7.41 (d, J = 8.3 Hz, 1H), 7.38 (d, J = 3.0 Hz, 1H), 7.23 (d, J = 4.7 Hz, 1H), 7.12 (t, J = 7.4 Hz, 1H), 7.02 (t, J = 7.4 Hz, 1H), 6.80 (d, J = 4.7 Hz, 1H), 6.46 (d, J = 3.0 Hz, 1H), 5.09 (s, 2H). LC/MS (10-99%) M/Z: M^+1 *obs* = 412.2; t_R = 3.43 min.

[00191] 2-(2-Metyl-2,3-dihydro-indol-1-yl)-*N*-[4-(thiazol-2-ylsulfamoyl)-phenyl]- acetamide

Synthesized according to **general procedure 2**: 2-chloroacetamide (0.5 g, 1.5 mmol), 2-methylindoline (1.0 mL, 7.5 mmol) in DMF (5 mL). Purified by chromatography (gradient of 0-10% MeOH/DCM) to provide 640 mg (100%) of a white solid. ^{1}H-NMR (DMSO-d_6) 12.70

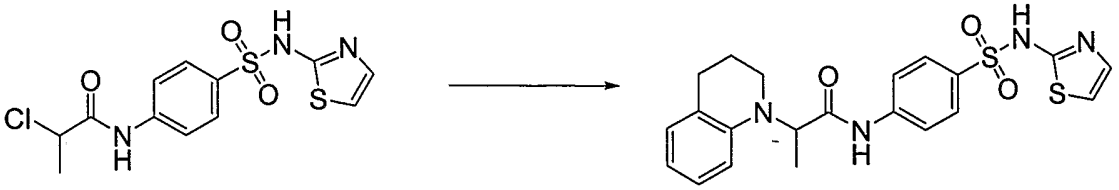
(bs, 1H), 10.26 (s, 1H), 7.72-7.78 (m, 4H), 7.25 (d, J = 4.6 Hz, 1H), 7.01 (d, J = 7.2 Hz, 1H), 6.95 (t, J = 7.6 Hz, 1H), 6.82 (d, J = 4.6 Hz, 1H), 6.57 (dt, J = 0.8 Hz, 1H), 6.39 (d, J_d = 0.8 Hz, J_t = 8.0 Hz, 1H) (3.41 (t, J = 5.6 Hz, 2H), 2.73 (t, J = 6.3 Hz, 2H), 1.86-1.95 (m, 2H). LC/MS (10-99%) M/Z: M^+1 *obs* = 429.2; t_R = 2.97 min.

[00192] 2-Chloro-*N*-[4-(thiazol-2-ylsulfamoyl)-phenyl]-propionylamide



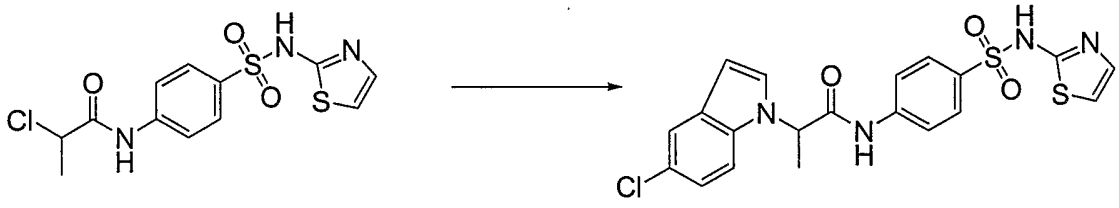
Synthesized according to **general procedure 1**: N'-(2-thiazolyl)sulfanilamide (1.00 g, 3.9 mmol), pyridine (0.6 mL), 2-Chloropropionyl chloride (0.5 mL, 4.7 mmol, 1.2 equiv) in DCM (50 mL). Yield: 1.34 g (99%) of a crude white solid. ^{1}H-NMR (DMSO-d_6) 10.65 (s, 1H),7.73-7.79 (m, 4H), 7.25 (d, J = 4.3, 1H), 6.83 (d, J = 4.6, 1H), 4.69 (q, J = 3.3, 1H), 1.61 (d, J = 6.6, 3H). LC/MS (10-99%) M/Z: M^+1 *obs* = 346.1; t_R = 2.22 min.

[00193] 2-(3,4-Dihydro-2*H*-quinolin-1-yl)-*N*-[4-(thiazol-2-ylsulfamoyl)-phenyl]-propionamide



Synthesized according to **general procedure 2**: 2-chloropropionylamide (173 mg, 0.5 mmol), tetrahydro-quinoline (0.19 mL, 1.5 mmol) in DMF (1 mL), microwaved at 200 °C for 450 s. The reaction mixture was diluted with 50% MeOH/DMSO and purified by HPLC (gradient of 1-99% CH_3CN/water). ^{1}H-NMR (DMSO-d_6) 10.29 (s, 1H), 7.72-7.79 (m, 4H), 7.25 (d, J = 4.6, 1H), 6.81-6.99 (m, 2H), 6.82 (d, J = 4.6, 1H), 6.65 (d, 8.2, 1H), 6.54 (td, J_d = 0.6, J_t =7.3, 1H), 4.58 (q, J = 6.8, 1H), 3.47 (bs, 1H), 3.25 (t, J = 5.5, 2H), 2.70 (t, J = 6.2, 2H), 1.81-1.96 (m, 2H), 1.35 (d, J = 6.9, 3H). LC/MS (10-99%) M/Z: M^+1 *obs* = 443.3; t_R = 3.13 min.

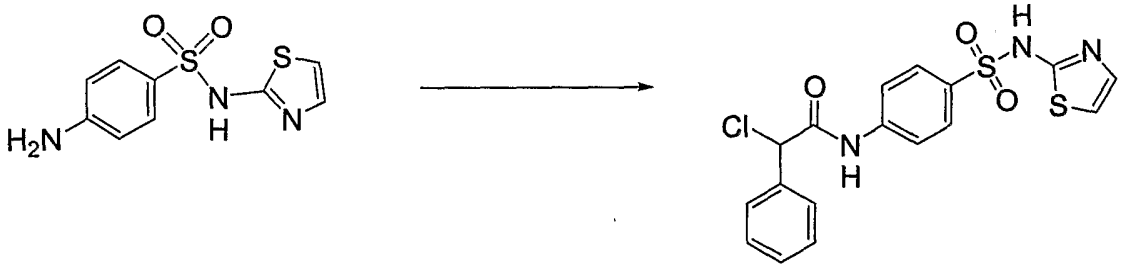
[00194] 2-(5-Chloro-indol-1-yl)-*N*-[4-(thiazol-2-ylsulfamoyl)-phenyl]-propionamide



Synthesized according to **general procedure 3**: 6-Chloroindole (0.1 g, 0.7 mmol), NaH (60% in oil, 0.14 g, 3.6 mmol), 2-chloropropionylamide (250 mg, 0.7 mmol). The product was isolated by HPLC (gradient of 10-99% CH_3CN/water). ^{1}H-NMR (DMSO-

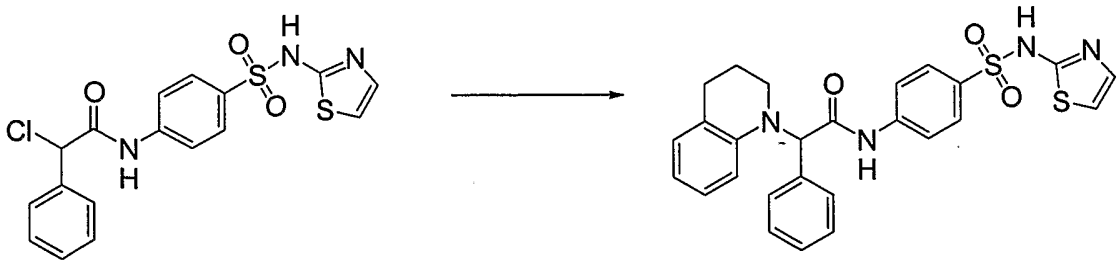
d_6) 10.71 (bs, 1H), 7.71-7.83 (m, 4H), 7.65 (d, J = 1.6, 1H), 7.58-7.59 (m, 1H), 7.56 (s, 1H), 7.24 (d, 4.6, 1H), 7.05 (dd, J = 1.8, 8.4, 1H), 6.81 (d, J = 4.6, 1H), 6.53 (dd, J = 0.5, 2.8, 1H), 5.37 (q, J = 7.0, 1H), 1.75 (d, J = 6.9, 3H). LC/MS (10-99%) M/Z: M^+1 *obs* = 461.3; t_R = 2.90 min.

[00195] 2-Chloro-2-phenyl-*N*-[4-(thiazol-2-ylsulfamoyl)-phenyl]-acetamide



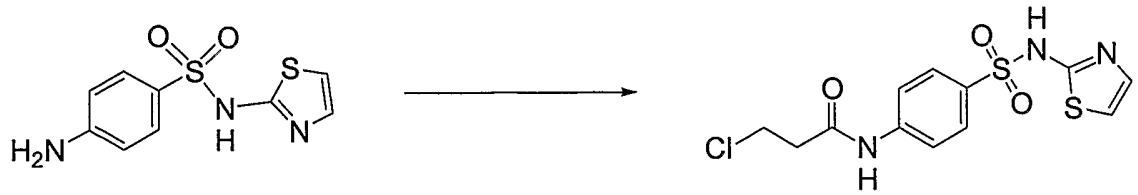
Synthesized according to **general procedure 1**: *N'*-(2-thiazolyl)sulfanilamide (5.60 g, 22 mmol), pyridine (3.6 mL, 44 mmol), 2-chloro-2-phenyl acetylchloride (3.8 mL, 26.4 mmol, 1.2 equiv) in DCM (400 mL). Yield: 6.73 g (75%) of a white solid. ^{1}H-NMR (DMSO-d_6) δ 10.85 (s, 1H), 7.78-7.72 (m, 4H), 7.60-7.57 (m, 2H), 7.45-7.37 (m, 3H), 7.25 (d, J = 4.6 Hz, 1H), 6.82 (d, J = 4.6 Hz, 1H), 5.77 (s, 1H). LC/MS (10-99%) M/Z: M^+1 *obs* = 408.1; t_R = 2.61 min.

[00196] 2-(3,4-Dihydro-2*H*-quinolin-1-yl)-2-phenyl-*N*-[4-(thiazol-2-ylsulfamoyl)-phenyl]-acetamide



Synthesized according to **general procedure 2**: 2-chloro-2-phenyl acetamide (61 mg, 0.15 mmol), tetrahydroquinoline (94 µL, 0.75 mmol) in DMF (0.75 mL), microwaved at 200 °C for 300 s. The reaction mixture was diluted with 50% MeOH/DMSO (0.75 mL) and purified by HPLC (gradient of 1-99% CH_3CN/water). ^{1}H-NMR (DMSO-d_6) δ 10.74 (s, 1H), 7.79-7.74 (m, 4H), 7.44-7.31 (m, 5H), 7.25 (d, J = 4.6 Hz, 1H), 6.99 (d, J = 7.4 Hz, 1H), 6.95 (d, J = 7.6 Hz, 1H), 6.82 (d, J = 4.6 Hz, 1H), 6.70 (d, J = 8.1 Hz, 1H), 6.58-6.55 (m, 1H), 5.75 (s, 1H), 3.40-3.36 (m, 1H), 2.94-2.89 (m, 1H), 2.79-2.61 (m, 2H), 1.83-1.67 (m, 2H). LC/MS (10-99%) M/Z: M^+1 *obs* = 505.3; t_R = 3.20 min.

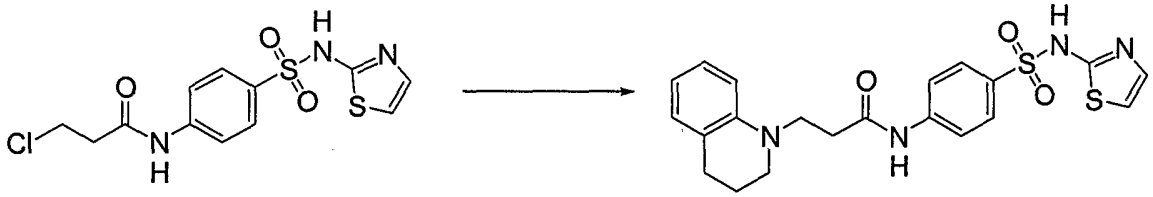
[00197] 3-Chloro-*N*-[4-(thiazol-2-ylsulfamoyl)-phenyl]-propionamide



Synthesized according to **general procedure 1**: *N'*-(2-thiazolyl)sulfanilamide (8.37 g, 32.8 mmol), pyridine (5.3 mL, 65.6 mmol), 2-chloro-propionylchloride (3.8 mL, 39.4 mmol, 1.2 equiv) in DCM (400 mL). Yield: 2.70 g (24%) of a white solid. ^{1}H-

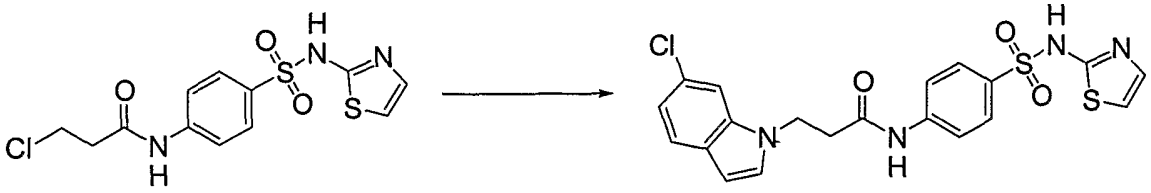
NMR (DMSO-d_6) δ 10.41 (s, 1H), 7.77-7.72 (m, 4H), 7.25 (d, J = 4.6 Hz, 1H), 6.82 (d, J = 4.6 Hz, 1H), 3.88 (t, J = 6.2 Hz, 2H), 2.86 (t, J = 6.2 Hz, 2H). LC/MS (10-99%) M/Z: M^+1 *obs* = 346.1; t_R = 1.94 min.

[00198] 2-(3,4-Dihydro-2*H*-quinolin-1-yl)-*N*-[4-(thiazol-2-ylsulfamoyl)-phenyl]-propionamide



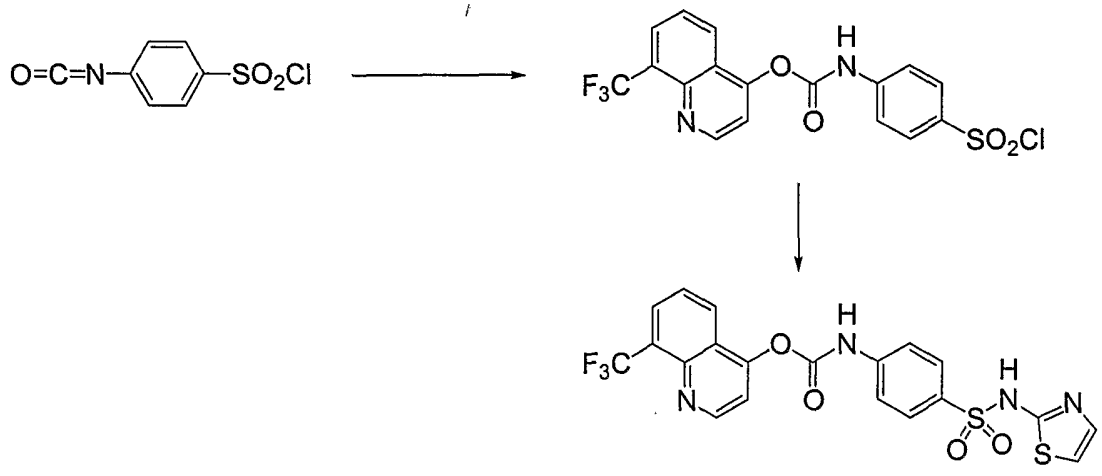
Synthesized according to **general procedure 2**: 3-chloro-propionamide (173 mg, 0.5 mmol), tetrahydroquinoline (188 µL, 1.5 mmol) in DMF (5.0 mL), microwaved at 200 °C for 300 s. The reaction mixture was diluted with 50% MeOH/DMSO (5.0 mL) and purified by HPLC (gradient of 1-99% CH_3CN/water). ^{1}H-NMR (DMSO-d_6) δ 10.32 (s, 1H), 7.75-7.70 (m, 4H), 7.25 (d, J = 4.6 Hz, 1H), 7.00-6.96 (m, 1H), 6.87 (dd, J = 7.3, 1.4 Hz, 1H), 6.82 (d, J = 4.6 Hz, 1H), 6.64 (d, J = 7.9 Hz, 1H), 6.48 (dt, J = 10.0, 3.6 Hz, 1H), 3.59 (t, J = 7.0 Hz, 2H), 3.25 (t, J = 5.6 Hz, 2H), 2.69-2.53 (m, 4H), 1.86-1.80 (m, 2H). LC/MS (10-99%) M/Z: M^+1 *obs* = 443.3; t_R = 2.42 min.

[00199] 3-(6-Chloro-indol-1-yl)-*N*-[4-(Thiazol-2-ylsulfamoyl)-phenyl]-propionamide



Synthesized according to **general procedure 3**: 6-Chloroindole (109 mg, 0.72 mmol), NaH (60% in oil, 144 mg, 3.60 mmol), 3-chloropropionamide (250 mg, 0.72 mmol). The product was isolated by HPLC (gradient of 10-99% CH_3CN/water). ^{1}H-NMR (DMSO-d_6) δ 10.25 (s, 1H), 7.73-7.64 (m, 4H), 7.53 (d, J = 8.3 Hz, 1H), 7.37 (d, J = 3.1 Hz, 1H), 7.21 (d, J = 4.5 Hz, 1H), 7.02 (dd, J = 8.4, 1.9 Hz, 1H), 6.43 (d, J = 0.8 Hz, 1H), 4.50 (t, J = 6.6 Hz, 2H), 2.84 (t, J = 6.7 Hz, 2H). LC/MS (10-99%) M/Z: M^+1 *obs* = 461.1; t_R = 2.84 min.

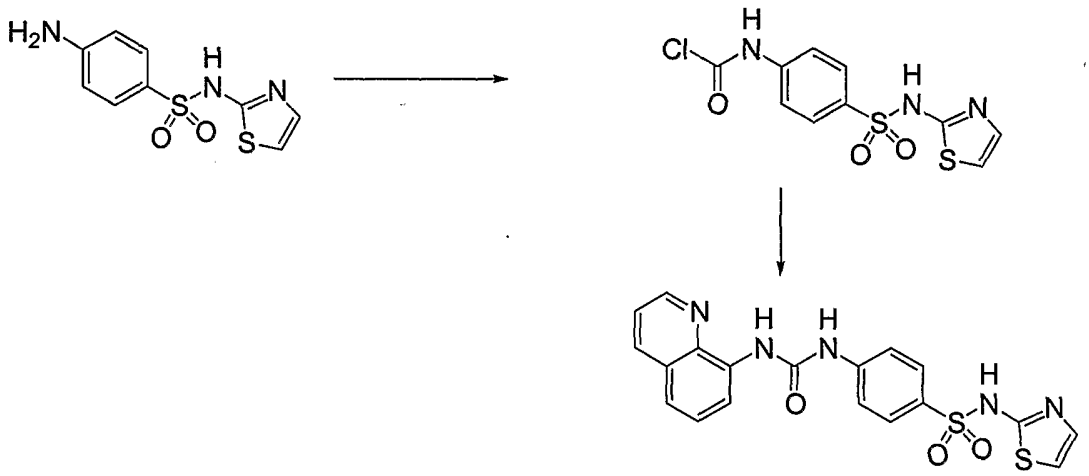
[00200] [4-(Thiazol-2-ylsulfamoyl)-phenyl]-carbamic acid 8-trifluoromethyl-quinolin-4-yl ester



To a solution of 8-trifluoromethyl-quinolin-4-ol (107 mg, 0.50 mmol) in THF (5 mL) was added 4-isocyanatobenzene-sulfonyl chloride (109 mg, 0.50 mmol) at RT. The resulting mixture was stirred at ambient temperature for 1 h. Then, a solution of 2-

aminothiazole (50 mg, 0.50 mmol) in pyridine (5 mL) was added and stirring was continued for 65 h. The solvents were evaporated under a stream of nitrogen, the residue was dissolved in DMSO (2 mL) and purified by preparative LC/MS (gradient of 5-95% CH_3CN/water). ^{1}H-NMR (DMSO-d_6) δ 9.63 (s, 1H), 9.10 (s, 1H), 8.28-8.22 (m, 2H), 7.97-7.95 (m, 2H), 7.81-7.77 (m, 3H), 7.52-7.51 (m, 1H), 7.41-7.40 (m, 2H), 7.15-7.14 (m, 1H). LC/MS (5-95%) M/Z: M^+1 *obs* = 495.4; t_R = 10.45.

[00201] 4-(3-Quinolin-8-yl-ureido)-*N*-thiazol-2-yl-benzenesulfonamide

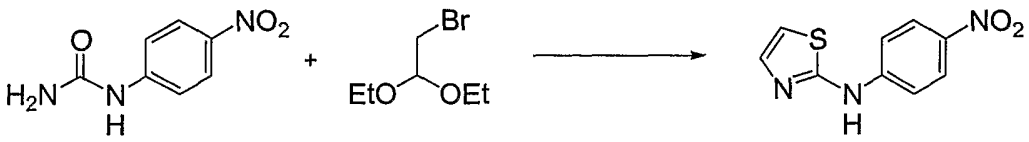


Method A: To a solution of sulfathiazole (102 mg, 0.40 mmol) and *N,N*-diisopropylethylamine (0.17 mL, 0.95 mmol) in acetonitrile (10 mL) was added a 20% phosgene solution in toluene (20% w/w in toluene, 1 mL). The reaction mixture was stirred under rflux for 2 h. The excess of phosgene and solvent were evaporated *in vacuo* and coevaporated with acetonitrile (5 mL). Then, the crude product was suspended in acetonitrile (5 mL), and a solution of 8-aminoquinoline (58 mg, 0.40 mmol) in acetonitrile (1 mL) was

added. The resulting mixture was stirred at reflux for 16 h. After cooling to RT, the reaction mixture was filtered and washed with acetonitrile (5 mL), water (2 x 5 mL) and diisopropylether (5 mL). The urea precipitated during the washing steps and was collected by filtration. The solid was washed with water (5 mL) and diisopropylether (5 mL) and dried *in vacuo* to give the product (18 mg, 11%). ^{1}H-NMR (DMSO-d_6) δ 10.24 (s, 1H), 9.80 (s, 1H), 8.94-8.93 (m, 1H), 8.57-8.55 (m, 1H), 8.42-8.40 (m, 1H), 7.76-7.57 (m, 7H), 7.25-7.24 (m, 1H), 6.82-6.81 (m, 1H). LC/MS (5-95%) M/Z: M^+1 *obs* = 424.6; t_R = 8.44.

Method B: To a solution of 8-aminoquinoline (72 mg, 0.50 mmol) in acetonitrile (5 mL) was added diphosgene (66 µL, 0.55 mmol). The mixture was stirred under reflux for 2 h. Then, sulfathiazole (125 mg, 0.49 mmol) and triethylamine (167 µL, 1.12 mmol) were added. The mixture was stirred under reflux for another 2 h and then allowed to reach ambient temperature overnight. Water (5 mL) was added, and the solid was filtered off, washed with water and cold acetonitrile and dried *in vacuo*.

[00202] (4-Nitrophenyl)-thiazol-2-yl-amine



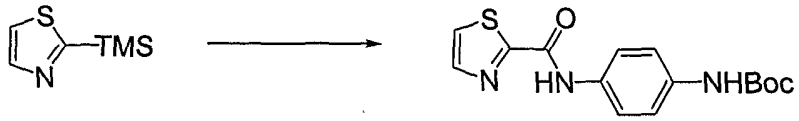
To a suspension of 1-(4-nitrophenyl)-2-thiourea (5.00 g, 25.4 mmol) in acetic acid (40 mL) was added bromoacetaldehyde diethyl acetal (3.94 mL, 25.4 mmol) at RT. The resulting mixture was heated to 100 °C for 2h. After cooling to RT, the solvent was

removed *in vacuo*. The residue was diluted with 1M NaOH (100 mL) and EtOAc (100 mL). The phases were separated, and the aqueous phase was extracted with EtOAc (2 x 100 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated. Purification by column chromatography (20-80% EtOAc in hexanes) afforded the product as a yellow solid (2.75 g, 49%). ^{1}H-NMR (400 MHz, DMSO-d_6) δ 11.02 (s, , 8.231H), 8.23 (d, J = 9.3 Hz, 2H), 7.85 (d, J = 9.3 Hz, 2H), 7.41 (d, J = 3.6 Hz, 1H), 7.15 (d, J = 3.6 Hz, 1H). LC/MS (10-99%) M/Z: M^+1 *obs* = 222.1; t_R = 2.50 min.

[00203] ***N*-Thiazol-2-yl-benzene-1,4-diamine**

A mixture of 4-Nitrophenyl)-thiazol-2-yl-amine (917 mg, 4.15 mmol) and tin(II) chloride (2.36, 12.5 mmol) in EtOH (40 mL) and 1M HCl (40 mL) was heated to 80 °C for 6h. After cooling to RT, water (100 mL) and EtOAc (100 mL) were added and the phases were separated. The aqueous phase was neutralized by addition of 1M $NaHCO_3$ and extracted with EtOAc (4 x 150 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated. The residue was filtered through a silica pad (hexanes:EtOAc, 1:1), and the filtrate was concentrated to give the product as a yellow-white solid (340 mg, 39%). ^{1}H-NMR (400 MHz, DMSO-d_6) δ 9.56 (s, 1H), 7.21 (d, J = 6.6 Hz, 2H), 7.12 (d, J = 3.6 Hz, 1H), 6.70 (d, J = 3.7 Hz, 1H), 6.53 (d, J = 6.6 Hz, 2H), 4.81 (s, 2H). LC/MS (10-99%) M/Z: M^+1 *obs* = 192.3; t_R = 0.39 min.

[00204] **{4-[(Thiazole-2-carbonyl)-amino]-phenyl}-carbamic acid *tert*-butyl ester**

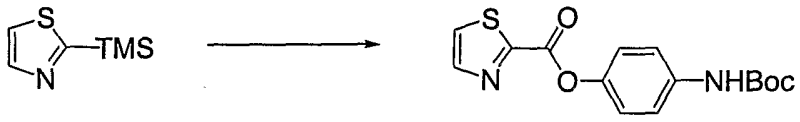


To a solution of 2-TMS-thiazole (2.25 mL, 14.1 mmol) in DCM (5 mL) at 0 °C was slowly added a solution of phosgene in toluene (20%, 7.45 mL, 14. 1 mmol) over 15 Min. After stirring for 2h at RT, the resulting solution was slowly added *via* syringe to a solution of *N*-BOC-1,4-phenylenediamine (4.42 g, 21.2 mmol) and pyridine (2.3 mL, 28.2 mmol) in DCM (100 mL) at 0 °C. After stirring for 20 h at RT, the reaction mixture was quenched by addition of sat. $NaHCO_3$ (100 mL), EtOAc (150 mL) was added, and the phases were separated. The aqueous phase was extracted with EtOAc (2 x 75 mL), and the combined organic extracts were dreid over $MgSO_4$ and concentrated *in vacuo*. Purification by column chromatography (10-50% EtOAc in hexanes) afforded the product as an orange solid (452 mg, 10%). ^{1}H-NMR (400 MHz, DMSO-d_6) δ 10.66 (s, 1H), 9.34 (s, 1H), 8.12 (d, J = 3.1 Hz, 1H), , 8.09 (d, J = 3.1 Hz, 1H), 7.72 (d, J = 7.0 Hz, 2H), 7.42 (d, J = 8.9 Hz, 2H), 1.48 (s, 9H). LC/MS (10-99%) M/Z: M^+1 *obs* = 320.3; t_R = 2.90 min.

[00205] **Thiazole-2-carboxylic acid (4-amino-phenyl)-amide**

To a solution of the *N*-BOC-protected amine (452 mg, 1.42 mmol) in DCM (2.5 mL) was added TFA (2.5 mL). After stirring for 1h at RT, the reaction mixture was poured into sat. $NaHCO_3$ (50 mL) and extracted with EtOAc (2 × 50 mL). The combined organic extracts were dried over $MgSO_4$, concentrated *in vacuo* and used without further purification in the next reaction. ^{1}H-NMR (400 MHz, DMSO-d_6) δ 10.26 (s, 1H), 7.99 (d, J = 3.1 Hz, 1H), 7.97 (d, J = 3.1 Hz, 1H), 7.37 (d, J = 8.8 Hz, 2H), 6.45 (d, J = 8.8 Hz, 2H), 4.92 (s, 2H). LC/MS (10-99%) M/Z: M^+1 *obs* = 220.3; t_R = 0.57 min.

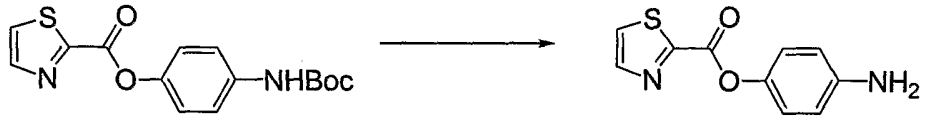
[00206] Thiazole-2-carboxylic acid 4-*tert*-butoxycarbonylamino-phenyl ester



To a solution of 2-TMS-thiazole (2.25 mL, 14.1 mmol) in DCM (5 mL) at 0 °C was slowly added a solution of phosgene in toluene (20%, 7.45 mL, 14. 1 mmol) over 15 Min. After stirring for 2h at RT, the resulting solution was slowly added *via* syringe to a solution of *N*-BOC-4-hydroxyaniline (4.39 g, 21.2 mmol) and pyridine (2.3 mL, 28.2 mmol) in DCM (100 mL) at 0 °C. After stirring for 20 h at RT, the reaction mixture was quenched by addition of sat. $NaHCO_3$ (100 mL), EtOAc (150 mL) was added, and the phases were separated. The aqueous phase was extracted with

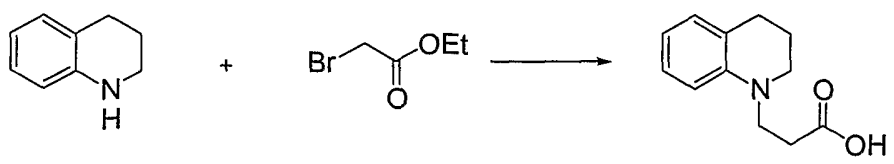
EtOAc (2 x 75 mL), and the combined organic extracts were dried over $MgSO_4$ and concentrated *in vacuo*. Purification by column chromatography (10-50% EtOAc in hexanes) afforded the product as a green solid (518 mg, 12%). ^{1}H-NMR (400 MHz, DMSO-d_6) δ 9.49 (s, 1H), 8.29 (d, J = 3.0 Hz, 1H), 8.22 (d, J = 3.0 Hz, 1H), 7.53 (d, J = 8.9 Hz, 2H), 7.23 (d, J = 6.9 Hz, 2H), 1.48 (s, 9H). LC/MS (10-99%) M/Z: M^+1 *obs* = 321.1; t_R = 2.94 min.

[00207] Thiazole-2-carboxylic 4-amino-phenyl ester



To a solution of the *N*-BOC-protected amine (515 mg, 1.61 mmol) in DCM (2.5 mL) was added TFA (2.5 mL). After stirring for 1h at RT, the reaction mixture was poured into sat. $NaHCO_3$ (50 mL) and extracted with EtOAc (2 x 50 mL). The combined organic extracts were dried over $MgSO_4$, concentrated *in vacuo* and used without further purification in the next reaction. ^{1}H-NMR (400 MHz, DMSO-d_6) δ 8.25 (d, J = 3.0 Hz, 1H), 8.19 (d, J = 3.0 Hz, 1H), 6.94 (d, J = 8.8 Hz, 2H), 6.59 (d, J = 8.8 Hz, 2H), 5.17 (s, 2H). LC/MS (10-99%) M/Z: M^+1 *obs* = 221.1; t_R = 0.59 min.

[00208] 3-(3,4-Dihydro-2*H*-quinolin-1-yl)-propionic acid

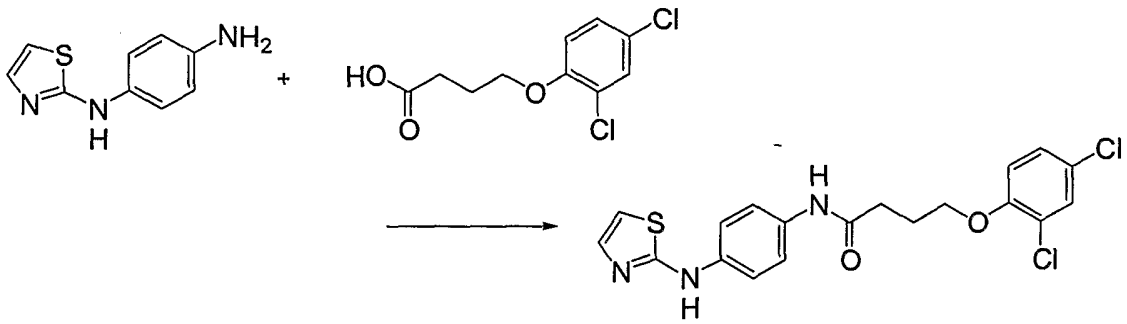


A solution of ethyl bromoacetate (0.75 g, 4.5 mmol) and 1,2,3,4-tetrahydroquinoline (0.57 mL, 4.5 mmol) in DMF (10 mL) was microwaved at 200°C for 300 s. The solvent was removed *in vacuo*, and the residue was redissolved in MeOH (12.5 mL). 1M NaOH (12.5 mL) was added, and the reaction mixture was heated to 80 °C for 2.5 h. After cooling to RT, EtOAc (30 mL) and water (30 mL) were added, the phases were separated, the aqueous layer was acidified to pH 2-3 by addition of 6M HCl and extracted with EtOAc (3 × 30 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated *in vacuo* to give the product (640 mg, 75%) as a white solid. ^{1}H-NMR (400 MHz, DMSO-d_6) δ 6.94-6.88 (m, 2H), 1H), 6.38 (d, J = 8.2 Hz, 1H), 3.98 (s, 2H), 3.32 (t, J = 5.6 Hz, 2H), 2.69 (t, J = 6.3 Hz, 2H), 1.92-1.84 (m, 2H). LC/MS (10-99%) M/Z: M^+1 *obs* = 192.3; t_R = 2.39 min.

[00209] General procedure 4 for amide couplings:

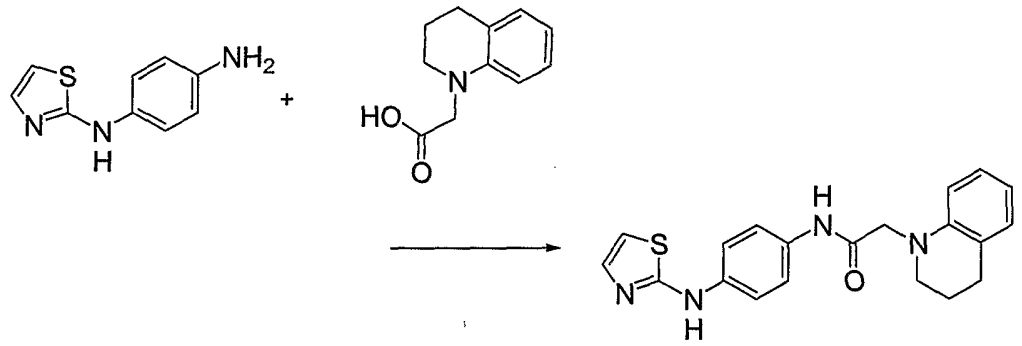
A mixture of the corresponding acid (0.2 mmol), amine (0,2 mmol), triethylamine (28 µL, 0.2 mmol) and HATU (76 mg, 0.2 mmol) in pyridine (0.5 mL) was microwaved at 200 °C for 420 s. The reaction mixture was diluted with 50% DMSO/MeOH (0.5 mL), filtered and purified by HPLC (gradient of 10-99% CH_3CN/water).

[00210] 4-(2,4-Dichloro-phenoxy)-*N*-[4-(thiazol-2-ylamino)-phenyl]-butyramide



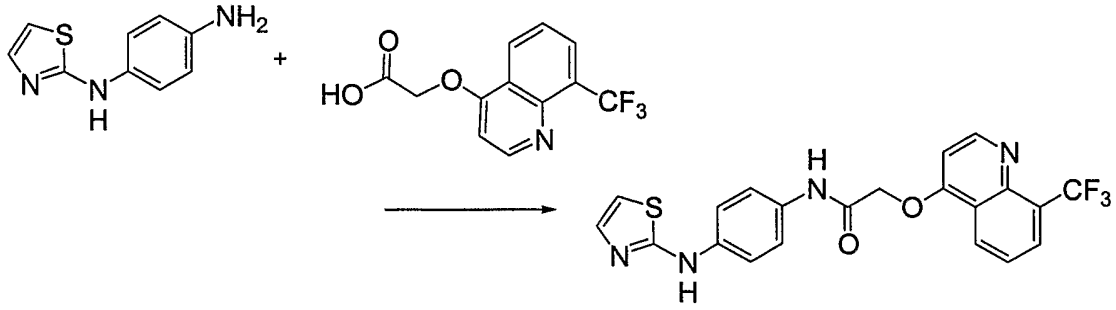
Synthesized according to **general procedure 4**. ^{1}H-NMR (400 MHz, DMSO-d_6) δ 10.09 (s, 1H), 9.86 (s, 1H), 7.58-7.50 (m, 5H), 7.37 (dd, J = 8.9, 2.6 Hz, 1H), 7.23-7.19 (m, 2H), 6.86 (d, J = 3.7 Hz, 1H), 4.12 (t, J = 6.3 Hz, 2H), 2.56-2.45 (m, 2H), 2.09-2.02 (m, 2H). LC/MS (10-99%) M/Z: M^+1 *obs* = 422.1; t_R = 2.67 min.

[00211] 2-(3,4-Dihydro-2*H*-quinolin-1-yl)-*N*-[4-thiazol-2-ylamino)-phenyl]-acetamide



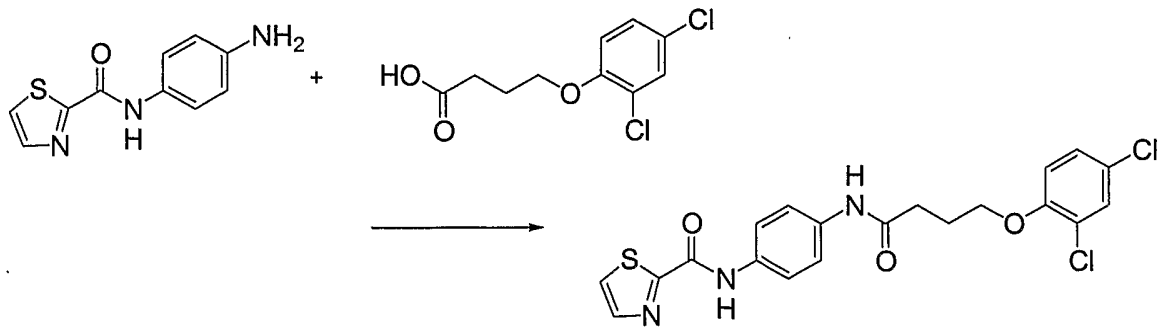
Synthesized according to **general procedure 4**. ^{1}H-NMR (400 MHz, DMSO-d_6) δ 10.15 (s, 1H), 9.88 (s, 1H), 7.56-7.51 (m, 4H), 7.23 (d, J = 3.7 Hz, 1H), 6.95-6.87 (m, 3H), 6.50 (td, J = 7.3, 0.9 Hz, 1H), 6.44 (d, J = 8.1 Hz, , 4.02 (s, 2H), 3.42 (t, J = 5.6 Hz, 2H), 2.72 (t, J = 6.3 Hz, 2H), 1.96-1.90 (m, 2H). LC/MS (10-99%) M/Z: M^+1 *obs* = 365.1; t_R = 2.41 min.

[00212] ***N*-[4-(Thiazol-2-ylamino)-phenyl]-2-(8-trifluoromethyl-quinolin-4-yloxy)-acetamide**



Synthesized according to **general procedure 4**. ^{1}H-NMR (400 MHz, DMSO-d_6) δ 10.23 (s, 1H), 10.19 (s, 1H), 8.90 (d, J = 5.3 Hz, 1H), 8.63 (d, J = 7.6 Hz, 1H), 8.22 (d, J = 6.8 Hz, 1H), 7.75 (t, J = 7.9 Hz, 1H), 7.61-7.52 (m, 4H), 7.24 (d, J = 3.7 Hz, 1H), 7.17 (d, J = 5.3 Hz, 1H), 6.89 (d, J = 3.7 Hz, 1H), 5.08 (s, 2H) . LC/MS (10-99%) M/Z: M^+1 *obs* = 445.3; t_R = 2.29 min.

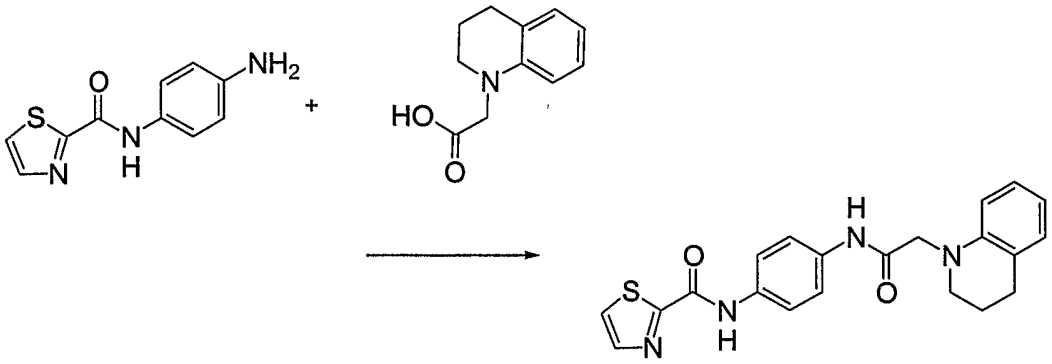
[00213] **Thiazole-2-carboxylic acid {4-[4-(2,4-dichloro-phenoxy)-butyrylamino]phenyl}-amide**



Synthesized according to **general procedure 4**. ^{1}H-NMR (400 MHz, DMSO-d_6) δ H NMR (400 MHz, DMSO-d6) δ 10.72 (s, 1H), 9.98 (s, 1H), 8.13 (d, J = 3.1 Hz, 1H), 8.10 (d, J = 3.1 Hz, 1H), 7.79-

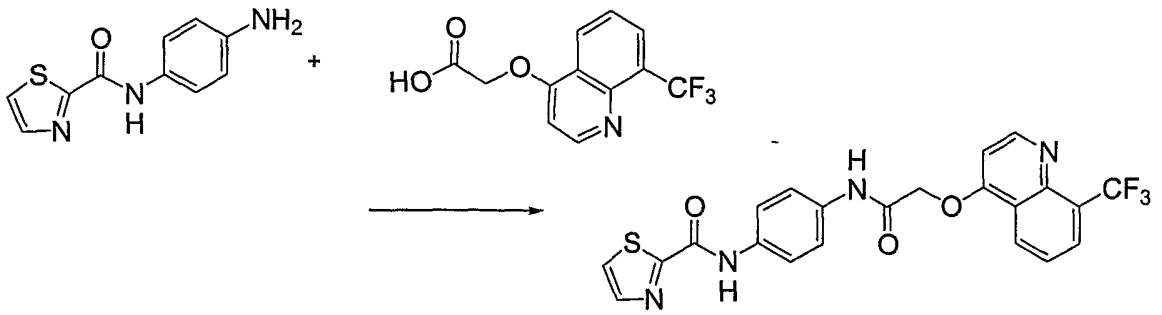
7.75 (m, 2H), 7.59-7.56 (m, 3H), 7.37 (dd, *J* = 8.9, 2.6 Hz, 1H), 7.20 (d, *J* = 8.9 Hz, 1H), 4.13 (t, *J* = 6.3 Hz, 2H), 3.37-3.31 (m, 2H), 2.09-2.03 (m, 2H). LC/MS (10-99%) M/Z: M^+1 *obs* = 450.3; t_R = 3.34 min.

[00214] Thiazole-2-carboxylic acid [4-(2,3,4-dihydro-2*H*-quinolin-1-yl-acetylamino)-phenyl]-amide



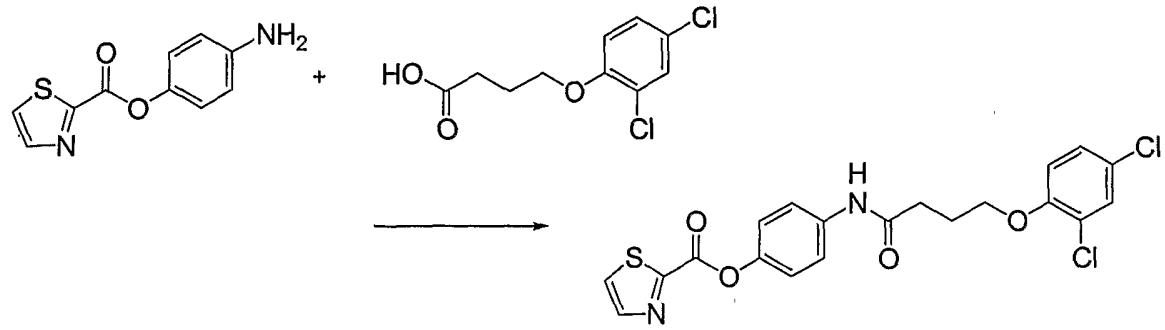
Synthesized according to **general procedure 4**. ^{1}H-NMR (400 MHz, DMSO-d_6) δ H NMR (400 MHz, DMSO-d6) δ 10.73 (s, 1H), 10.00 (s, 1H), 8.13 (d, *J* = 3.1 Hz, 1H), 8.10 (d, *J* = 3.1 Hz, 1H), 7.78 (d, *J* = 9.0 Hz, 2H), 7.58 (d, *J* = 9.0 Hz, 2H), 6.96-6.89 (m, 2H), 6.52-6.44 (m, 2H), 4.05 (s, 2H), 3.42 (t, *J* = 5.6 Hz, 2H), 2.73 (t, *J* = 6.3 Hz, 2H), 1.96-1.90 (m, 2H). LC/MS (10-99%) M/Z: M^+1 *obs* = 393.1; t_R = 3.07 min.

[00215] Thiazole-2-carboxylic acid {4-[2-(8-triffuoromethyl-quinolin-4-yloxy)-acetylamino]-phenyl}-amide



Synthesized according to **general procedure 4**. ^{1}H-NMR (400 MHz, DMSO-d_6) δ 10.78 (s, 1H), 10.34 (s, 1H), 8.90 (d, J = 5.3 Hz, , 8.63 (d, J = 8.1 Hz, 1H), 8.22 (d, J = 7.0 Hz, 1H), 8.14 (d, J = 3.1 Hz, 1H), 8.11 (d, J = 3.1 Hz, 1H), 7.84-7.82 (m, 2H), 7.76 (t, J = 7.9 Hz, 1H), 7.63-7.61 (m, 2H), 7.18 (d, J = 5.3 Hz, 1H), 5.11 (s, 2H). LC/MS (10-99%) M/Z: M^+1 *obs* = 473.1; t_R = 2.82 min.

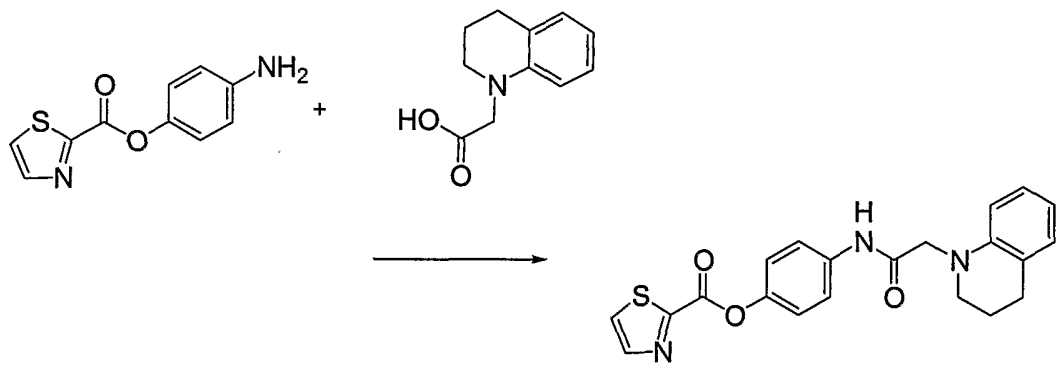
[00216] Thiazole-2-carboxylic acid 4-[4-(2,4-dichloro-phenoxy)-butyrylamino]-phenyl ester



Synthesized according to **general procedure 4**. ^{1}H-NMR (400 MHz, DMSO-d_6) δ H NMR (400 MHz, DMSO-d6) δ 10.11 (s, 1H), 8.30 (d, J = 3.0 Hz, 1H), 8.24 (d, J = 3.0 Hz, 1H), 7.71-7.67 (m, 2H), 7.58 (d, J = 2.6 Hz, 1H), 7.38 (dd, J = 8.9, 2.6 Hz, 1H), 7.30-7.26 (m, 2H), 7.21 (d, J = 8.9 Hz, 1H), 4.14 (t, J = 6.3 Hz, 2H),

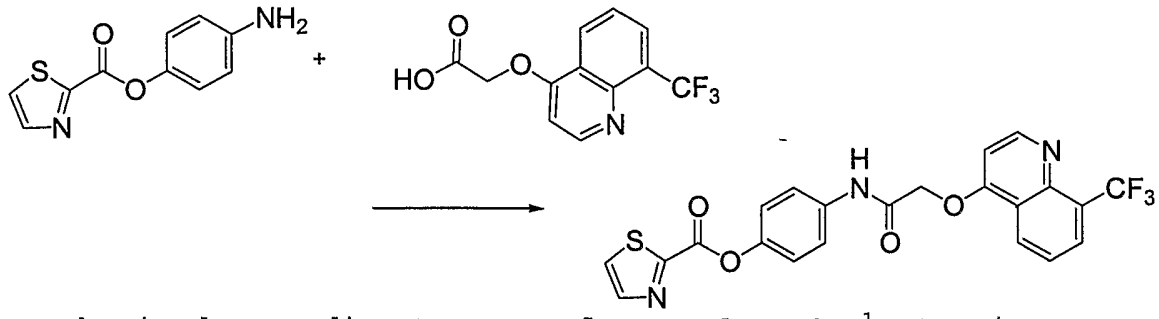
2.55 (t, 2H), , 2.34-2.30 (m, 2H). LC/MS (10-99%) M/Z: M^+1 *obs* = 451.0; t_R = 3.58 min.

[00217] Thiazole-2-carboxylic acid 4-(2,3,4-dihydro-2*H*-quinolin-1-yl-acetylamino)-phenyl ester



Synthesized according to **general procedure 4.** ^{1}H-NMR (400 MHz, DMSO-d_6) δ H NMR (400 MHz, DMSO-d6) δ 10.14 (s, 1H), 8.30 (d, J = 3.0 Hz, 1H), 8.23 (d, J = 3.0 Hz, 1H), 7.72-7.68 (m, 2H), 7.31-7.27 (m, 2H), 6.96-6.90 (m, 2H), 6.51 (dt, J = 9.7, 3.9 Hz, 1H), 6.45 (d, J = 8.1 Hz, 1H), 4.08 (s, 2H), 3.43 (t, J = 5.6 Hz, 2H), 2.73 (t, J = 6.3 Hz, 2H), 1.96-1.90 (m, 2H). LC/MS (10-99%) M/Z: M^+1 *obs* = 394.2; t_R = 3.30 min.

[00218] Thiazole-2-carboxylic acid 4-[2-(8-triffuoromethyl-quinolin-4-yloxy)-acetylamino]-phenyl ester



Synthesized according to **general procedure 4**. ^{1}H-NMR (400 MHz, DMSO-d_6) δ H NMR (400 MHz, DMSO-d6) δ 10.47 (s, 1H), 8.90 (d, J = 5.3 Hz, 1H), 8.63 (d, J = 7.7 Hz, 1H), 8.31 (d, J = 3.0 Hz, 1H), 8.24 (d, J = 3.0 Hz, 1H), 8.22 (d, J = 7.0 Hz, 1H), 7.78-7.71 (m, 3H), 7.36-7.32 (m, 2H), 7.19 (d, J = 5.3 Hz, 1H), 5.14 (s, 2H). LC/MS (10-99%) M/Z: M^+1 *obs* = 474.0; t_R = 3.06 min.

[00239] The analytical data for selected compounds recited in **FIGURE 1** are shown below in Table 2.

Table 2

Cmpd #	LC/MS M^+	RT (min)
4	390.20	2.51
36	440.00	4.30
38	441.00	2.43
43	388.00	2.56
63	447.20	3.06
74	408.00	3.95
91	440.30	2.96
110	454.10	2.97
124	374.00	2.59
127	428.00	2.87
142	495.00	3.23
143	486.20	2.96
144	453.00	3.01
147	445.20	3.23
155	467.20	3.11
157	403.00	3.16
161	400.00	2.63
162	411.00	2.18
163	411.00	1.99
164	401.00	2.18
165	425.00	2.13
166	411.00	2.86
167	414.00	2.81
168	440.00	2.90
170	442.20	1.85
171	427.10	3.09
172	402.30	2.53
173	447.30	3.03
174	427.30	2.61
175	404.00	2.55
186	408.00	2.62
193	475.00	3.11
225	426.00	2.86
232	480.00	3.16
233	501.20	3.29
234	498.20	3.25
235	484.00	3.49
236	498.20	3.51
237	511.20	3.26
238	509.20	3.26
239	511.20	3.31
240	481.00	3.24
241	511.20	3.34
242	432.20	2.97
243	453.00	3.12
244	450.00	3.07
245	436.20	3.32
246	463.20	3.09
247	461.20	3.05
248	463.20	3.13
249	433.20	3.03
250	428.20	2.89
251	461.20	3.07
252	479.00	3.25
253	479.00	3.12
254	466.00	3.10
255	515.00	3.84
256	463.20	3.15
257	449.20	3.10
258	454.00	3.04
259	411.00	3.11
260	446.20	3.02
261	469.00	3.20
262	452.00	3.41
263	397.00	3.04
264	450.00	3.37

Cmpd #	LC/MS M	RT (min)
265	463.20	3.19
266	469.00	3.07
267	473.00	3.19
268	483.00	3.17
269	405.20	2.70
270	415.00	2.59
271	420.80	2.72
272	401.00	2.56
273	406.00	2.55
274	411.20	2.81
275	417.20	2.90
276	397.20	2.76
277	427.20	2.96
278	402.20	2.75
279	458.20	2.98
280	474.20	1.98
281	389.00	3.05
282	431.20	3.15
283	465.80	3.14
284	481.00	3.21
285	487.00	3.27
286	484.20	3.21
287	470.20	3.46
288	484.20	3.47
289	497.20	3.21
290	495.20	3.20
291	497.20	3.24
292	466.80	3.16
293	497.20	3.28
294	472.20	3.09
295	432.20	2.79
296	447.20	2.90
297	453.20	2.95
298	463.20	2.92
299	461.40	2.89
300	463.20	3.00
301	433.40	2.85
302	438.20	2.79
303	389.20	2.35
304	374.60	2.92
305	417.00	3.06
306	470.20	3.07
307	470.00	3.34
308	485.20	3.08
309	483.00	3.15
310	452.00	2.95
311	536.20	3.48
312	592.20	3.55
313	596.20	3.62
314	514.20	3.27
315	526.20	3.31
316	542.40	3.53

Cmpd #	LC/MS M	RT (min)
317	562.40	3.53
318	500.00	3.37
319	527.20	3.37
320	487.00	3.09
321	455.80	3.31
322	481.00	3.05
323	404.20	2.49
324	397.20	2.37
325	471.20	3.66
326	457.40	3.60
327	471.20	3.74
328	485.40	3.78
329	471.20	3.81
330	485.40	3.87
331	473.20	3.42
332	417.20	3.22
333	431.40	3.36
334	443.40	3.42
335	459.40	3.72
336	493.20	3.67
337	489.00	3.69
338	432.20	3.00
339	417.20	2.81
340	435.20	2.43
341	441.20	2.57
342	426.00	2.39
343	409.20	2.69
344	415.00	2.82
345	400.00	2.65
346	459.20	3.10
347	465.00	3.18
348	461.20	3.18
349	466.80	3.26
350	452.00	3.07
351	421.00	2.55
352	427.00	2.69
353	411.60	2.51
354	385.00	2.62
355	391.20	2.69
356	376.00	2.55
357	410.20	2.62
358	476.20	3.22
359	482.20	3.26
360	467.00	3.12
361	410.20	2.78
362	467.90	4.06
363	474.86	4.05
364	459.86	3.87
365	437.89	3.79
366	467.90	4.10
367	474.85	4.23
368	459.84	3.95

Cmpd #	LC/MS M	RT (min)
369	475.99	4.30
370	465.92	4.13
371	460.95	3.95
372	467.96	4.00
373	451.92	3.83
374	466.90	4.29
375	451.95	4.10
376	424.90	3.63
377	438.90	3.93
378	433.20	2.80
379	433.20	2.80
380	424.00	2.85
381	443.20	2.94
382	449.00	3.10
383	434.00	2.96
384	487.20	2.57
385	472.20	2.41
386	439.20	2.71
387	445.40	2.84
388	430.10	2.79
389	425.20	2.89
390	431.00	2.98
391	416.20	2.82
392	429.20	3.27
393	420.20	3.15
394	537.20	3.58
395	528.20	3.50
396	525.40	3.45
397	519.00	3.40
398	510.20	3.29
399	500.00	3.19
400	514.00	3.04
401	455.40	3.74
402	521.40	3.79
403	459.00	1.70
404	408.20	2.63
405	414.20	2.74
406	399.00	2.60
407	422.20	2.89
408	428.20	2.96
409	413.00	2.84
410	429.50	2.68
411	399.10	2.51
412	417.10	2.78
413	483.30	3.08
414	413.30	2.83
415	411.30	2.83
416	427.00	2.90
417	459.00	2.32
418	509.00	3.32
419	475.00	3.10
420	500.00	3.23

Cmpd #	LC/MS M+	RT (min)
421	500.00	3.21
422	470.00	3.19
423	447.00	3.05
424	433.00	2.86
425	399.00	2.58
426	451.00	2.81
428	502.00	4.42
429	432.00	4.29
430	486.00	4.41
431	486.00	4.36
432	436.00	4.09
439	462.00	4.54
440	434.00	4.09
441	424.00	4.19
442	415.00	3.82
443	432.00	3.72
444	454.00	4.19
448	404.00	4.15
471	100.00	3.30
472	497.20	3.60
473	443.40	3.15
474	100.00	3.37
475	158.00	2.98
476	436.00	4.12
477	432.00	4.49
478	418.00	4.27
479	454.00	4.12
480	420.00	3.97
481	442.00	4.20
482	537.00	3.40
484	456.00	4.07
485	470.00	4.30
486	466.00	4.02
487	434.00	3.92
488	484.00	4.44
489	447.00	3.47
490	444.00	3.69
491	472.00	4.52
492	520.00	4.47
493	458.00	3.70
494	509.00	3.60
495	445.00	3.84
496	461.00	3.82
497	464.00	4.15
498	461.00	4.00
499	432.00	3.95
500	504.00	4.41
501	504.00	4.44
502	472.00	4.44
503	520.00	4.38
504	473.00	3.45
505	471.00	3.62

Cmpd #	LC/MS M+	RT (min)
506	416.00	3.45
507	462.00	3.38
508	454.00	3.80
509	459.00	3.99
510	451.00	3.26-
511	475.00	4.02
512	443.00	5.27
513	492.00	5.43
514	435.00	3.63
515	477.00	3.74
516	487.00	4.39
517	521.00	4.39
518	500.00	4.19
519	482.00	3.77
520	470.00	3.87
521	488.00	4.30
522	470.00	3.94
523	451.00	4.01
524	453.00	4.02
525	480.00	4.07
526	470.00	3.89
527	463.00	3.95
528	521.00	4.39
529	482.00	4.04
530	502.00	4.46
531	454.00	4.15
532	447.00	3.74
533	433.00	3.40
534	460.00	3.32
535	474.00	3.50
536	434.00	3.34
537	476.00	4.12
538	455.00	3.41
539	441.00	5.36
540	442.00	3.12
541	510.00	4.44,
542	450.00	5.70
543	443.00	4.72
544	451.00	4.31
545	441.00	5.10
546	444.00	3.81
547	444.00	4.72
548	426.00	3.57
549	459.00	3.95
550	442.30	0.57
551	381.10	2.36
552	456.30	2.98
553	492.30	3.17
554	424.10	2.46
555	466.10	3.07
556	400.30	2.70
557	479.10	2.23

Cmpd #	LC/MS M+	RT (min)
558	506.10	3.12
559	436.00	2.55
560	418.00	2.68
561	450.00	2.79
562	429.00	2.71
563	415.00	2.59
564	460.00	3.63
565	462.00	5.07
566	436.00	3.69
567	448.00	3.45
568	523.00	5.15
569	448.00	3.57
570	504.00	4.00
571	500.00	4.14
572	448.00	3.52
573	477.00	3.67
574	465.00	4.97
575	467.00	2.58
576	444.00	4.38
577	490.00	4.79
578	399.10	2.29
579	413.30	2.43
580	400.30	1.73
581	428.30	1.88
582	427.30	2.65
583	427.30	2.51
584	477.10	2.93
585	431.30	2.55
586	411.10	2.75
587	414.30	2.86
588	442.00	4.89
589	470.00	3.42
590	260.10	3.20
591	246.30	3.10
592	430.30	2.68
593	234.10	2.71
594	416.30	2.60
595	425.10	1.79
596	425.10	1.78
597	457.30	2.18
598	444.00	2.84
599	464.00	3.07
600	484.00	3.10
601	494.00	3.04
602	500.00	3.00
603	500.00	3.05
604	530.00	3.18
605	470.00	4.51
606	473.00	4.66
607	457.00	2.78
608	418.00	3.09
609	397.00	2.01

Cmpd #	LC/MS M⁻	RT (min)
610	429.00	2.14
611	486.00	3.29
612	500.00	3.37
613	474.00	3.01
614	446.00	3.68
615	441.00	1.87
616	442.00	2.29
617	443.00	2.67
618	442.00	2.21
619	430.00	3.04
620	442.00	2.77
621	430.00	2.80
622	430.00	3.06
623	414.00	1.93
624	439.00	2.19
625	443.00	2.31
626	425.00	2.11
627	434.00	2.85
628	464.00	2.93
629	429.00	2.78
630	433.00	2.71
631	449.00	2.87
632	497.00	3.03
633	485.00	3.28
634	442.00	2.29
635	442.00	2.25
636	473.00	2.62
637	475.00	2.93
638	442.00	2.91
639	442.00	3.05
640	475.00	2.12
641	459.00	2.02
642	459.00	1.84
643	430.00	2.14
644	509.00	2.43
645	413.00	2.55
646	399.00	2.36
647	528.00	2.30
648	563.30	4.71
649	563.30	4.71
650	487.30	3.13
651	517.10	3.28
652	517.10	3.32
653	528.90	3.45
654	308.10	3.25
655	497.10	3.12
656	489.00	1.98
657	445.00	2.64

Cmpd #	LC/MS M⁻	RT (min)
658	429.00	1.92
659	487.00	3.41
660	459.00	2.83
682	480.00	3.19
683	438.00	-
684	426.00	
685	426.00	
686	440.00	
687	464.00	
688	440.00	
689	444.00	
690	456.00	
691	460.00	
693	440.00	
694	443.00	2.99
695	443.00	2.83
696	463.00	3.08
697	457.00	2.44
698	471.00	2.57
699	443.00	2.48
700	471.00	2.49
701	576.00	3.54
702	628.00	3.67
703	610.00	3.69
704	611.00	3.68
705	594.00	3.52
706	555.00	3.64
707	515.00	3.36
708	447.00	2.82
709	443.00	2.00
710	457.00	3.10
711	457.00	3.13
712	443.00	3.13
713	443.00	3.16
714	523.00	2.64
715	463.00	3.04
716	443.00	1.92
717	367.00	0.68
718	383.00	0.62
719	403.00	1.68
720	381.00	1.17
721	461.00	2.90
722	443.00	2.42
723	461.00	2.84
724	461.00	2.84
725	429.00	2.76
726	443.00	2.67
727	505.00	3.20

Cmpd #	LC/MS M⁻	RT (min)
728	395.00	1.55
729	395.00	1.68
730	409.00	1.82
731	417.00	1.65
732	399.00	1.40
733	417.00	1.56
734	445.00	2.70
735	445.00	2.70
736	409.00	1.40
737	424.00	0.86
738	424.00	0.67
739	395.00	1.49
740	447.00	2.41
741	443.00	2.58
742	495.00	3.00
743	445.00	2.70
744	461.00	2.80
745	452.00	2.50
746	449.00	2.70
747	444.00	2.88
748	424.60	4.37
749	424.60	4.54
750	424.60	8.44
751	423.60	5.40
752	494.60	7.21
753	448.60	5.50
754	459.40	9.11
755	424.60	5.39
756	424.60	5.28
757	424.60	4.55
758	424.40	4.92
759	495.40	10.29
760	422.00	2.66
761	475.00	2.95
762	475.00	2.95
763	462.00	2.94
764	429.00	2.76
765	443.00	2.67
766	457.00	3.03
767	443.00	1.75
768	503.00	1.74
769	365.00	2.42
770	445.00	2.29
771	450.00	3.59
772	393.00	3.07
773	473.00	2.82
774	495.00	3.09

[00325] **ASSAYS FOR DETECTING AND MEASURING NaV INHIBITION PROPERTIES OF COMPOUNDS**

[00326] A) Optical methods for assaying NaV inhibition properties of compounds:

[00327] 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).

[00328] B) VIPR® optical membrane potential assay method with chemical stimulation

[00329] Cell Handling and Dye Loading

[00330] 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 □L 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.

[00331] Analysis of VIPR® Data:

[00332] 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:

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

[00333] 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.

[00334] 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

[00335] Cell Culture

[00336] 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.

[00337] C) VIPR® optical membrane potential assay method with electrical stimulation

[00338] 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.

[00339] 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.

[00340] ***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_2O
Hank's Balanced Salt Solution (Hyclone #SH30268.02) supplemented with 10 mM HEPES (Gibco #15630-080)

[00341] ***Loading protocol:***

[00342] **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.

[00343] 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 .

[00344] 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.

[00345] 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.

[00346] Reagents

[00347] 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

[00348] 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.

[00349] Data Analysis

[00350] 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:

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

[00351] 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.

[00352] 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.

[00353] ELECTROPHYSIOLOGY ASSAYS FOR NaV ACTIVITY AND INHBITION OF TEST COMPOUNDS

[00354] 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.

[00355] VOLTAGE-CLAMP assay in DRG neurons

[00356] 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).

[00357] 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.

[00358] Solutions

[00359] 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.

[00360] 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 x 10^{-3}).

[00361] CURRENT-CLAMP assay for NaV channel inhibition activity of compounds

[00362] 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.

[00363] Compounds of the invention as depicted generally herein and in Table 2 were found to inhibit voltage-gated sodium channels at 25.0 μM or less.

[00364] **ASSAYS FOR DETECTING AND MEASURING CaV INHIBITION PROPERTIES OF COMPOUNDS**

[00365] A) Optical methods for assaying CaV inhibition properties of compounds:

[00366] 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).

[00367] VIPR® optical membrane potential assay method with electrical stimulation

[00368] 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.

[00369] 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_2O

370mM Barium Chloride (Sigma Cat# B6394) in H_2O

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

[00370] Loading Protocol:

[00371] **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.

[00372] **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.

[00373] **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.

[00374] 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.

[00375] Assay Protocol

[00376] Insert or use electrodes into each well to be assayed.

[00377] 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.

[00378] Data Analysis

[00379] 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:

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

[00380] 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.

[00381] 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.

[00382] ELECTROPHYSIOLOGY ASSAYS FOR CaV ACTIVITY AND INHBITION OF TEST COMPOUNDS

[00383] 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.

[00384] VOLTAGE-CLAMP assay in HEK293 cells expressing CaV2.2

[00385] 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 M. 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).

[00386] 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.

[00387] Solutions

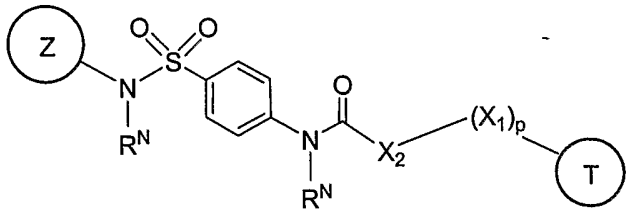
[00388] Intracellular solution (in mM): Cs-F (130), NaCl (10), $MgCl_2$ (1), EGTA (1.5), $CaCl_2$ (0.1), HEPES (10), glucose (2), pH = 7.42, 290 mOsm.

[00389] 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).

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

Claims

1. A compound of formula I-A:



I-A;

wherein:

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

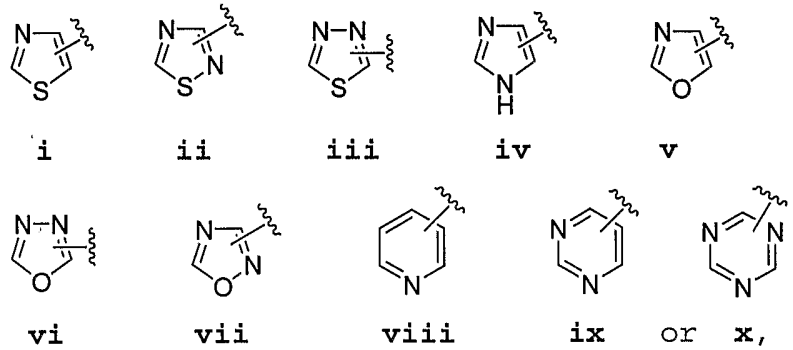
X_1 is O, S, or NR^X

p is 0 or 1;

R^X is H or R^2;

X_2 is C_{1-3} aliphatic, optionally substituted with up to 2 substituents independently selected from R^1, R^4, or R^5;

Z is selected from:



i **ii** **iii** **iv** **v**

vi **vii** **viii** **ix** or **x**,

T is a 8-14 membered aromatic or non-aromatic bicyclic or tricyclic ring, having 0-5 heteroatoms selected from O, S, N, NH, S(O) or SO_2;

wherein each of Z and T optionally comprises up to 4 substituents independently selected from R^1, R^2, R^3, R^4, or R^5;

wherein the phenylene ring attached to the sulfonyl is optionally substituted with up to 3 substituents selected from R^1 and R^2;

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

n is 0, 1 or 2;

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

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

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

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

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

$N(R^6)_2$, $N(R^5)_2$, $N(R^5R^6)$, $NR^5C(O)R^5$, $NR^6C(O)R^6$, $NR^6C(O)R^5$, $NR^6C(O)OR^6$, $NR^5C(O)OR^6$, $NR^6C(O)OR^5$, $NR^5C(O)OR^5$, $NR^6C(O)N(R^6)_2$, $NR^6C(O)NR^5R^6$, $NR^6C(O)N(R^5)_2$, $NR^5C(O)N(R^6)_2$, $NR^5C(O)NR^5R^6$, $NR^5C(O)N(R^5)_2$, $NR^6SO_2R^6$, $NR^6SO_2R^5$, $NR^5SO_2R^5$, $NR^6SO_2N(R^6)_2$, $NR^6SO_2NR^5R^6$, $NR^6SO_2N(R^5)_2$, $NR^5SO_2NR^5R^6$, $NR^5SO_2N(R^5)_2$, $N(OR^6)R^6$, $N(OR^6)R^5$, $N(OR^5)R^5$, $N(OR^5)R^6$, $P(O)(OR^6)N(R^6)_2$, $P(O)(OR^6)N(R^5R^6)$, $P(O)(OR^6)N(R^5)_2$, $P(O)(OR^5)N(R^5R^6)$, $P(O)(OR^5)N(R^6)_2$, $P(O)(OR^5)N(R^5)_2$, $P(O)(OR^6)_2$, $P(O)(OR^5)_2$, or $P(O)(OR^6)(OR^5)$;

R^5 is a cycloaliphatic, aryl, heterocyclic, or heteroaryl ring optionally substituted up to 3 R^1 substituents;

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

R^7 is a cycloaliphatic, aryl, heterocyclic, or heteroaryl ring and each R^7 is optionally substituted up to 2 substituents independently chosen from H, aliphatic, or $(CH_2)_n$-Z';

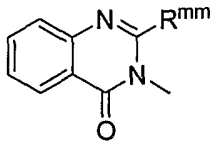
Z' is selected from halo, CN, NO_2, $C(halo)_3$, $CH(halo)_2$, $CH_2(halo)$, $-OC(halo)_3$, $-OCH(halo)_2$, $-OCH_2(halo)$,OH, S-aliphatic, S(O)-aliphatic, SO_2-aliphatic, NH_2, NH-aliphatic, $N(aliphatic)_2$, $N(aliphatic)R^8$, COOH, C(O)O(-aliphatic), or O-aliphatic; and

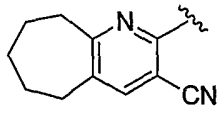
R^8 is an amino protecting group;

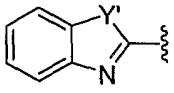
provided that:

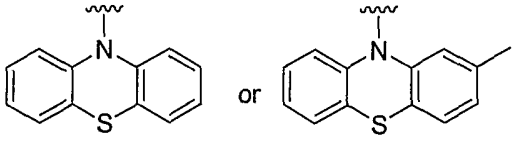
a) when both R^N are hydrogen, and T is isoindol-1,3-dione-2-yl optionally substituted with up to 4 halo atoms,

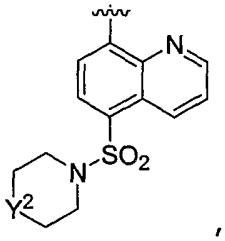
then Z is not pyridyl, thiazol-2-yl, 4-(4-methoxyphenyl)thiazol-2-yl, 2-ethyl-1,3,4-thiadiazol-5-yl, optionally substituted pyrimidin-2-yl, 5-methyl-isoxazolyl, 3,4-dimethyl-isoxazoly, or 2-methyl-isoxazolyl;

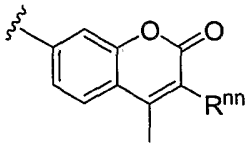
b) when both R^N are hydrogen, and T is  , optionally substituted with up to 4 halo atoms, wherein R^{mm} is phenyl optionally substituted with C_{1-4} alkyl or hydrogen, then Z is not optionally substituted pyrimidin-2-yl, 2-pyridyl, or thiazol-2-yl;

c) when both R^N are hydrogen, X_2 is $-CH_2-$, p is 1, X_1 is S, and T is  , then Z is not 3,4-dimethylisoxazolyl, pyrimidin-2-yl, thiazol-2-yl, or 4,6-dimethyl-pyrimidin-2-yl;

c) when both R^N are hydrogen, X_2 is $-CH_2-$ and X_1 is S, or X_2 is CH=CH and X_1 is absent, and T is optionally substituted  , wherein Y' is O, S, or NH, then Z is not pyrimidinyl optionally substituted with up to 2 methyl or methoxy groups, 2-pyridyl, thiazol-2-yl, 2-methoxy-pyrazin-3-yl, 3-chloro-pyridazin-6-yl, 3,4-dimethyl-isoxazolyl, or 2-ethyl-1,3,4-thiadiazol-5-yl;

d) when both R^N are hydrogen, X_2 is $-CH_2-CH_2-$, X_1 is absent, and T is  , then Z is not thiazol-2-yl, 2,6-dimethyl-pyrimidin-4-yl, or 3,4-dimethyl-isoxazol-5-yl;

e) when both R^N are hydrogen, X_2 is $-CH_2-$, X_1 is O or S, and T is  , wherein Y^2 is O or CH_2, then Z is not thiazol-2-yl, or 4,6-dimethyl-pyrimidin-2-yl, or pyrimidin-2-yl;

f) when both R^N are hydrogen, X_2 is $-CH_2-$, X_1 is O, T is  , wherein R^{nn} is hydrogen or halo, then Z is not thiazol-2-yl, 4-methyl-pyrimidin-2-yl, 4,6-dimethylpyrimidin-2-yl, pyrimidin-2-yl, or 5-methyl-isoxazol-3-yl;

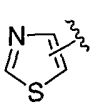
g) when both R^N are hydrogen, X_2 is $-CH_2-$, X_1 is absent, T is 1,4-dihydro-quinoxalin-2,3-dione-4-yl, then Z is not 5-methylisoxazol-3-yl, thiazol-2-yl, 4,6-dimethyl-pyrimidin-2-yl, pyrimidin-2-yl, or 2-pyridyl;

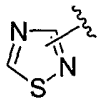
h) when both R^N are hydrogen, X_2 is $-CH_2-$, X_1 is absent, and T is 2,3-dihydro-phthalazin-1,4-dione-2-yl, then Z is not pyridyl, thiazol-2-yl, or optionally substituted pyrimidin-2-yl;

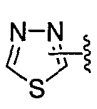
i) when both R^N are hydrogen, X_2 is $-CH_2-$, X_1 is absent, and T is adamantyl or haloadamantyl, then Z is not 3,4-dimethylisoxazol-5-yl, thiazol-2-yl, or 4-methyl-pyrimidin-2-yl;

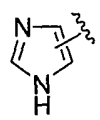
j) the compounds of Table A and Table B, wherein R^N is hydrogen, are excluded.

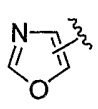
2. The compound according to claim 1, wherein, Z is selected from:


i

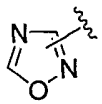

ii

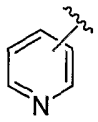

iii

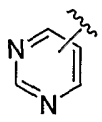

iv


v


vi

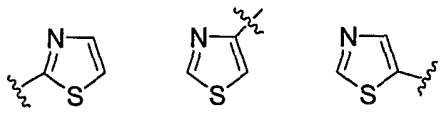

vii


viii


ix or **x**,

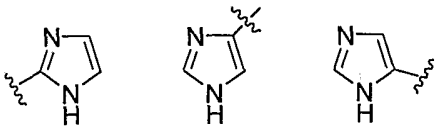
wherein Z has up to two substituents selected from R^1, R^2, or R^5.

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

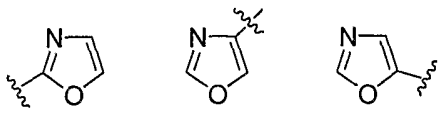

i-a **i-b** or **i-c**.

4. The compound according to claim 3, wherein Z is formula **i-a**.

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

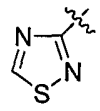
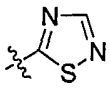
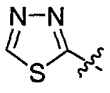

iv-a **iv-b** or **iv-c**.

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



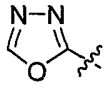
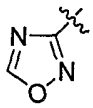
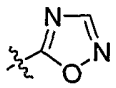
v-a **v-b** or **v-c**.

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

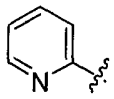
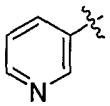
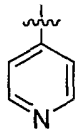
ii-a **ii-b** or **iii-a**.

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

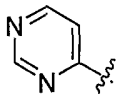
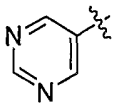
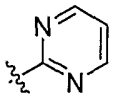
vi-a **vii-a** or **vii-b**.

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

viii-a **viii-b** or **viii-c**.

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

ix-a **ix-b** or **ix-c**.

11. The compound according to claim 1, wherein R^6 is hydrogen.

12. The compound according to claim 1, wherein R^6 is unsubstituted C1-4 alkyl.

13. The compound according to claim 1, wherein X^2 is selected from $-CH_2-$, $-CH_2-CH_2-$, $-(CH_2)_3-$, $-C(Me)_2-$, $-CH(Me)-$, $-C(Me)=CH-$, $-CH=CH-$, $-CH(Ph)-$, $-CH_2-CH(Me)-$, $-CH(Et)-$, $-CH(i-Pr)-$, or cyclopropylene.

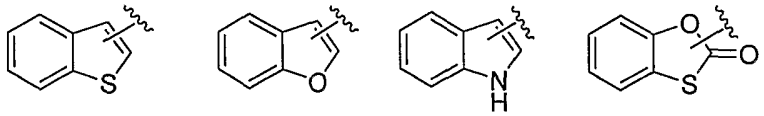
14. The compound according to claim 1, wherein p is 1 and X_1 is O.

15. The compound according to claim 1, wherein p is 1, and X_1 is S.

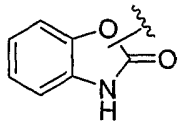
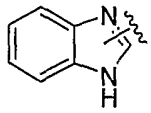
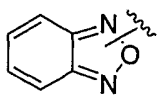
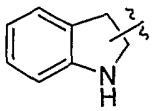
16. The compound according to claim 1, wherein T naphthyl, tetralin, or decalin, optionally substituted with up to 3 substituents independently selected from halo, cyano, trifluoromethyl, OH, C_{1-4} alkyl, C_{2-4} alkenyl, C_{1-4} alkoxy, trifluoromethoxy, $C(O)NH_2$, NH_2, $NH(C_{1-4}$ alkyl), $N(C_{1-4}$ alkyl)$_2$, $NHC(O)C_{1-4}$ alkyl, 1-pyrrolidinyl, 1-piperidinyl, 1-morpholinyl, or $C(O)C_{1-4}$ alkyl.

17. The compound according to claim 16, wherein T is optionally substituted napthyl.

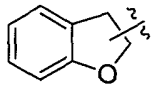
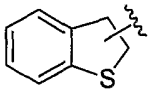
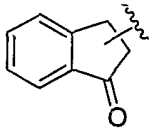
18. The compound according to claim 1, wherein T is selected from:



p **q** **r** **s**

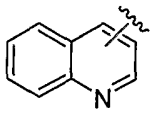
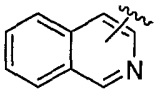
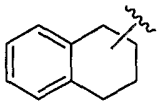
s **t** **u** **v**

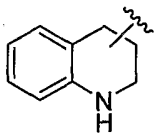
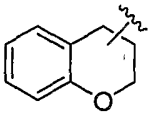
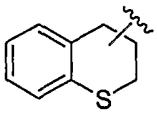
w **x** or **af,**

wherein T is optionally substituted with up to three substituents independently selected from halo, cyano, trifluoromethyl, OH, C_{1-4} alkyl, C_{2-4} alkenyl, C_{1-4} alkoxy, trifluoromethoxy, $C(O)NH_2$, NH_2, $NH(C_{1-4}$ alkyl), $N(C_{1-4}$ alkyl$)_2$, $NHC(O)C_{1-4}$ alkyl, or $C(O)C_{1-4}$ alkyl.

19. The compound according to claim 1, wherein T is selected from:

y **z** **aa**

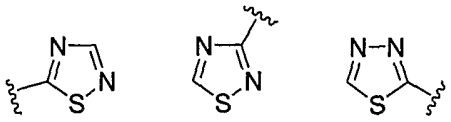
ac **ad** or **ae,**

wherein T is optionally substituted with up to three substituents independently selected from halo, cyano, trifluoromethyl, OH, C_{1-4} alkyl, C_{2-4} alkenyl, C_{1-4} alkoxy, trifluoromethoxy, $C(O)NH_2$, NH_2, $NH(C_{1-4}$ alkyl), $N(C_{1-4}$ alkyl$)_2$, $NHC(O)C_{1-4}$ alkyl, or $C(O)C_{1-4}$ alkyl.

20. The compound according to claim 1, p is 1.

21. The compound according to claim 1, p is 0.

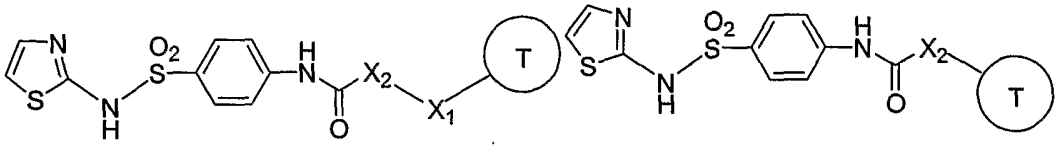
22. The compound according to claim 2, wherein Z is selected from:



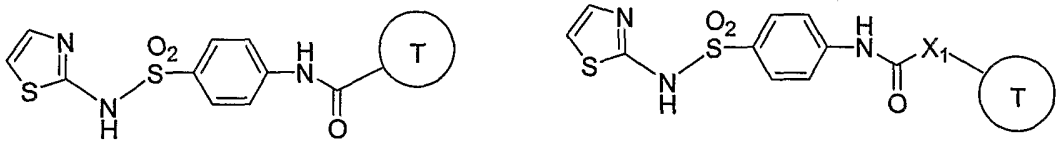
ii-a **ii-b** **iii-a.**

23. The compound according to claim 22, wherein Z is selected from **ii-a** or **ii-b.**

24. The compound according to claim 1, having formula:

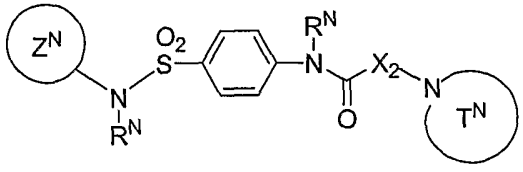


(IIA-i) (IIB-i)



(IIC-i) or (IID-i).

25. A compound having formula III:



III;

or a pharmaceutically acceptable salt thereof, wherein:

Z^N is a 5-7 membered monocyclic, unsaturated or aromatic, heterocyclic ring, having up to 4 heteroatoms independently selected from O, N, NH, S, SO, or SO_2;

each R^N is is independently hydrogen or C1-4 aliphatic optionally substituted with up to two substituents selected from R1, R4, or R5;

X_2 is C_{1-3} aliphatic, optionally substituted with up to 2 substituents independently selected from R^1, R^4, or R^5;

T^N is a 3-14 membered monocyclic, bicyclic, or tricyclic, saturated, unsaturated, or aromatic ring system having up to 5 heteroatoms independently selected from O, N, NH, S, SO, or SO_2;

wherein the phenylene ring attached to the sulfonyl is optionally substituted with up to 3 substituents selected from R^1 and R^2;

wherein Z^N and T^N each is independently and optionally substituted with up to 4 substituents independently selected from R^1, R^2, R^3, R^4, or R^5;

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

n is 0, 1 or 2;

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

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

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

R^3 is a cycloaliphatic, aryl, heterocyclic, or heteroaryl ring is optionally substituted up to 3 substituents, independently selected from R^1, R^2, R^4 or R^5;

R^4 is OR^5, OR^6, $OC(O)R^6$, $OC(O)R^5$, $OC(O)OR^6$, $OC(O)OR^5$, $OC(O)N(R^6)_2$, $OC(O)N(R^5)_2$, $OC(O)N(R^6R^5)$, $OP(O)(OR^6)_2$,

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

R^5 is a cycloaliphatic, aryl, heterocyclic, or heteroaryl ring is optionally substituted up to 3 R^1 substituents;

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

R^7 is a cycloaliphatic, aryl, heterocyclic, or heteroaryl ring and each R^7 is optionally substituted up to 2 substituents independently chosen from H, aliphatic, or $(CH_2)_n$-Z';

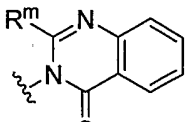
Z' is selected from halo, CN, NO_2, $C(halo)_3$, $CH(halo)_2$, $CH_2(halo)$, $-OC(halo)_3$, $-OCH(halo)_2$, $-OCH_2(halo)$,OH, S-aliphatic, S(O)-aliphatic, SO_2-aliphatic,

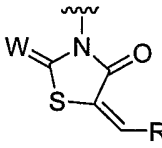
NH_2, NH-aliphatic, $N(aliphatic)_2$, $N(aliphatic)R^8$, COOH, C(O)O(-aliphatic), or O-aliphatic;

provided that:

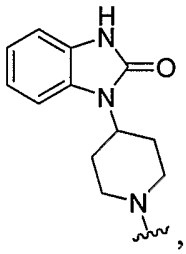
a) when both R^N are hydrogen, then T^N is not:

(i) 1,3-dione-isoindol-2-yl, 1,3-dione-isoindol-2-yl substituted with up to 4 halo substituents;

(ii)  , wherein R^m is methyl or phenyl optionally substitued with up to 4 halo;

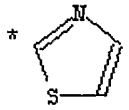
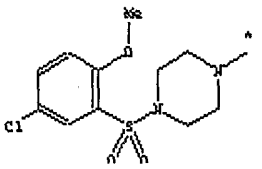
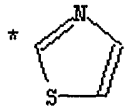
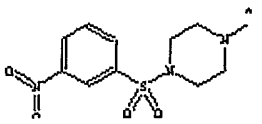
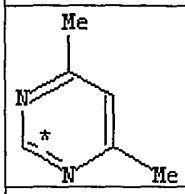
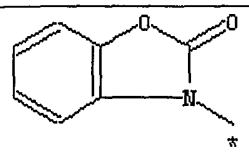
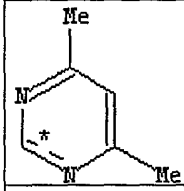
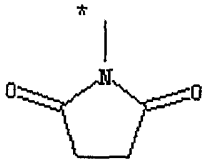
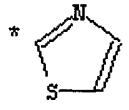
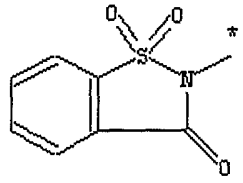
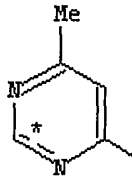
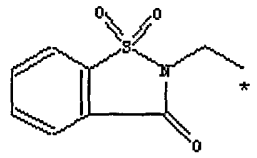
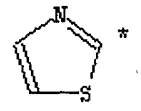
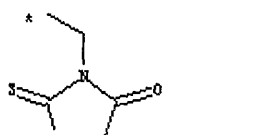
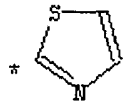
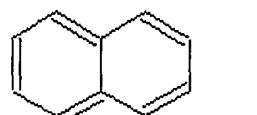
(iii)  , wherein W is O or S, and R^o is phenyl or substituted phenyl,

(iv) 4-methyl-1,4-dihydro-quinoxalin-1-yl,

(v)  ,

and further provided that:

(b) when both R^N are hydrogen, then the following compounds are excluded:

Z^N	X_2, together with T^N
	
	
	
	
	
	
	
	

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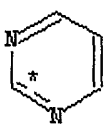	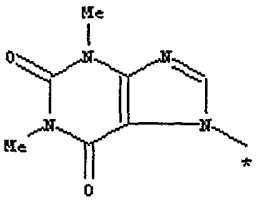
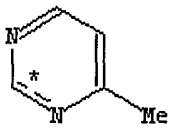	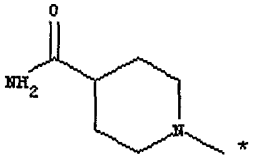
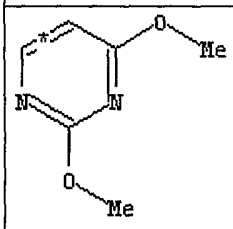	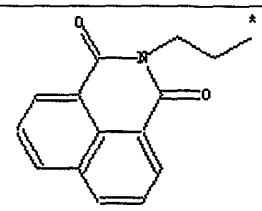
	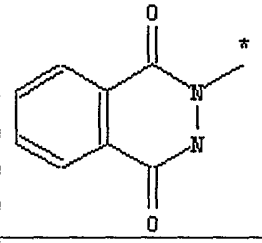
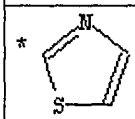	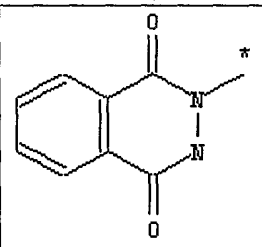
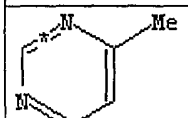	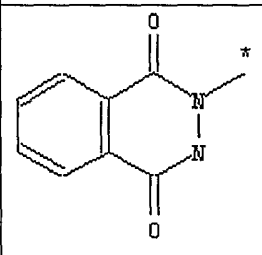

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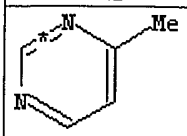	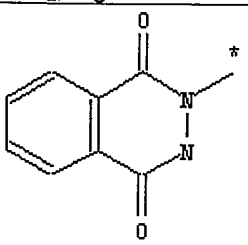
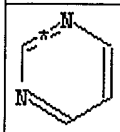	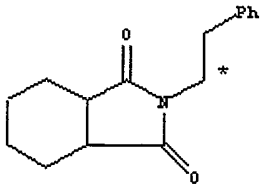
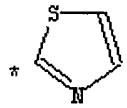	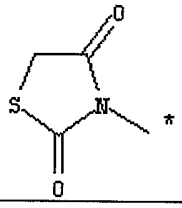
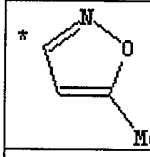	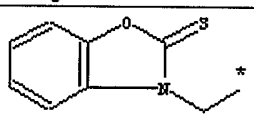
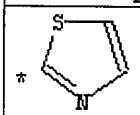	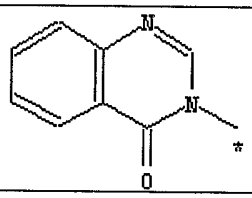
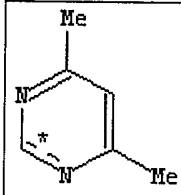	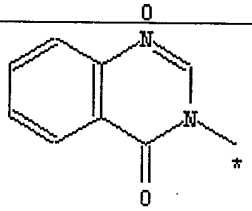
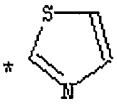	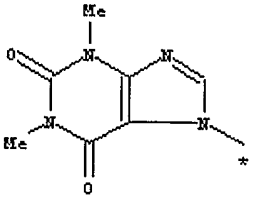

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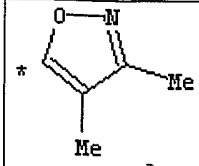
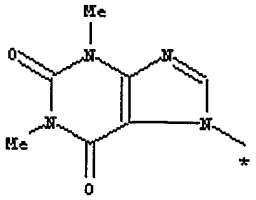
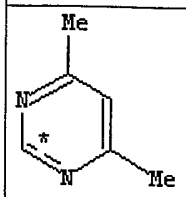
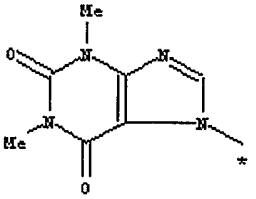
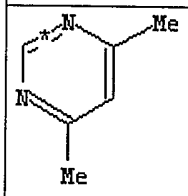
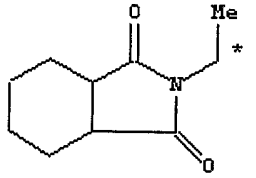
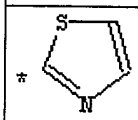
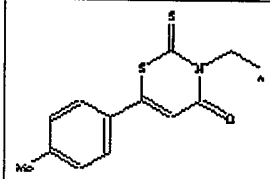
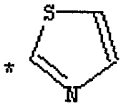
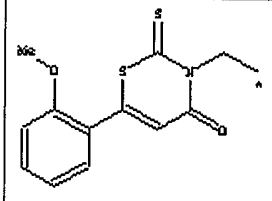
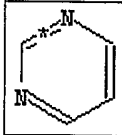
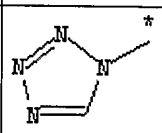
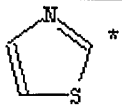
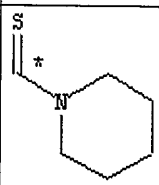
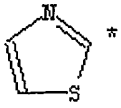
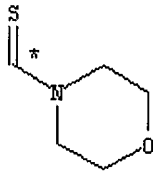
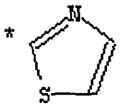
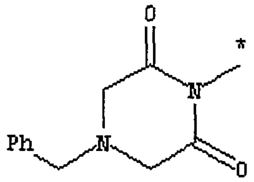
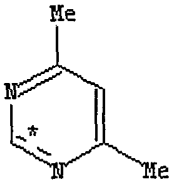
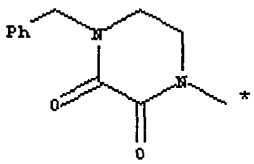
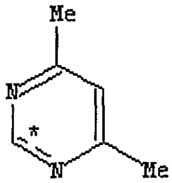
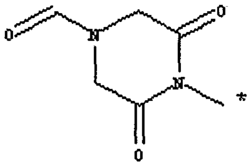
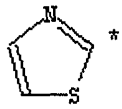
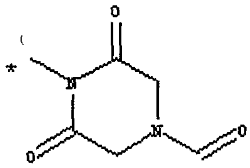
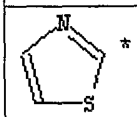
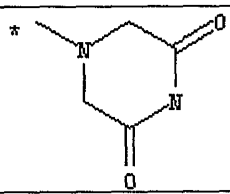
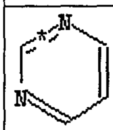
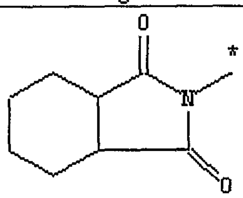
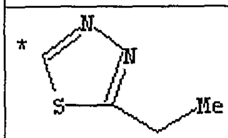
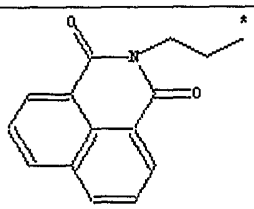
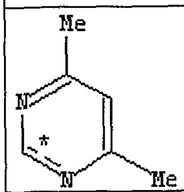
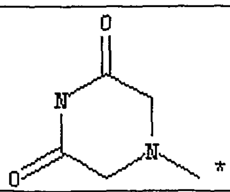
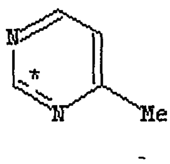
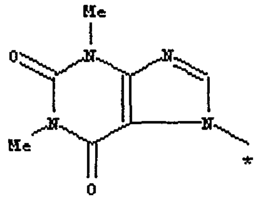
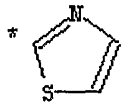
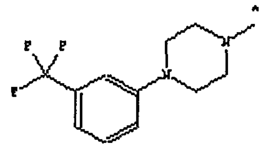
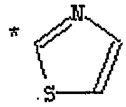
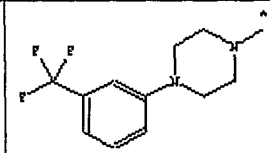
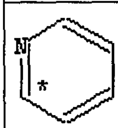
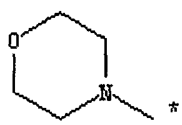
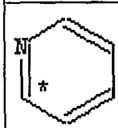
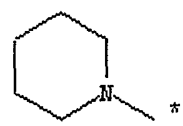
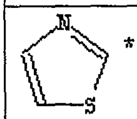
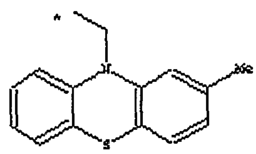
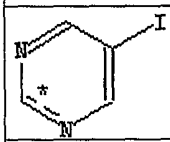
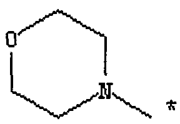
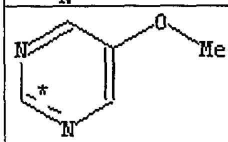
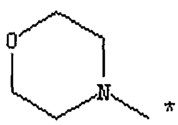
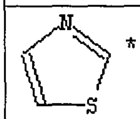
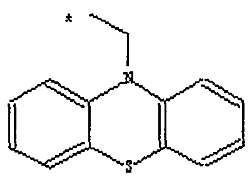
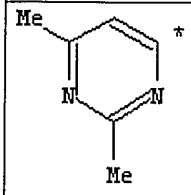
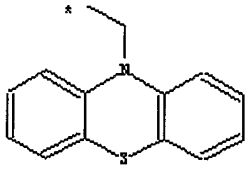
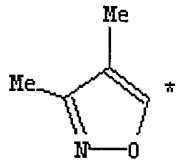
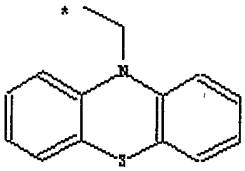
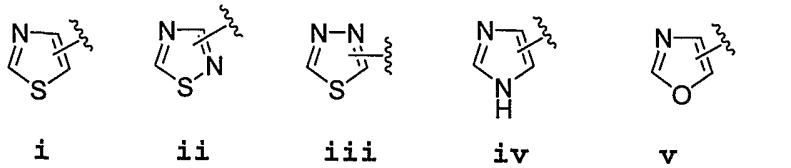
	
	
	
	
	
	
	
	

Z^N	X_2, together with T^N
	
	
	
	
	
	
	
	

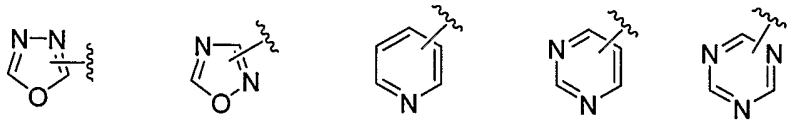
Z^N	X_2, together with T^N
	
	
	
	
	
	
	
	
	

Z^N	X_2, together with T^N
	
	

26. The compound according to claim 25, wherein Z^N is selected from:

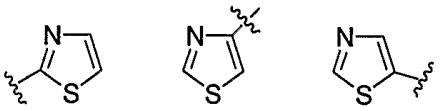


i **ii** **iii** **iv** **v**



vi **vii** **viii** **ix** or **x.**

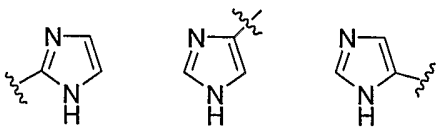
27. The compound according to claim 26, wherein Z^N is selected from:



i-a **i-b** or **i-c.**

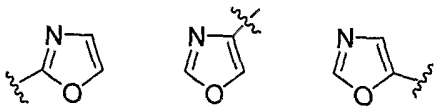
28. The compound according to claim 27, wherein Z^N is formula **i-a.**

29. The compound according to claim 26, wherein Z^N is selected from:



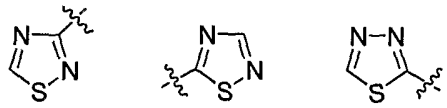
iv-a **iv-b** or **iv-c.**

30. The compound according to claim 26, wherein Z^N is selected from:



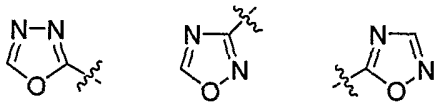
v-a **v-b** or **v-c**.

31. The compound according to claim 26, wherein Z^N is selected from:



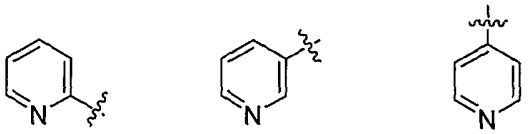
ii-a **ii-b** or **iii-a**.

32. The compound according to claim 26, wherein Z^N is selected from:



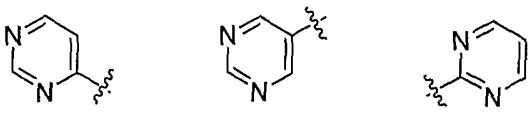
vi-a **vii-a** or **vii-b**.

33. The compound according to claim 26, wherein Z^N is selected from:



viii-a **viii-b** or **viii-c**.

34. The compound according to claim 26, wherein Z^N is selected from:



ix-a **ix-b** or **ix-c**.

35. The compound according to claim 25, wherein each R^N is hydrogen.

36. The compound according to claim 1, wherein each R^N is unsubstituted C1-4 alkyl.

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

38. The compound according to claim 37, wherein X_2 is selected from $-CH_2-$, $-CH(Me)-$,$-C(Me)_2-$, $-CH_2-CH_2-$, or $-(CH_2)_3-$.

39. The compound according to claim 38, wherein X_2 is $-CH_2-$

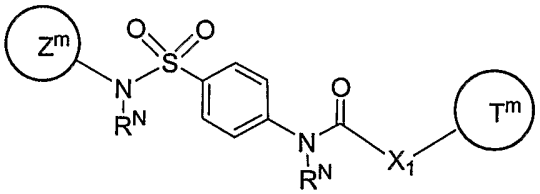
40. The compound according to claim 25, wherein TN is an optionally substituted 5-6 membered monocyclic ring.

41. The compound according to claim 40, wherein T^N is selected from 1-pyrrolyl, 2,3-dihydro-1H-pyrrol-1-yl, 1-pyrazolyl, 1-imidazolyl, 1-pyrrolidinyl, 1,2,3,4-tetrahydropyrid-1-yl, 1,2,3,6-tetrahydropyrid-1-yl, 1-zpiperidinyl, 1-piperazinyl, 1-morpholinyl, 1-azepinyl, or 1-azepanyl, wherein said ring is optionally substituted with up to 3 substituents.

42. The compound according to claim 41, wherein T^N is fused to a phenyl ring, wherein said phenyl ring.

43. The compound according to claim 41 or 42, wherein said substituents are independently selected from halo, cyano, trifluoromethyl, OH, C_{1-4} alkyl, C_{2-4} alkenyl, C_{1-4} alkoxy, trifluoromethoxy, $C(O)NH_2$, NH_2, $NH(C_{1-4}$ alkyl), $N(C_{1-4}$ alkyl$)_2$, $NHC(O)C_{1-4}$ alkyl, or $C(O)C_{1-4}$ alkyl.

44. A compound having formula IV:



(IV);

or a pharmaceutically acceptable salt thereof;

wherein:

Z^M is a 5-7 membered monocyclic, unsaturated or aromatic, heterocyclic ring, having up to 4 heteroatoms independently selected from O, N, NH, S, SO, or SO_2;

each R^N is is independently hydrogen or C1-4 aliphatic optionally substituted with up to two substituents selected from R1, R4, or R5;

T^M is a 8-14 membered aromatic or non-aromatic bicyclic or tricyclic ring, having 0-5 heteroatoms selected from O, S, N, NH, S(O) or SO_2;

wherein Z^M and T^M each is independently and optionally substituted with up to 4 substituents independently selected from R^1, R^2, R^3, R^4, or R^5;

wherein the phenylene ring attached to the sulfonyl is optionally substituted with up to 3 substituents selected from R^1 and R^2;

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

n is 0, 1 or 2;

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

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

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

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

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

$P(O)(OR^6)N(R^5)_2$, $P(O)(OR^5)N(R^5R^6)$, $P(O)(OR^5)N(R^6)_2$, $P(O)(OR^5)N(R^5)_2$, $P(O)(OR^6)_2$, $P(O)(OR^5)_2$, or $P(O)(OR^6)(OR^5)$;

R^5 is a cycloaliphatic, aryl, heterocyclic, or heteroaryl ring, optionally substituted with up to 3 R^1 substituents;

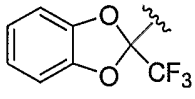
R^6 is H or aliphatic, wherein R^6 is optionally substituted with a R^7 substituent;

R^7 is a cycloaliphatic, aryl, heterocyclic, or heteroaryl ring and each R^7 is optionally substituted with up to 2 substituents independently chosen from H, aliphatic, or $(CH_2)_n$-Z';

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

provided that:

(a) when Z is optionally substituted pyrimidinyl or thiazolyl, both R^6 are hydrogen, and X1 is NH, then T is not optionally substituted adamantyl;

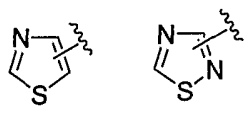
(b) when Z is optionally substituted pyridyl, pyrimidinyl, isoxazolyl, or thiazolyl, both R_6 are hydrogen, and X_1 is NH, then T is not  , optionally substituted with up to two halo atoms;

(c) when both R_6 are hydrogen, and X_1 is NH, then T is not 1-naphthyl, 2-naphthyl, or 7-hydroxynaphth-1-yl;

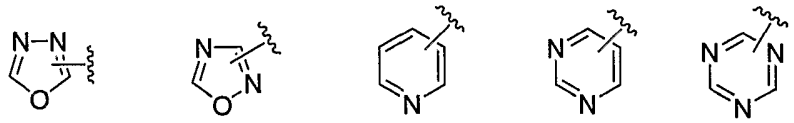
(d) when Z is pyrimidinyl, 5-methylisoxazolyl, or pyridyl, both R_6 are hydrogen, and X_1 is NH, then T is not subtituted purinyl; and

(e) when Z is thiazol-2-yl, both R_6 are hydrogen, and X_1 is NH, then T is not substituted 3*H*-isobenzofuran-1-one-7-yl.

45. The compound according to claim 44, wherein Z^M is selected from:

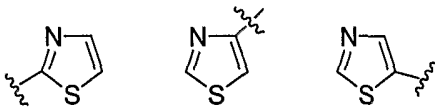


i **ii** **iii** **iv** **v**



vi **vii** **viii** **ix** or **x.**

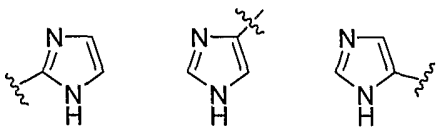
46. The compound according to claim 45, wherein Z^M is selected from:



i-a **i-b** or **i-c.**

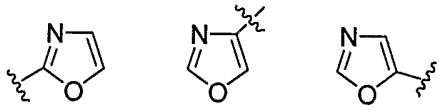
47. The compound according to claim 46, wherein Z^M is formula **i-a.**

48. The compound according to claim 44, wherein Z^M is selected from:



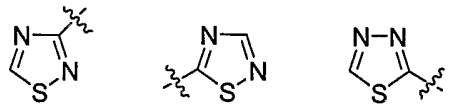
iv-a **iv-b** or **iv-c.**

49. The compound according to claim 44, wherein Z^M is selected from:



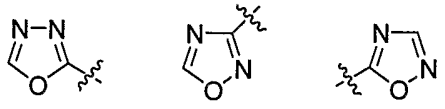
v-a **v-b** or **v-c.**

50. The compound according to claim 45, wherein Z^M is selected from:



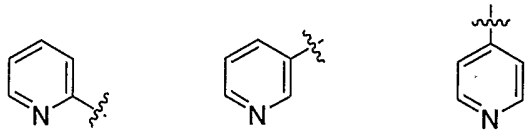
ii-a **ii-b** or **iii-a.**

51. The compound according to claim 45, wherein Z^M is selected from:



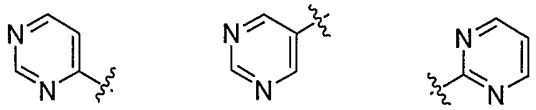
vi-a **vii-a** or **vii-b.**

52. The compound according to claim 45, wherein Z^M is selected from:



viii-a **viii-b** or **viii-c.**

53. The compound according to claim 45, wherein Z^M is selected from:



ix-a **ix-b** or **ix-c**.

54. The compound according to claim 44, wherein each R^N is hydrogen.

55. The compound according to claim 44, wherein each R^N is unsubstituted C1-4 alkyl.

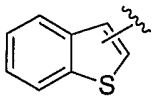
56. The compound according to claim 44, wherein Z^M is an optionally substituted 5-6 membered monocyclic ring.

57. The compound according to claim 44, wherein X_1 is NH.

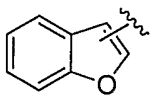
58. The compound according to claim 44, wherein X_1 is O.

59. The compound according to claim 44, wherein T^M is The compound according to claim 1, wherein T^M is phenyl or naphthyl, optionally substituted with up to 3 substituents independently selected from halo, cyano, trifluoromethyl, OH, C_{1-4} alkyl, C_{2-4} alkenyl, C_{1-4} alkoxy, trifluoromethoxy, $C(O)NH_2$, NH_2, $NH(C_{1-4}$ alkyl), $N(C_{1-4}$ alkyl)$_2$, $NHC(O)C_{1-4}$ alkyl, 1-pyrrolidinyl, 1-piperidinyl, 1-morpholinyl, or $C(O)C_{1-4}$ alkyl.

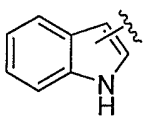
60. The compound according to claim 44, wherein T^M is selected from:



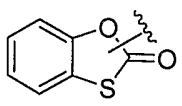
p



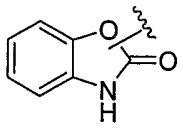
q



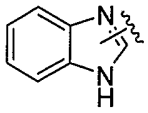
r



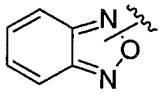
s



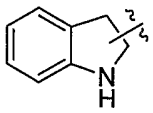
s



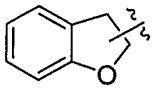
t



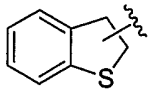
u



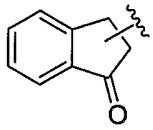
v



w



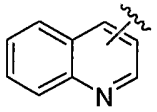
x or



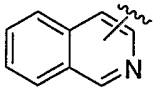
af,

wherein T is optionally substituted with up to three substituents independently selected from halo, cyano, trifluoromethyl, OH, C_{1-4} alkyl, C_{2-4} alkenyl, C_{1-4} alkoxy, trifluoromethoxy, $C(O)NH_2$, NH_2, $NH(C_{1-4}$ alkyl), $N(C_{1-4}$ alkyl$)_2$, $NHC(O)C_{1-4}$ alkyl, or $C(O)C_{1-4}$ alkyl.

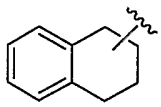
61. The compound according to claim 44, wherein T is selected from:



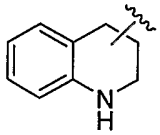
y



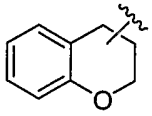
z



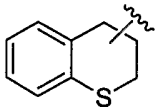
aa



ac



ad or



ae,

wherein T is optionally substituted with up to three substituents independently selected from halo, cyano, trifluoromethyl, OH, C_{1-4} alkyl, C_{2-4} alkenyl, C_{1-4} alkoxy, trifluoromethoxy, $C(O)NH_2$, NH_2, $NH(C_{1-4}$ alkyl), $N(C_{1-4}$ alkyl$)_2$, $NHC(O)C_{1-4}$ alkyl, or $C(O)C_{1-4}$ alkyl.

62. A compound having formula (V):

T_1-L_{11}–A-L_{22}–Z (V);

wherein:

T_1 is a 8-14 membered aromatic or unsaturated bicyclic or tricyclic ring, having 0-5 heteroatoms selected from O, S, N, NH, S(O) or SO_2;

L_{11} is $-(X_1)_p-(CHR^1)_r-(X_2)-Ry$;

wherein:

p is 0 or 1;

r is 0 or 1;

X_1 is O, S, or NRx, wherein R_x is H or R_2;

X_2 is R^2;

Ry is $-C(O)-NR^2-$;

L_{22} is $OC(O)$, $C(O)O$, $S(O)$, SO_2, $N(R^5)SO_2$, $N(R^6)SO_2$, $SO_2N(R^5)$, $SO_2N(R^6)$, $C(O)N(R^5)$, $C(O)N(R^6)$, $NR^5C(O)$, $NR^6C(O)$, $C(NOR^5)R^6$, $C(NOR^5)R^6$, $C(NOR^6)R^5$, $C(NOR^6)R^6$, $N(R^5)$, $N(R^6)$, $NR^5C(O)O$, $NR^6C(O)O$, $OC(O)NR^5$, $OC(O)NR^6$, $NR^5C(O)N(R^5)$, $NR^5C(O)N(R^6)$, $NR^6C(O)N(R^5)$, $NR^6C(O)N(R^6)$, $NR^5SO_2N(R^5)$, $NR^5SO_2N(R^6)$, $NR^6SO_2N(R^5)$, $NR^6SO_2N(R^6)$, $N(OR^5)$, or $N(OR^6)$;

A is a 5-7 membered monocyclic aromatic ring, having 0-4 heteroatoms;

Z is 2-thiazolyl;

wherein each of T, A, and Z is optionally substituted with up to 4 suitable substituents independently selected from R^1, R^2, R^3, R^4, or R^5;

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

n is 0, 1 or 2;

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

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

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

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

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

R^5 is a cycloaliphatic, aryl, heterocyclic, or heteroaryl ring is optionally substituted with up to 3 R^1 substituents;

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

R^7 is a cycloaliphatic, aryl, heterocyclic, or heteroaryl ring and each R^7 is optionally substituted with up to 2 substituents independently chosen from H, aliphatic, or $(CH_2)_n$-Z';

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

R^8 is an amino protecting group;

provided that:

(i) when:

L_{22} is SO_2, $N(R^5)SO_2$, $N(R^6)SO_2$, $SO_2N(R^5)$, $SO_2N(R^6)$, $C(O)N(R^5)$, $C(O)N(R^6)$, $NR^5C(O)$, or $NR^6C(O)$;

A is optionally substituted 5-6 membered monocyclic aromatic ring with 0-4 heteroatoms independently selected from N, S, or O;

X_2 is optionally substituted methylene or ethylene;

T_1 is an optionally substituted fused aromatic bicyclic ring system containing 0-4 heteroatoms independently selected from N, O, or S;

then:

r is 1;

(ii) when:

L_{22} is SO_2, $N(R^5)SO_2$, $N(R^6)SO_2$, $SO_2N(R^5)$, $SO_2N(R^6)$, $C(O)N(R^5)$, $C(O)N(R^6)$, $NR^5C(O)$, or $NR^6C(O)$;

A is an optionally substituted 5-6 membered monocyclic aromatic ring with 0-4 heteroatoms independently selected from N, S, or O;

p is 1;

X_2 is optionally substituted methylene, ethylene, or propylene;

T_1 is an optionally substituted fused aromatic bicyclic ring system containing 0-4 heteroatoms independently selected from N, O, or S;

then:

X_1 is not O or S;

(iii) when:

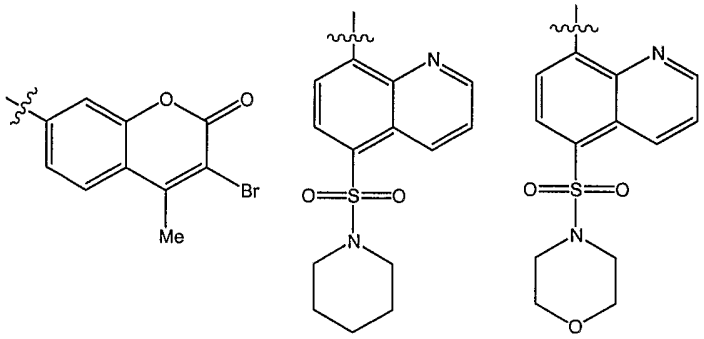
L_{11} is $-O-CH_2-C(O)-NH-$;

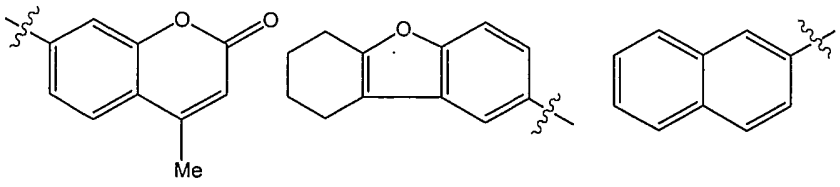
A is phenylene;

L_{22} is $-S(O)_2-NH-$;

then:

T_1 is not any of the following:





;

(iv) when:

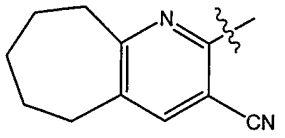
L_{11} is $-S-CH_2-C(O)-NH-$;

A is phenylene;

L_{22} is $-S(O)_2-NH-$;

then:

T_1 is not any of the following:



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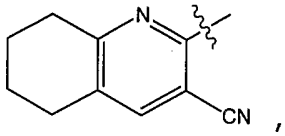

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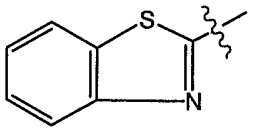

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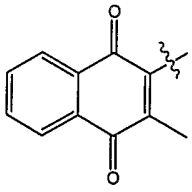
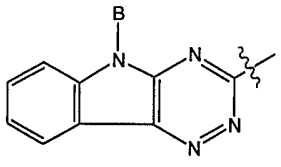


or


, wherein B is hydrogen, methyl, n-propyl, isopropyl, allyl, benzyl, or phenylethyl.

63. The compound according to claim 62, wherein T_1 is a 8-14 membered aromatic or non-aromatic bicyclic or tricyclic ring, having 0 heteroatoms.

64. The compound according to claim 63, wherein T_1 is naphthyl, anthracenyl, tetralinyl or decalinyl.

65. The compound according to claim 63, wherein T_1 is an 8-14 membered aromatic or non-aromatic bicyclic or tricyclic ring, having up to 5 heteroatoms.

66. The compound according to claim 65, wherein, T_1 is an 8-14 membered aromatic bicyclic ring, having up to 5 heteroatoms.

67. The compound according to claim 65, wherein T_1 is a 8-14 membered non-aromatic bicyclic ring, having up to 5 heteroatoms.

68. The compound according to claim 66, wherein T_1 is selected from quinolinyl, isoquinolinyl, benzofuranyl, benzothiophenyl, quinolinyl, isoquinolinyl, benzofuranyl, benzothiophenyl, indolizinyl, indolyl, isoindolyl, indolinyl, indazolyl, benzimidazolyl, benzothiazolyl, purinyl, cinnolinyl, phthalazine, quinazolinyl, quinaoxalinyl, naphthylirinyl, or pteridinyl.

69. The compound according to claim 66, wherein T_1 is a 8-14 membered non-aromatic tricyclic ring, having up to 5 heteroatoms.

70. The compound according to claim 65, wherein T_1 is an 8-14 membered aromatic tricyclic ring, having up to 5 heteroatoms.

71. The compound according to claim 65, wherein T_1 is selected from dibenzofuranyl, carbazolyl, acridinyl, phenazinyl, phenothiazinyl, phenoxazinyl, acridinyl, phenazinyl, phenothiazinyl, phenoxainyl, or carbazolyl.

72. The compound according to claim 62, wherein A is phenyl.

73. The compound according to claim 62, wherein A is a 5-6 membered monocyclic aromatic ring having 1-4 heteroatoms.

74. The compound according to claim 73, wherein A is 5-6 membered monocyclic aromatic ring having 1-3 heteroatoms.

75. The compound according to claim 74, wherein A is selected from thiazolyl, isothiazolyl, thiadiazolyl, thiaphenyl, furanyl, oxazolyl, isooxazolyl, oxadiazolyl, triazolyl, imidazolyl, pyrazolyl, pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, triazinyl, or pyrrolyl.

76. A pharmaceutical composition comprising a compound according to any one of claims 1-75, and a pharmaceutically acceptable adjuvant or carrier.

77. 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**:

$$T\text{---}L_1\text{---}A\text{---}L_2\text{---}Z \qquad (I);$$

or a pharmaceutically acceptable derivative thereof;

wherein:

L_1 is $-(X_1)_p-(X_2)_q-R_y-$;

wherein:

X_1 is O, S, or NR_X

p is 0 or 1;

q is 0 or 1;

R_X is H or R^2;

X_2 is R^2;

R_Y is $-C(O)-NR^2-$; or

L_2 and Ry are independently selected from $OC(O)$, $C(O)O$, $S(O)$, SO_2, $N(R^5)SO_2$, $N(R^6)SO_2$, $SO_2N(R^5)$, $SO_2N(R^6)$, $C(O)N(R^5)$, $C(O)N(R^6)$, $NR^5C(O)$, $NR^6C(O)$, $C(NOR^5)R^6$, $C(NOR^5)R^6$, $C(NOR^6)R^5$, $C(NOR^6)R^6$, $N(R^5)$, $N(R^6)$, $NR^5C(O)O$, $NR^6C(O)O$, $OC(O)NR^5$, $OC(O)NR^6$, $NR^5C(O)N(R^5)$, $NR^5C(O)N(R^6)$, $NR^6C(O)N(R^5)$, $NR^6C(O)N(R^6)$, $NR^5SO_2N(R^5)$, $NR^5SO_2N(R^6)$, $NR^6SO_2N(R^5)$, $NR^6SO_2N(R^6)$, $N(OR^5)$, or $N(OR^6)$;

Z is hydrogen, cycloaliphatic, heterocyclic, aryl, or heteroaryl ring;

T is aliphatic, cycloaliphatic, aryl, heteroaryl, or heterocyclic ring;

A is aryl or heteroaryl ring;

wherein each of T, A, and Z is optionally substituted with up to 4 suitable substituents independently selected from R^1, R^2, R^3, R^4, or R^5;

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

n is 0, 1 or 2;

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

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

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

R^3 is a cycloaliphatic, aryl, heterocyclic, or heteroaryl ring optionally comprising up to 3 substituents, independently selected from R^1, R^2, R^4 or R^5;

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

R^5 is a cycloaliphatic, aryl, heterocyclic, or heteroaryl ring is optionally substituted with up to 3 R^1 substituents;

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

R^7 is a cycloaliphatic, aryl, heterocyclic, or heteroaryl ring and each R^7 is optionally substituted with up to 2

substituents independently chosen from H, aliphatic, or $(CH_2)_n$-Z';

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

R^8 is an amino protecting group.

78. The method according to claim 77, wherein p is 0, and q is 0.

79. The method according to claim 77, wherein p is 0, and q is 1.

80. The method according to claim 77, wherein p is 1 and q is 1.

80. The method according to claim 77, wherein X_1 is O or NR_X.

81. The method according to claim 80, wherein X_1 is NR_X; and R_X is H.

82. The method according to claim 77, wherein X_2 is a straight or branched (C1-C6)alkyl or (C2-C6)alkenyl or alkynyl, optionally substituted with up to two substituents independently selected from R_1 and R_5.

83. The method according to claim 80, wherein X_2 is a straight or branched (C1-C6)alkyl optionally substituted with up to two substituents independently selected from R_1 and R_5.

84. The method according to claim 1, wherein R_y is H or straight or branched (C1-C6)alkyl or (C2-C6)alkenyl or alkynyl, optionally substituted with up to two substituents independently selected from R_1 and R_5.

85. The method according to claim 77, wherein Z is aryl or heteroaryl.

86. The method according to claim 85, wherein Z is phenyl or napthyl.

87. The method according to claim 85, wherein Z is heteroaryl.

88. The method according to claim 87, wherein Z is selected from thiazolyl, isothiazolyl, thiadiazolyl, thienyl, furanyl, oxazolyl, isoxazolyl, oxadiazolyl, triazolyl, imidazolyl, pyrazolyl, pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, triazinyl, or pyrrolyl.

89. The method according to claim 77, wherein A is aryl.

90. The method according to claim 89, wherein A is phenyl or naphthyl.

91. The method according to claim 77, wherein A is a monocyclic aromatic ring containing 1 to 3 heteroatoms selected from O, S, or NH.

92. The method according to claim 77, wherein A is pyridyl, pyrazyl, triazinyl, furanyl, pyrrolyl, thiophenyl, oxazolyl, isoxazole, isothiazole, oxadiazole, imidazolyl, triazolyl, thiadiazolyl, or pyrimidinyl.

93. The method according to claim 77, wherein A is a bicyclic or a tricyclic ring system with at least one aromatic ring, wherein said ring system contains 1-5 heteroatoms selected from O, S, or NH.

94. The method according to claim 93, wherein A is quinolinyl, isoquinolinyl, benzofuranyl, benzothiophenyl, quinolinyl, isoquinolinyl, benzofuranyl, benzothiophenyl, indolizinyl, indolyl, isoindolyl, indolinyl, indazolyl, benzimidazolyl, benzothiazolyl, purinyl, cinnolinyl, phthalazine, quinazolinyl, quinaoxalinyl, naphthylirinyl, pteridinyl, dibenzofuranyl, carbazolyl, acridinyl, phenazinyl, phenothiazinyl, phenoxazinyl, anthracenyl, fluorenyl, dibenzofuranyl, carbazolyl, acridinyl, phenazinyl, phenothiazinyl, or phenoxazinyl.

95. The method according to claim 77, wherein T is aliphatic or cycloaliphatic.

96. The method according to claim 95, wherein T is (C1-C6) straight or branched alkyl.

97. The method according to claim 95, wherein T is methyl, ethyl, propyl, isopropyl, butyl, isobutyl, t-butyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, norbornyl, or adamantyl.

98. The method according to claim 77, wherein T is an aryl ring or heteroaryl ring.

99. The method according to claim 98, wherein T is phenyl, napthyl, anthracenyl, thiophenyl, benzothiophenyl, pyridyl, furanyl, benzofuranyl, oxazolyl, quinolinyl phenyl, naphthyl, anthracenyl, thiophenyl, benzothiophenyl, pyridiyl, furanyl, benzofuranyl, oxazolyl, quinolinyl, pyrrolyl, thiazolyl, imidazolyl, pyrazolyl, isoxazolyl, isothiazolyl, oxadiazolyl, triazolyl, thiadiazolyl, pyridazinyl, pyrimidinyl, pyrazinyl, triazinyl, indolizinyl, indolyl, isoindolyl, indazolyl, benzimidazolyl, benzthiazolyl, purinyl, isoquinolinyl, cinnolinyl phthalazinyl, quinazolinyl, quinoxalinyl, napthyridinyl, pteridinyl, acridinyl, phenazinyl, phenothiazinyl, phenoxainyl, or carbazolyl.

100. The method according to claim 77, wherein T is a heterocyclic ring.

101. The method according to claim 100, wherein T is tetrahydrofuranyl, pyrrolidinyl, piperidinyl, morpholinyl, dithianyl, thiomorpholinyl, piperazinyl, quinuclidinyl, tetrahydrofuranyl, pyrrolidinyl, piperidinyl, morpholinyl, dithianyl, thiomorpholinyl, piperazinyl, quinuclidinyl,

dioxoianyl, imidazolidinyl, pyrazolidinyl, dioxanyl, piperazinyl, or trithianyl.

102. The method according to claim 77, wherein R^1 is oxo.

103. The method according to claim 77, wherein R^1 is R^6 or $(CH_2)_n$-Y.

104. The method according to claim 103, wherein R^1 is $(CH_2)_n$-Y, wherein n is 0.

105. The method according to claim 77 or 103, wherein R^2 is a straight or branched (C1-C6) alkyl or (C2-C6)alkenyl or alkynyl, optionally substituted with up to two R^1 substitutions.

106. The method according to claim 77, wherein:

Z is thiazol-2-yl;

A is phenyl, pyridyl, pyrazinyl, pyridazinyl, pyrimidinyl, triazinyl, or tetrazinyl;

L_1 is $-(X_1)_p-(X_2)_q-R_y-$;

wherein:

X_1 is O, S, or NR_x

p is 0 or 1;

q is 0 or 1;

R_x is H or R^2;

X_2 is R^2;

R_y is $-C(O)-NR^2-$; and

L_2 is $SO_2N(R^5)$ or $SO_2N(R^6)$.

107. The method according to claim 77, wherein said compound has formula I-A, formula IIA-i, formula IIB-i, formula IIC-i, formula IID-i, formula III, formula IV, or formula V.

108. A method of treating or lessening the severity of a disease, disorder, or condition selected from acute, chronic, neuropathic, or inflammatory pain, arthritis, migraine, cluster headaches, trigeminal neuralgia, herpetic neuralgia, general neuralgias, epilepsy or epileptic conditions, neurodegenerative disorders, psychiatric disorders such as anxiety and depression, myotonia, arrhythmia, movement disorders, neuroendocrine disorders, ataxia, multiple sclerosis, irritable bowel syndrome, incontinence, visceral pain, osteoarthritis pain, postherpetic neuralgia, diabetic neuropathy, radicular pain, sciatica, back pain, head or neck pain, severe or intractable pain, nociceptive pain, breakthrough pain, postsurgical pain, stroke, bipolar disorders, or cancer pain, comprising the step of administering to said patient an effective amount of a compound according of formula **I**.

109. The method according to claim 108, wherein said compound is according to any one of claims 1-77.

110. The method according to claim 108, wherein the disease, condition, or disorder is implicated in the activation or hyperactivity of voltage-gated sodium channels.

111. The method according to claim 108, wherein the disease, condition, or disorder is implicated in the activation or hyperactivity of voltage-gated calcium channels.

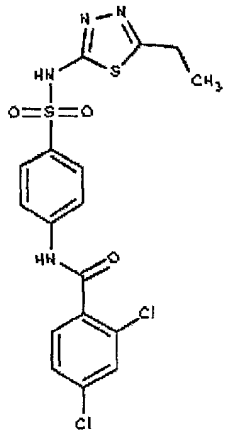
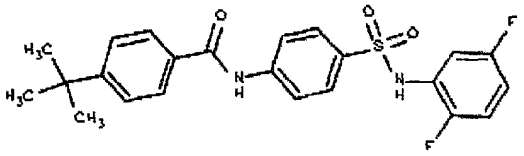
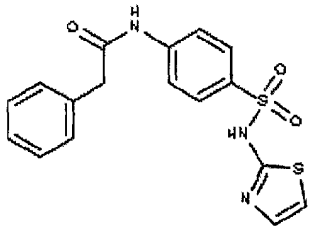
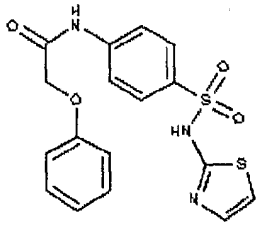
112. The method according to claim 111, wherein the disease, condition, or disorder is acute, chronic, neuropathic, inflammatory pain, or inflammatory breakthrough pain.

113. The method according to claim 108, wherein the disease, condition, or disorder is radicular pain, sciatica, back pain, head pain, neck pain, or neuropathies.

114. The method according to claim 108, wherein the disease, condition, or disorder is severe or intractable pain, acute pain, post-surgical pain, back pain, or cancer pain.

115. The method according to claim 77 or 108, wherein said compound is selected from Figure 1.

Figure 1-1

#	Compound
1	
2	
3	
4	

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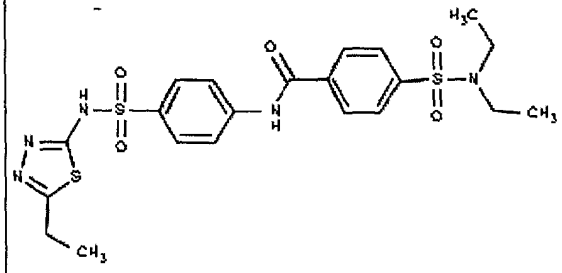
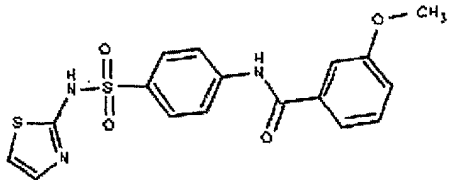
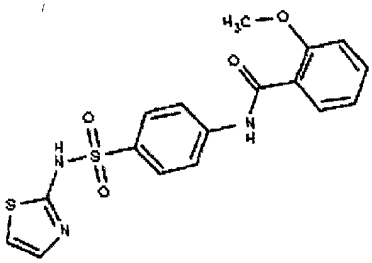
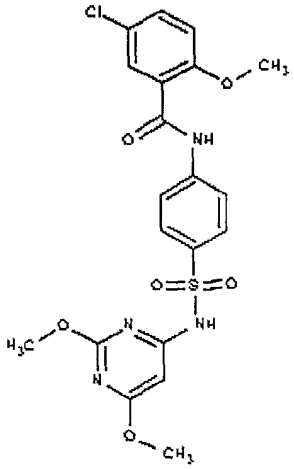
5	
6	
7	
8	

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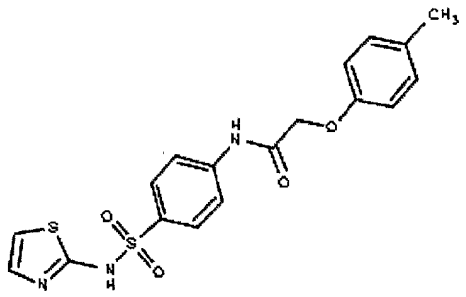
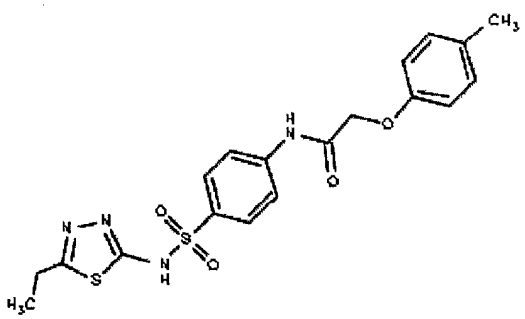
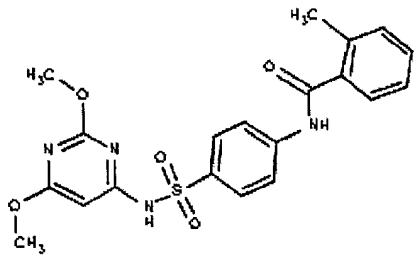
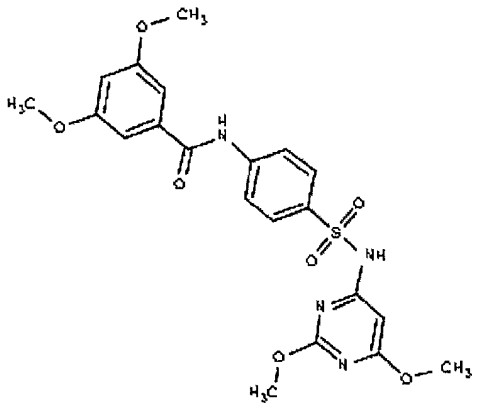
9	
10	
11	
12	

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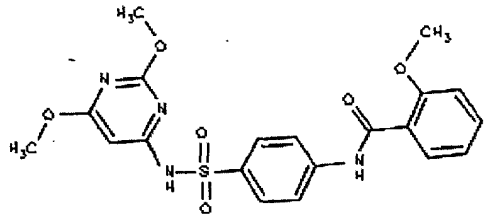
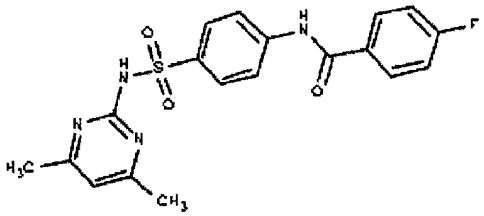
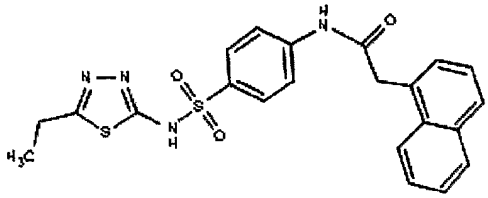
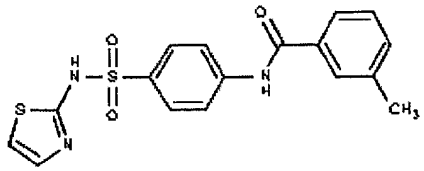
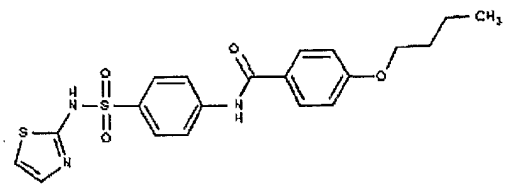
13	
14	
15	
16	
17	

Figure 1-3

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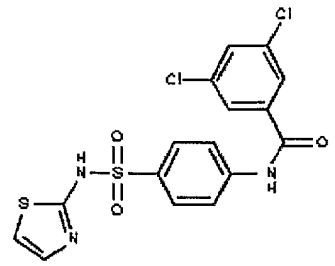
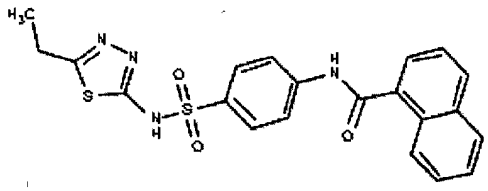
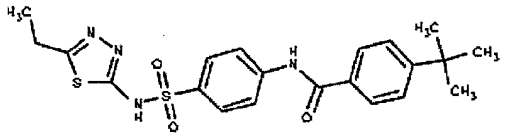
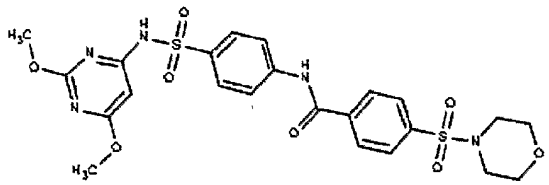
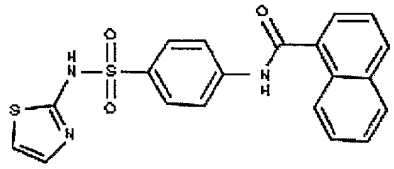
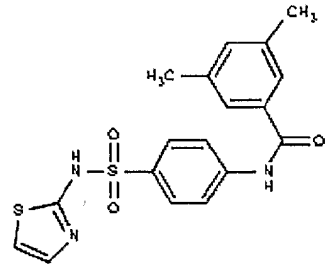
18	
19	
20	
21	
22	
23	

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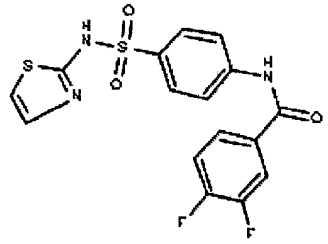
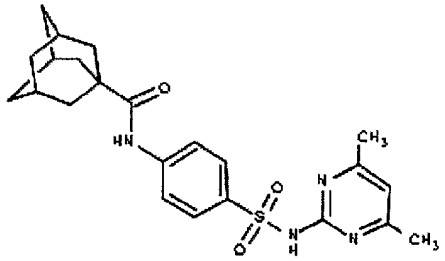
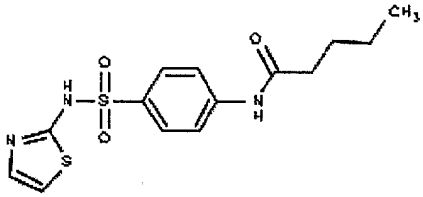
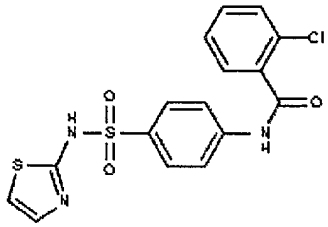
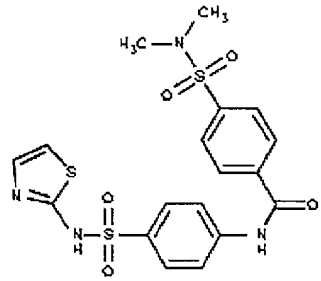
24	
25	
26	
27	
28	

Figure 1-4

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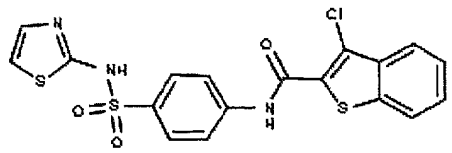
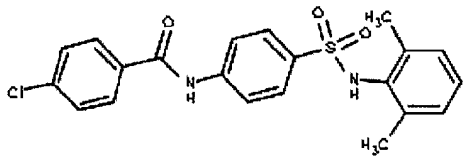
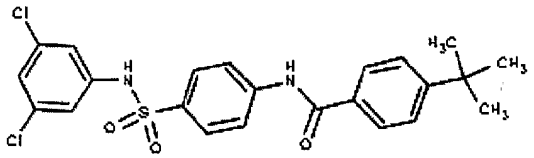
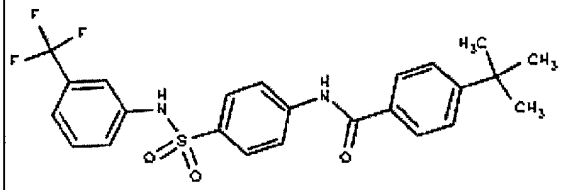
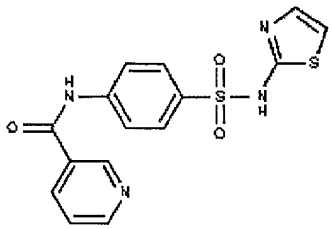
29	
30	
31	
32	
33	

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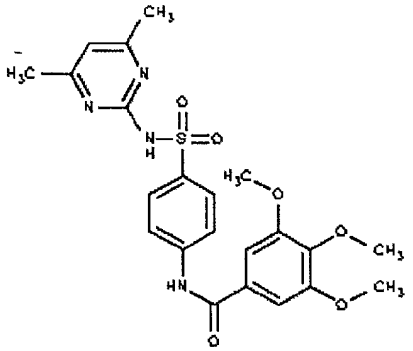
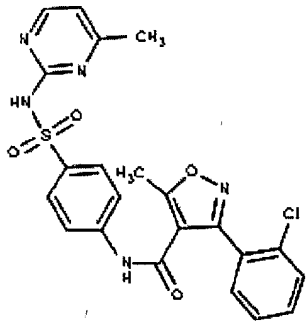
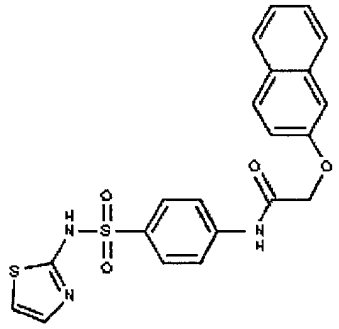
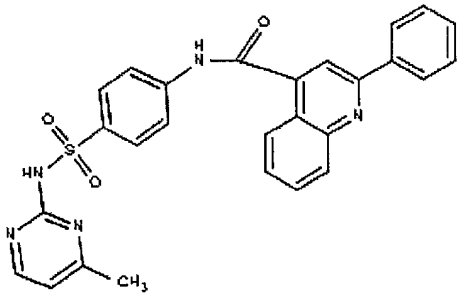
34	
35	
36	
37	

Figure 1-5

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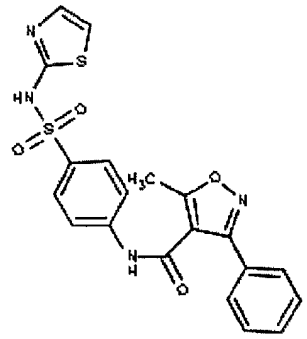
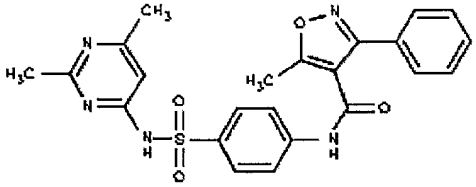
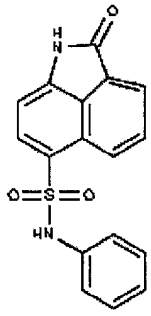
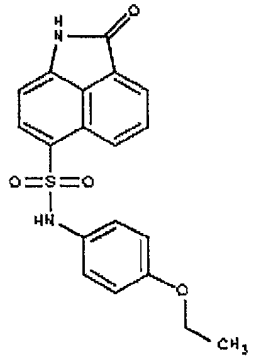
38	
39	
40	
41	

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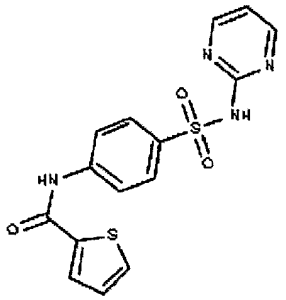
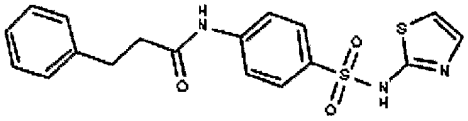
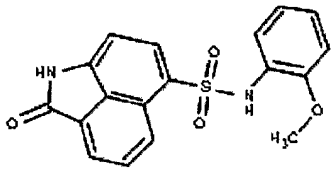
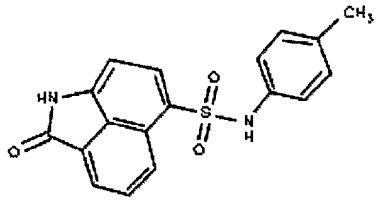
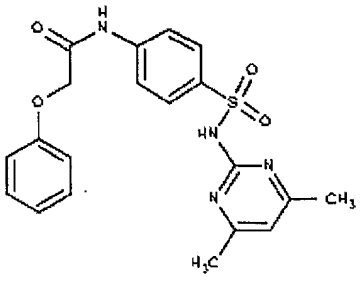
42	
43	
44	
45	
46	

Figure 1-6

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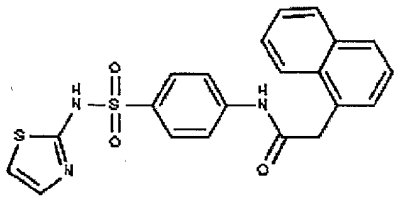
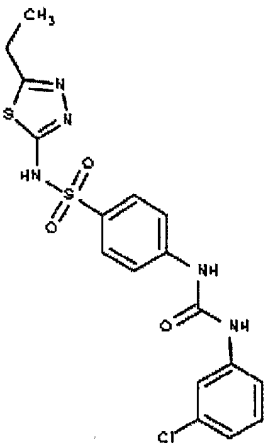
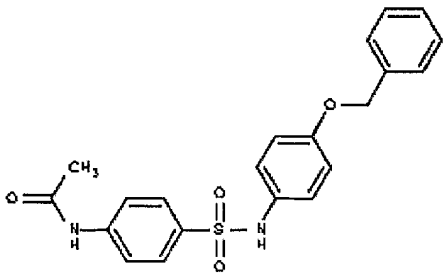
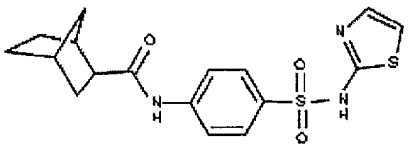
47	
48	
49	
50	

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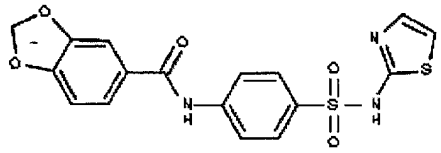
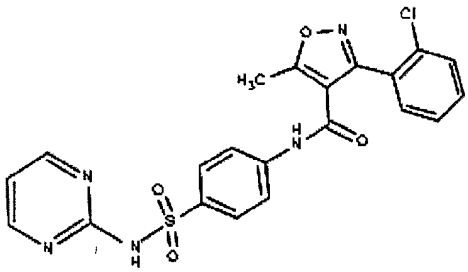
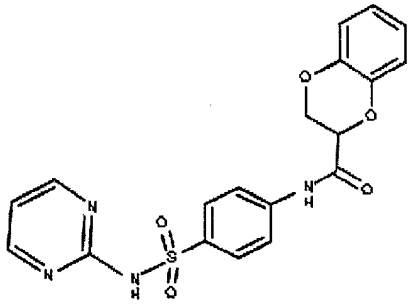
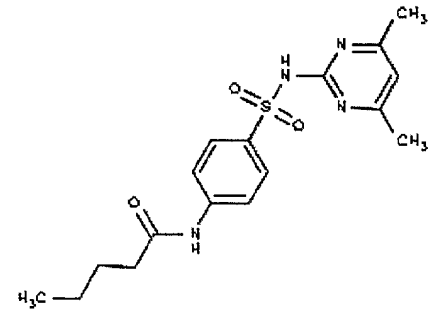
51	
52	
53	
54	

Figure 1-7

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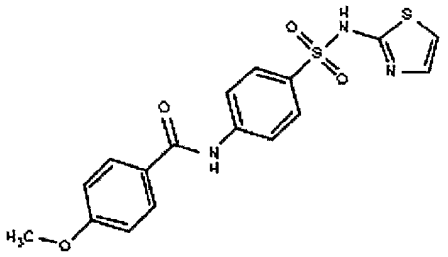
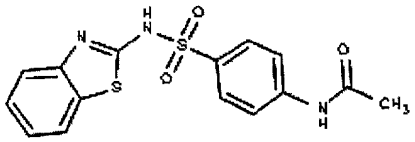
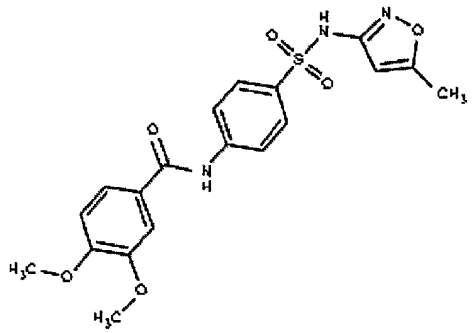
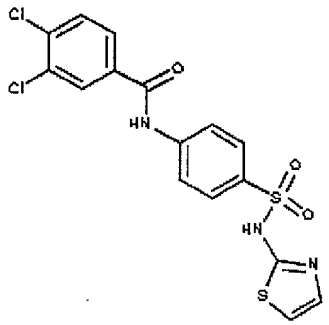
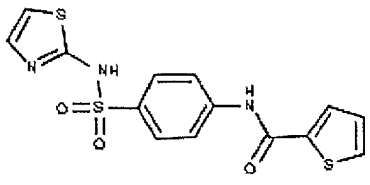
55	
56	
57	
58	
59	

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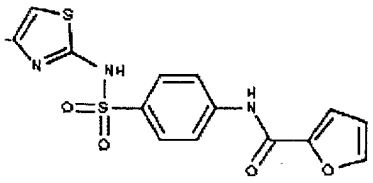
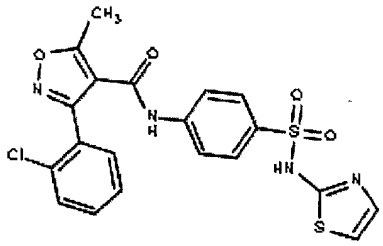
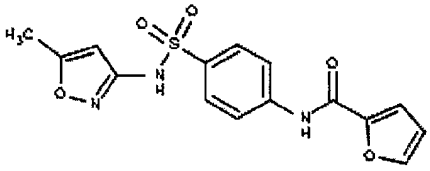
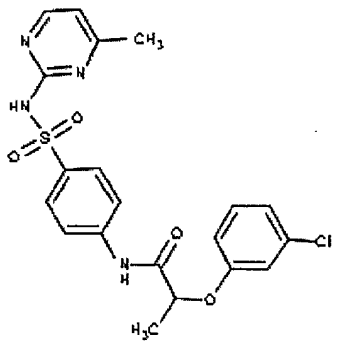
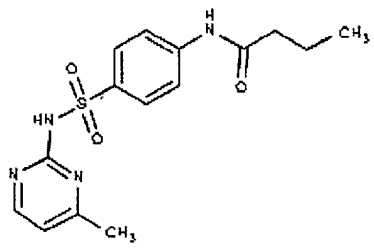
60	
61	
62	
63	
64	

Figure 1-8

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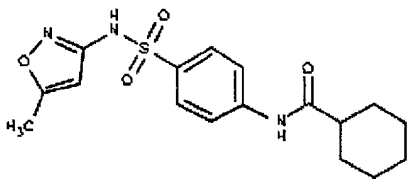
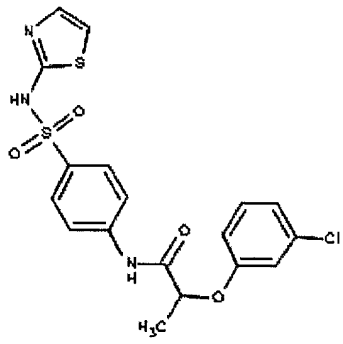
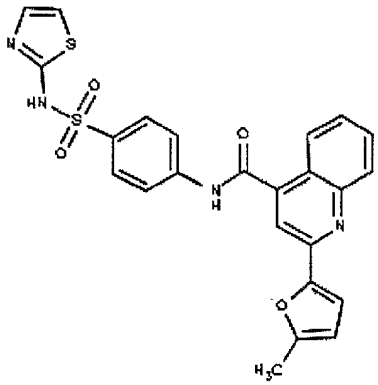
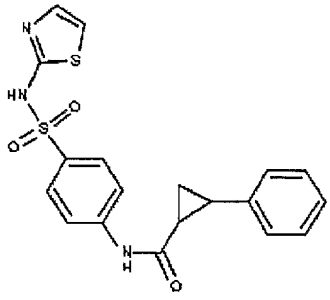
65	
66	
67	
68	

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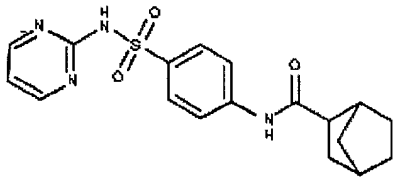
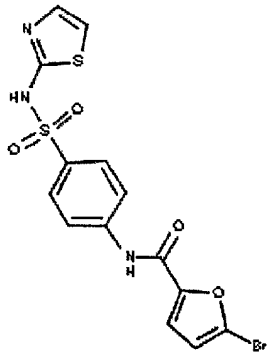
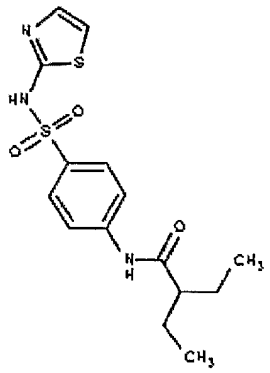
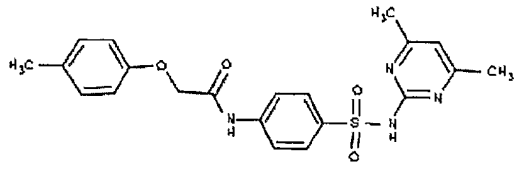
69	
70	
71	
72	

Figure 1-9

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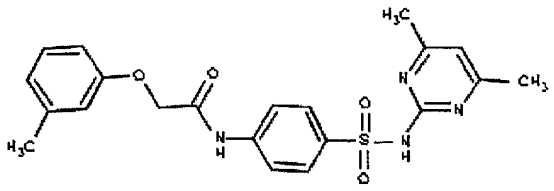
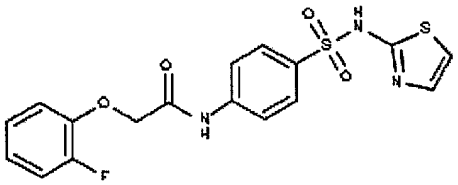
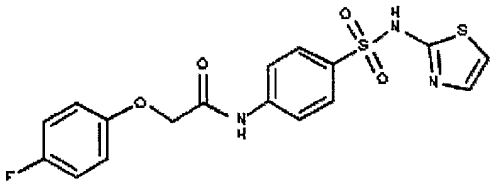
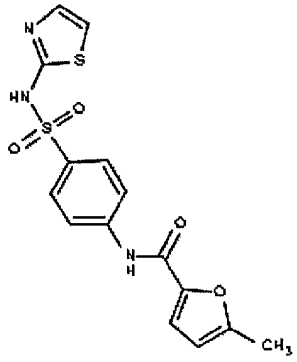
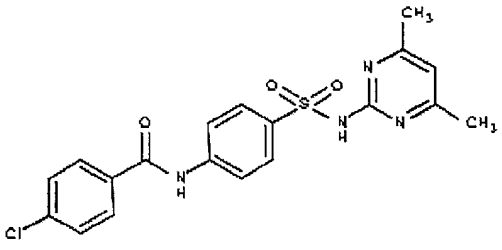
73	
74	
75	
76	
77	

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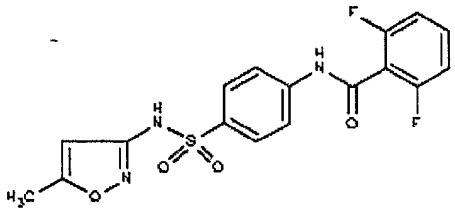
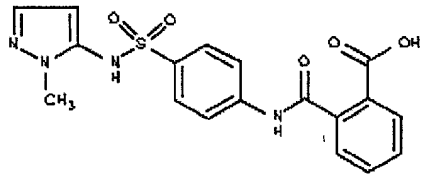
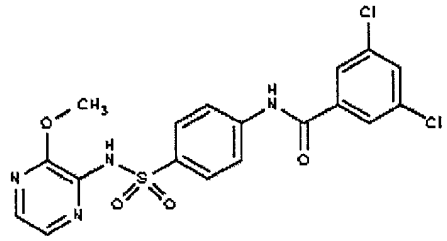
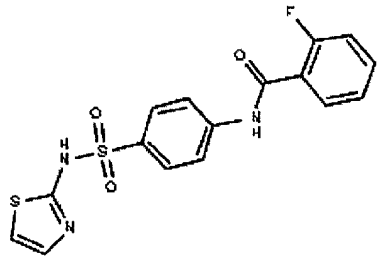
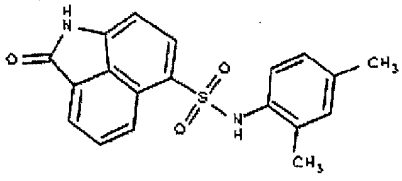
78	
79	
80	
81	
82	

Figure 1-10

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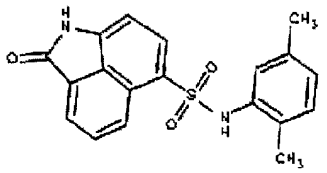
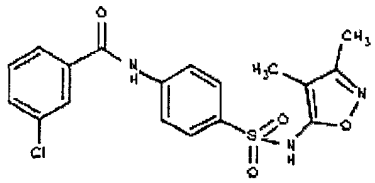
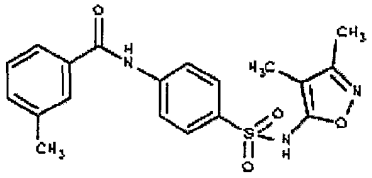
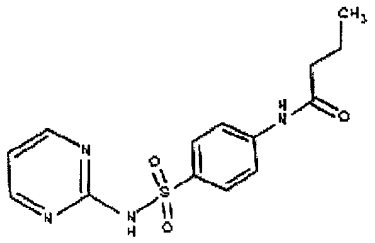
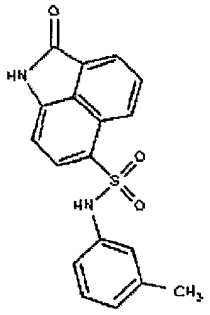
83	
84	
85	
86	
87	

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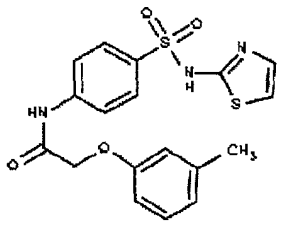
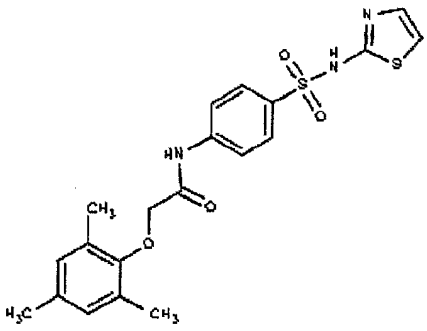
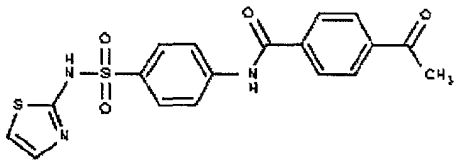
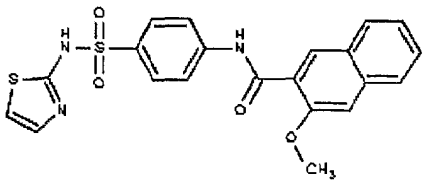
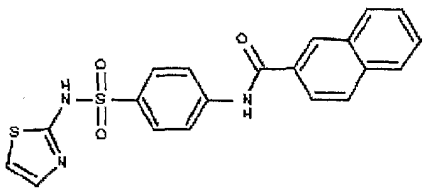
88	
89	
90	
91	
92	

Figure 1-11

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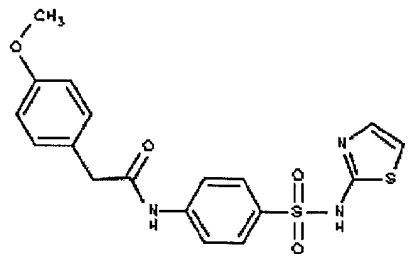
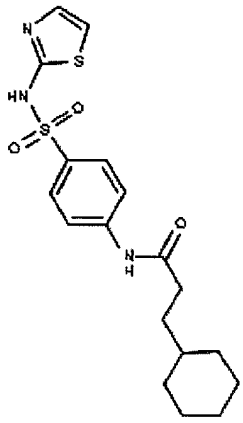
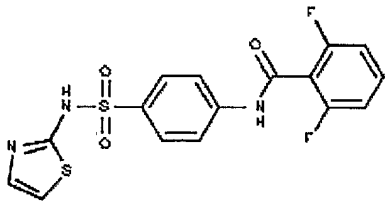
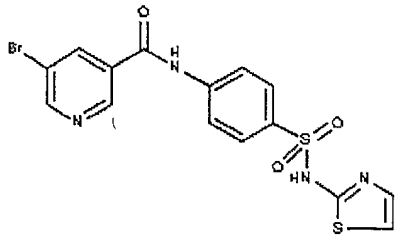
93	
94	
95	
96	

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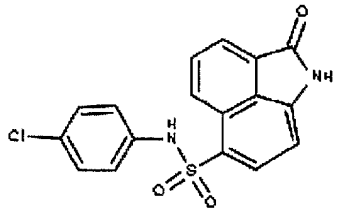
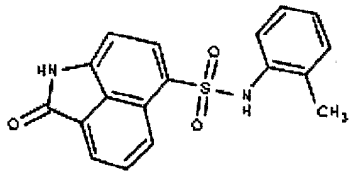
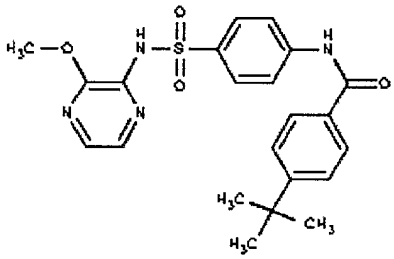
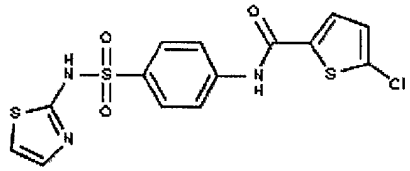
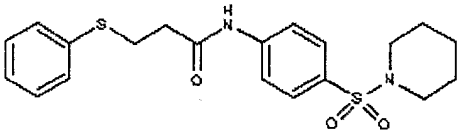
97	
98	
99	
100	
101	

Figure 1-12

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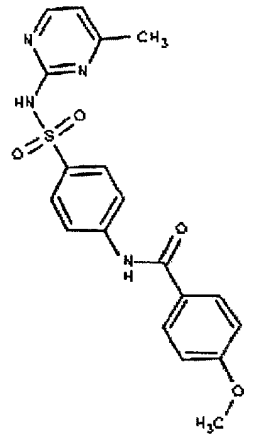
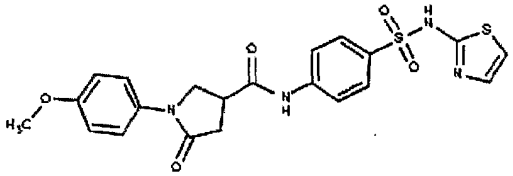
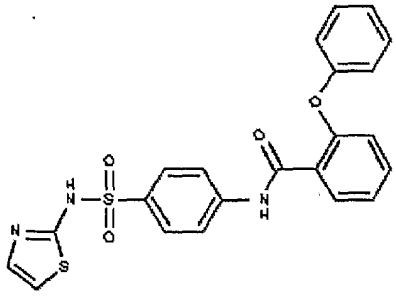
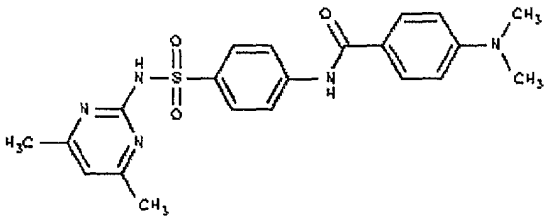
102	
103	
104	
105	

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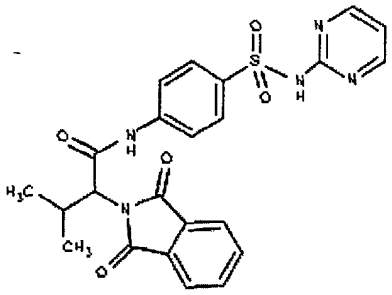
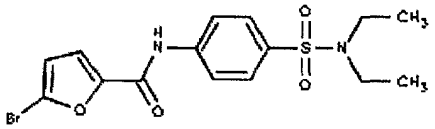
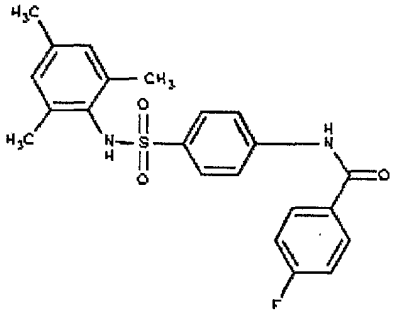
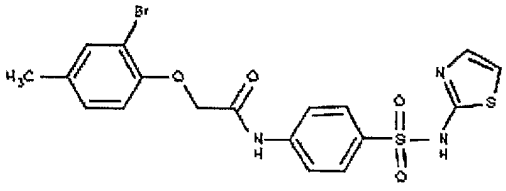
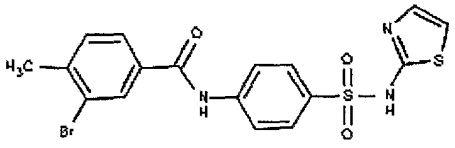
106	
107	
108	
109	
110	

Figure 1-13

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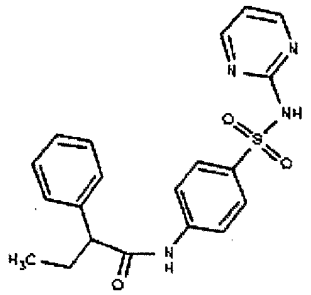
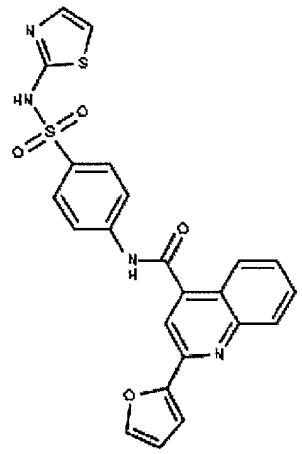
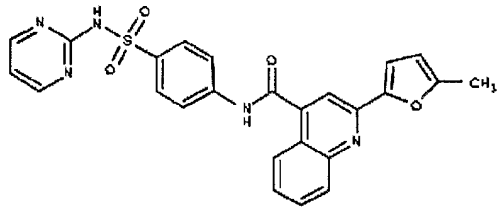
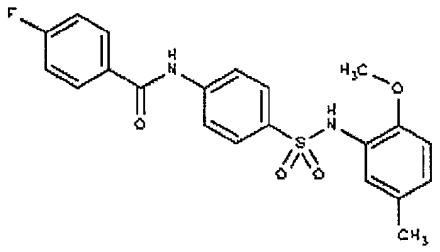
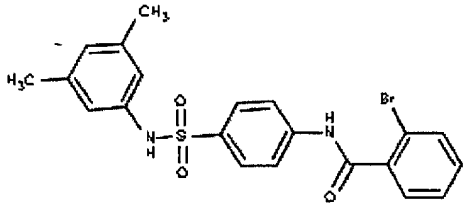
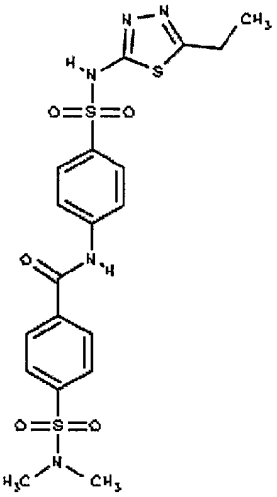
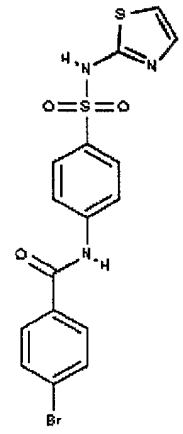
111	
112	
113	
114	
115	
116	
117	

Figure 1-14

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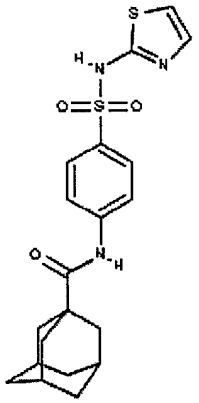
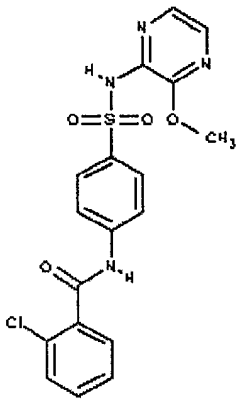
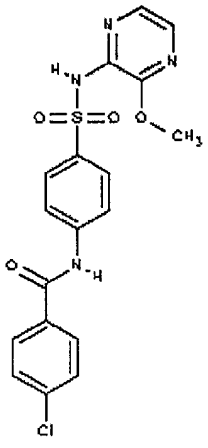
118	
119	
120	

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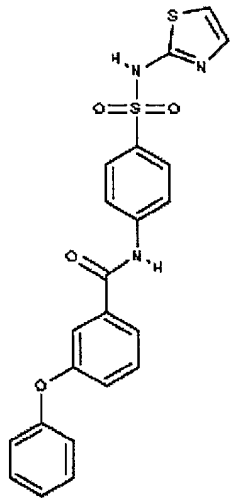
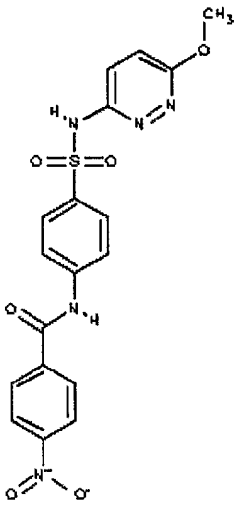
121	
122	

Figure 1-15

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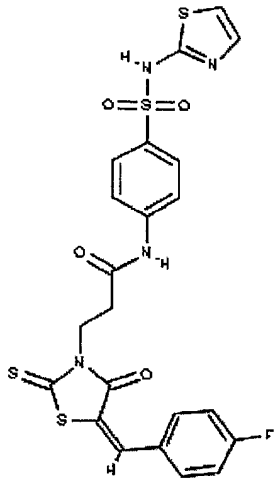
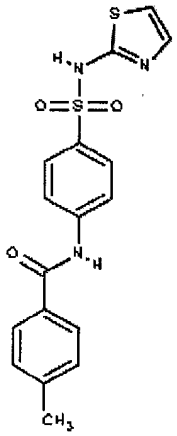
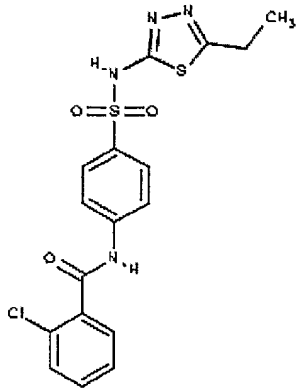
123	
124	
125	

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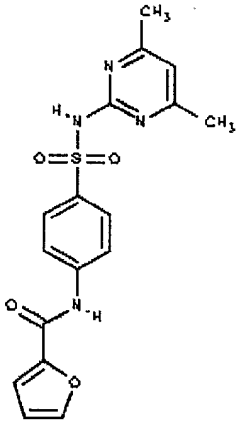
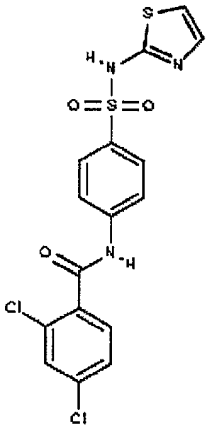
126	
127	

Figure 1-16

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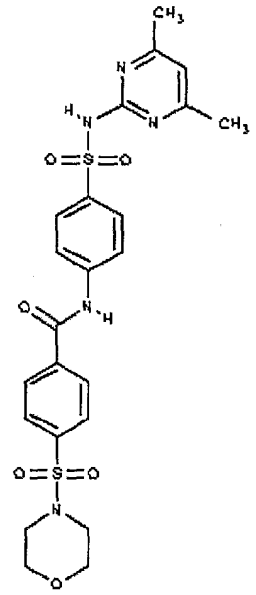
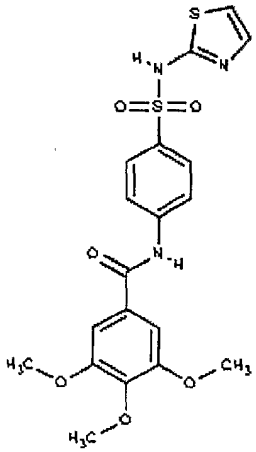
128	
129	

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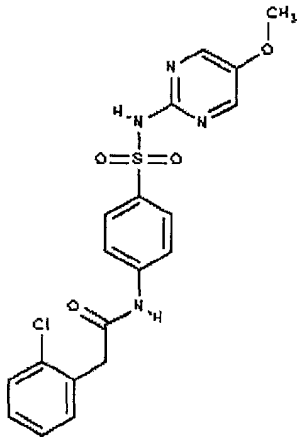
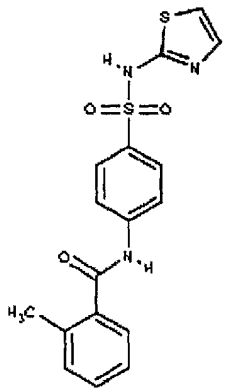
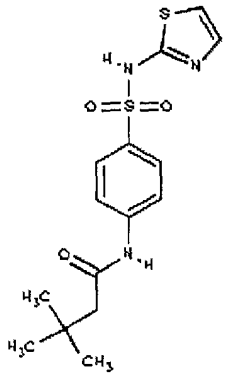
130	
131	
132	

Figure 1-17

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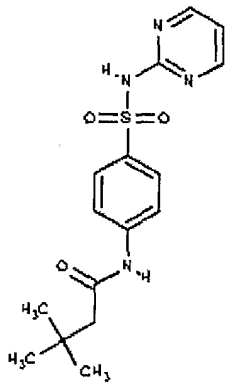
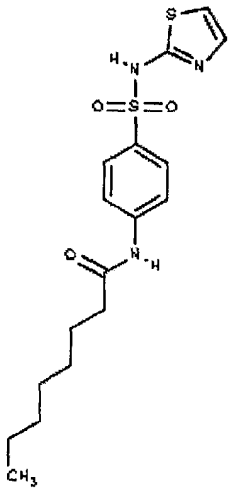
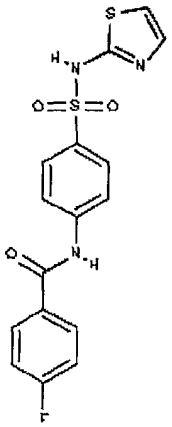
133	
134	
135	

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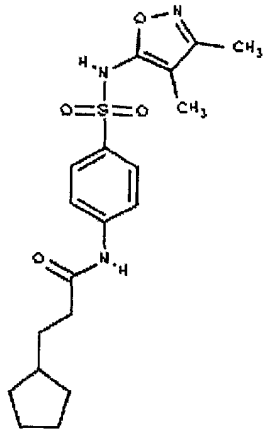
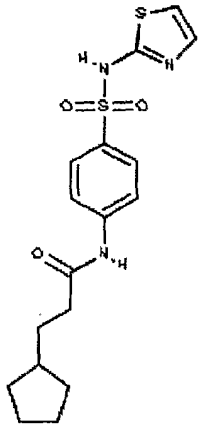
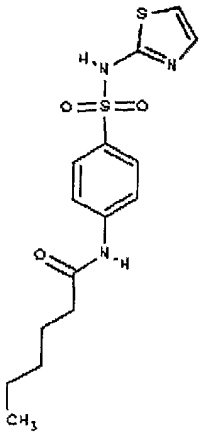
136	
137	
138	

Figure 1-18

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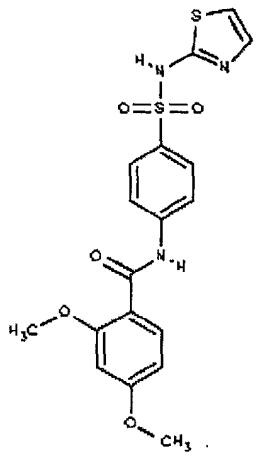
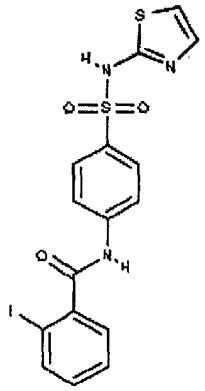
139	
140	

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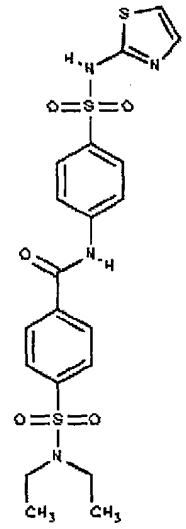
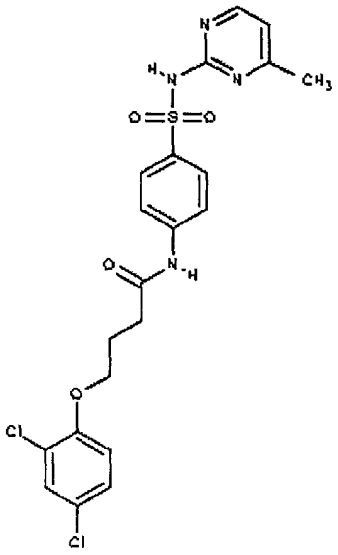
141	
142	

Figure 1-19

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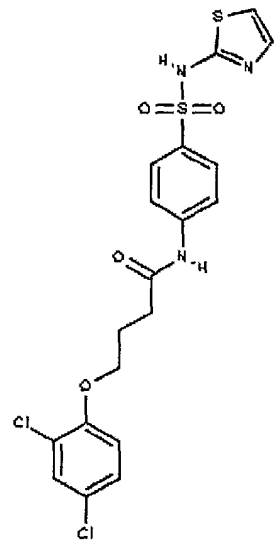
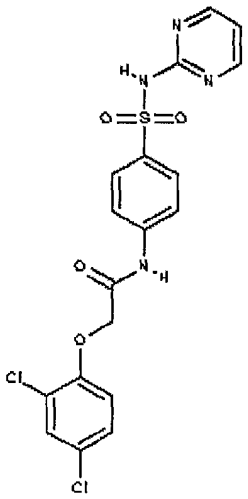
143	
144	

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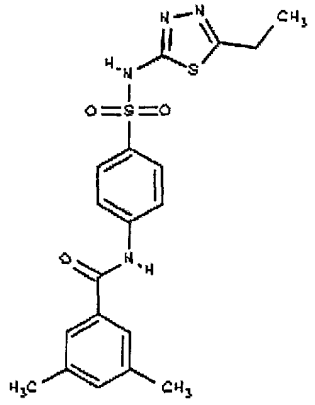
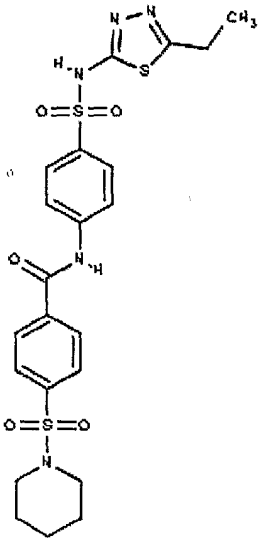
145	
146	

Figure 1-20

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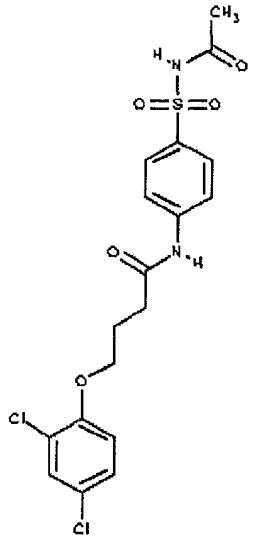
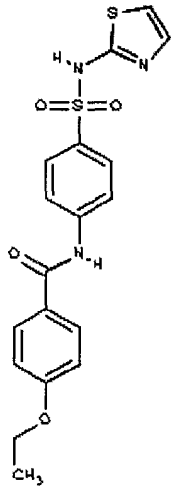
147	
148	

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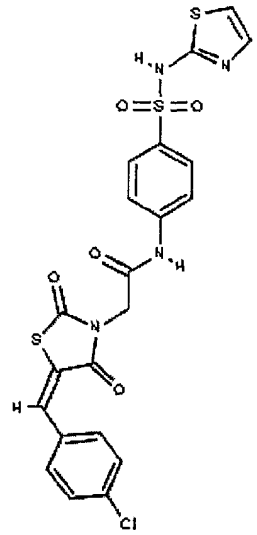
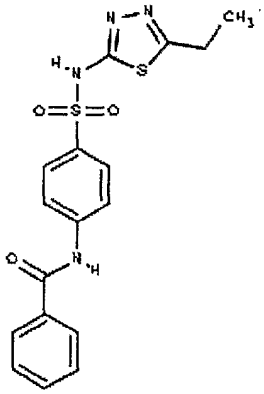
149	
150	

Figure 1-21

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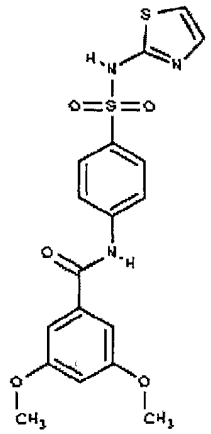
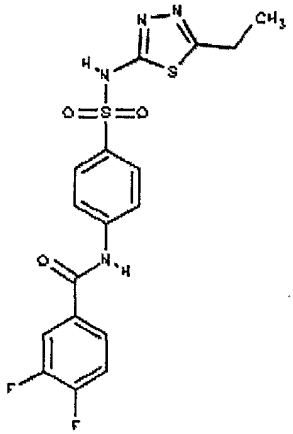
151	
152	

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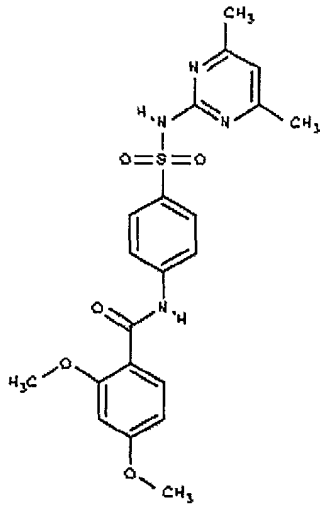
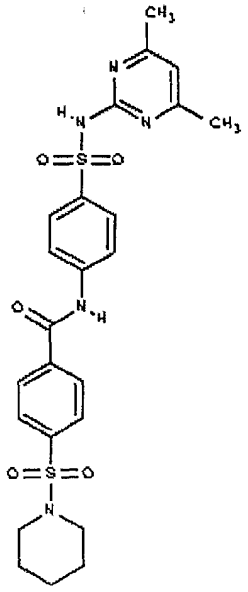
153	
154	

Figure 1-22

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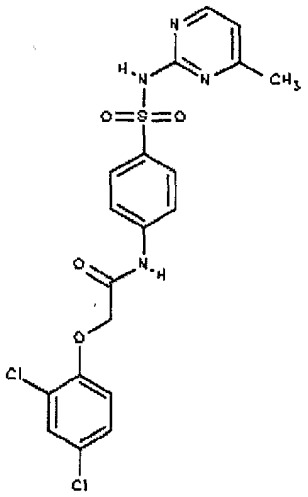
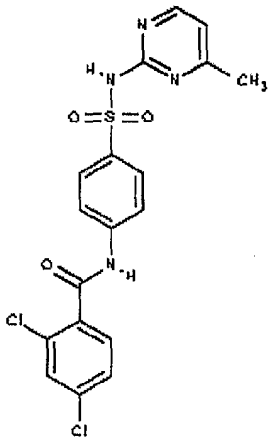
155	
156	

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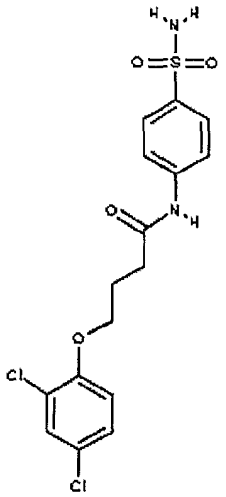
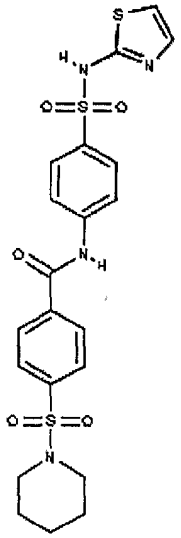
157	
158	

Figure 1-23

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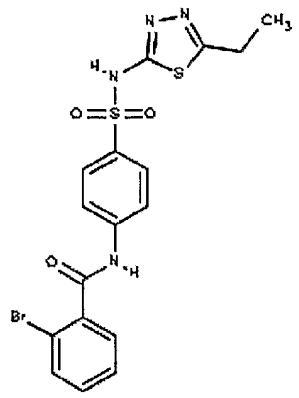
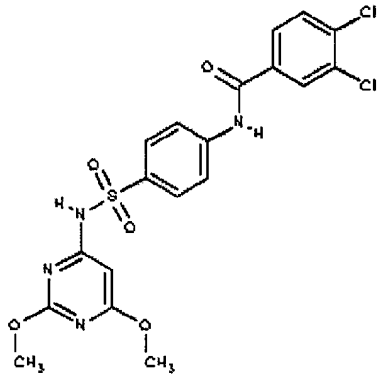
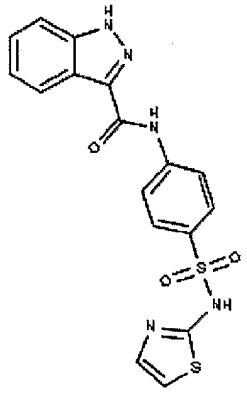
159	
160	
161	

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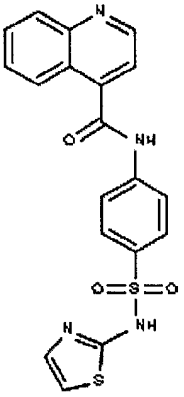
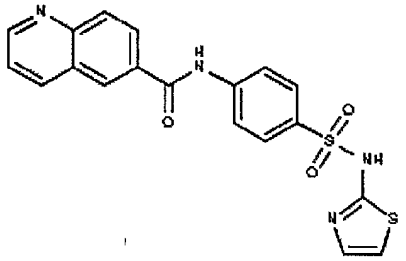
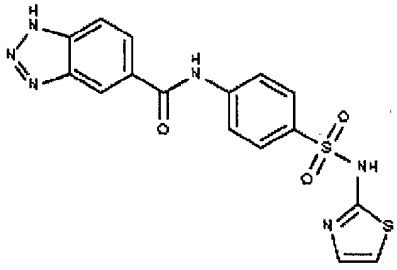
162	
163	
164	

Figure 1-24

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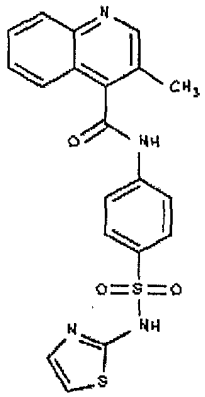
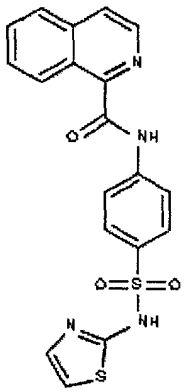
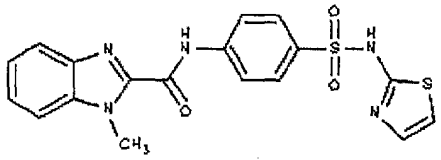
165	
166	
167	

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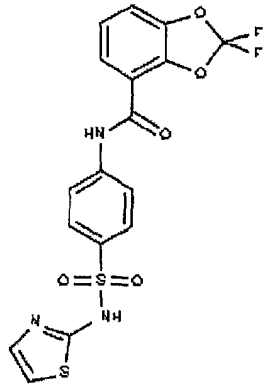
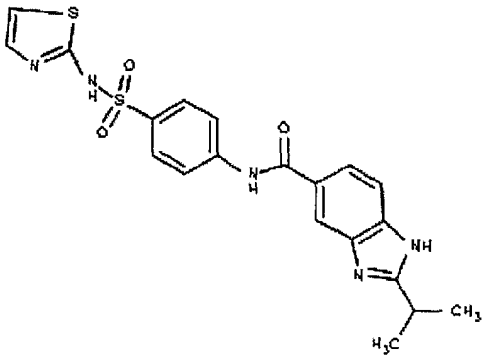
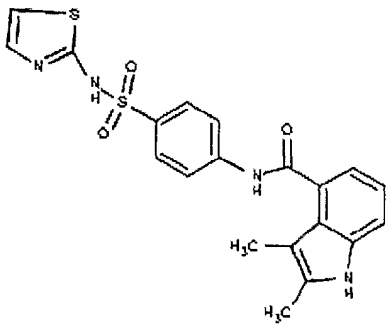
168	
170	
171	

Figure 1-25

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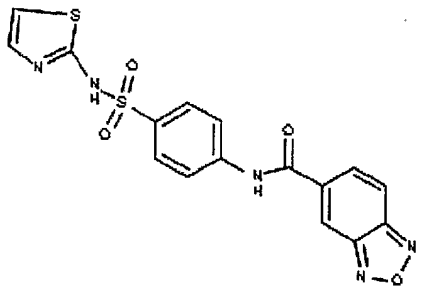
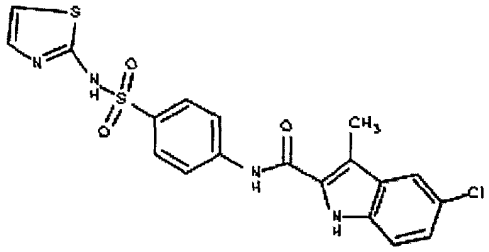
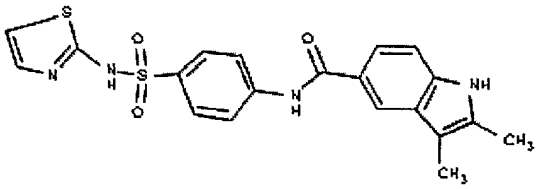
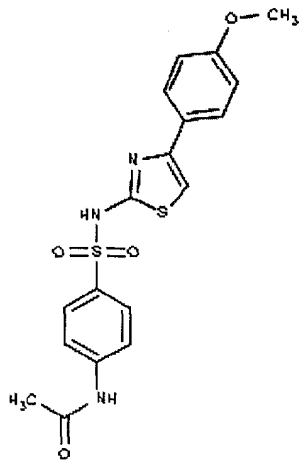
172	
173	
174	
175	

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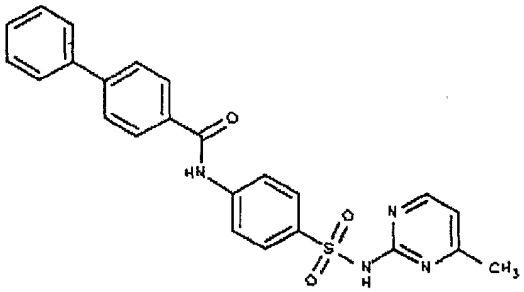
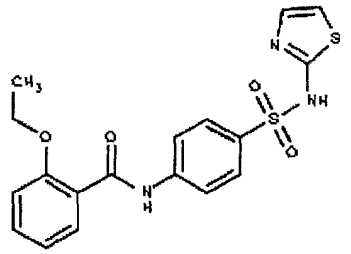
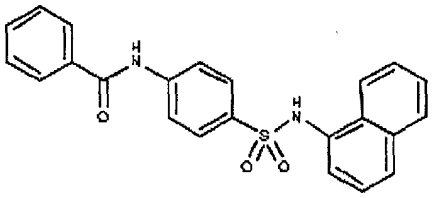
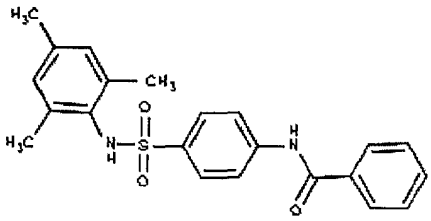
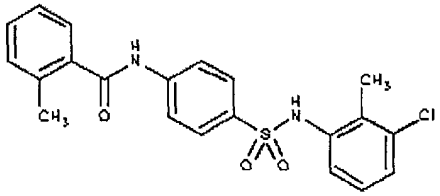
176	
177	
178	
179	
180	

Figure 1-26

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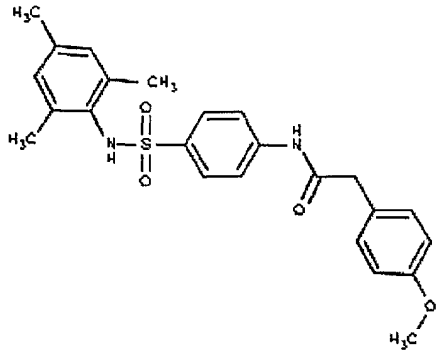
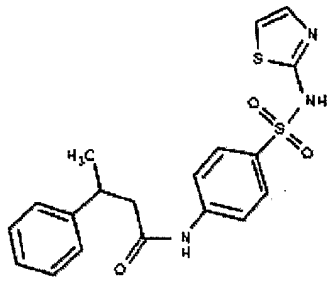
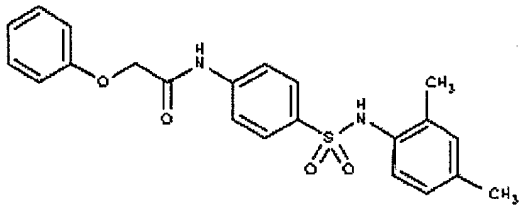
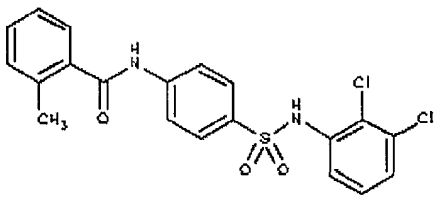
181	
182	
183	
184	

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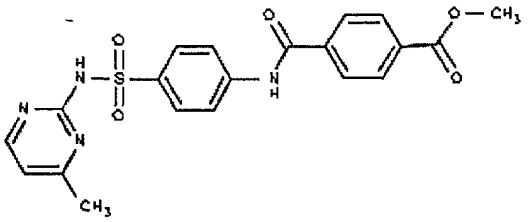
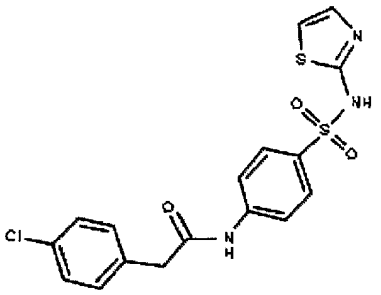
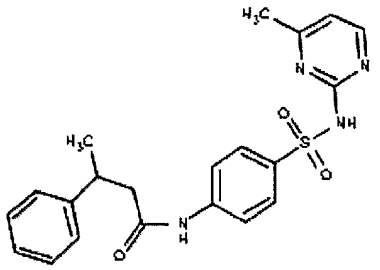
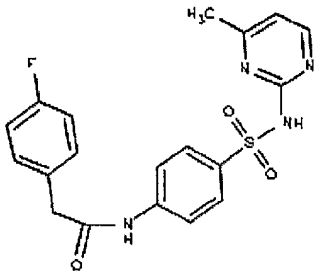
185	
186	
187	
188	

Figure 1-27

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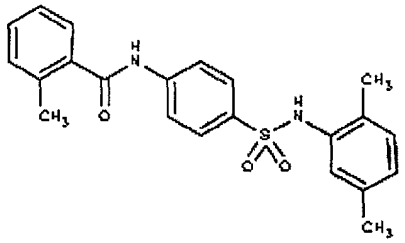
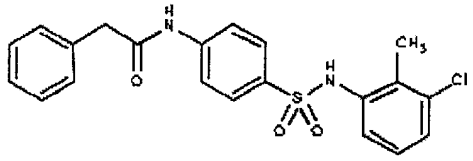
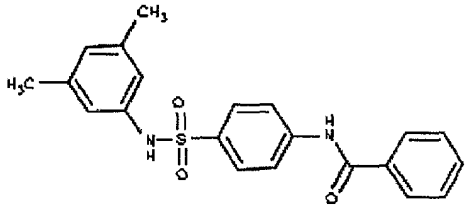
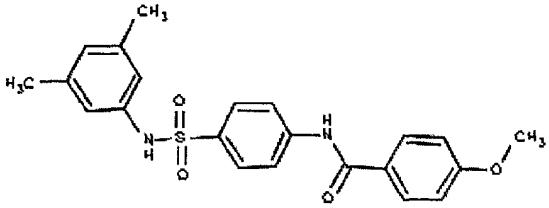
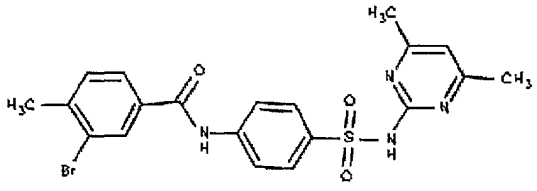
189	
190	
191	
192	
193	

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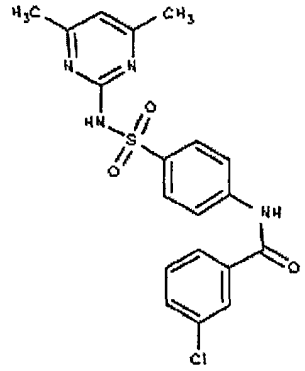
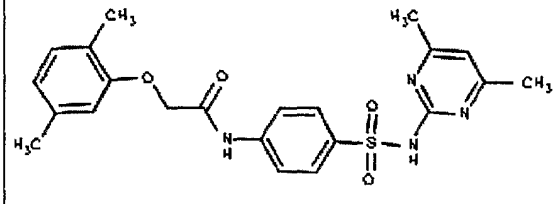
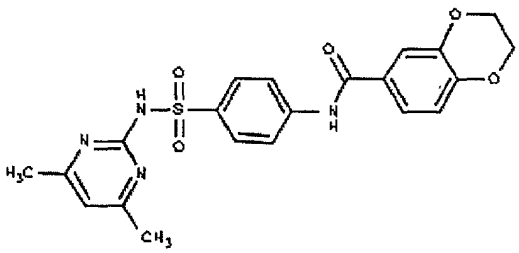
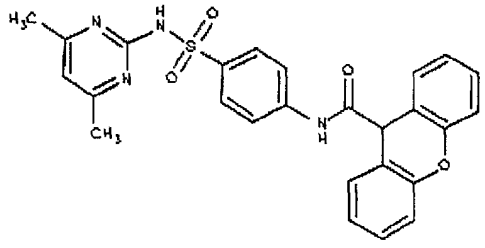
194	
195	
196	
197	

Figure 1-28

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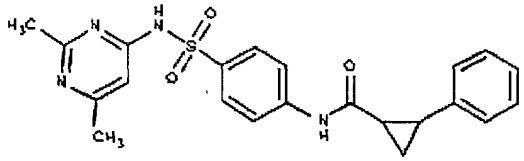
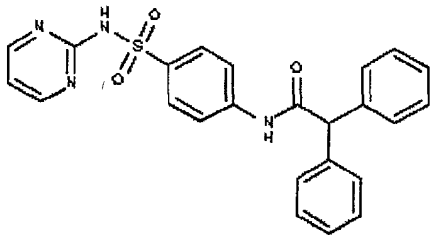
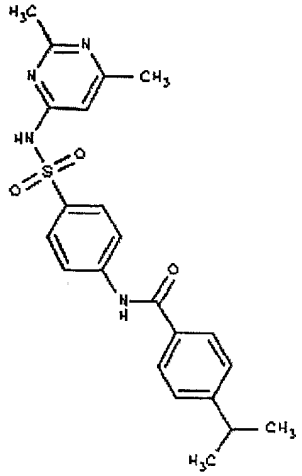
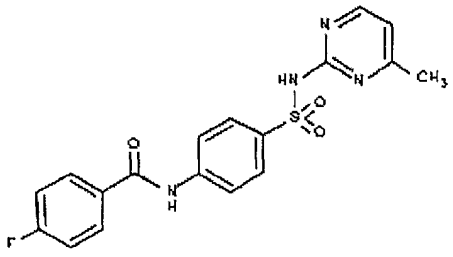
198	
199	
200	
201	

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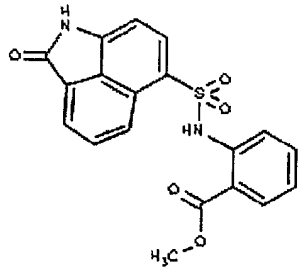
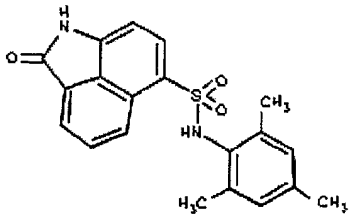
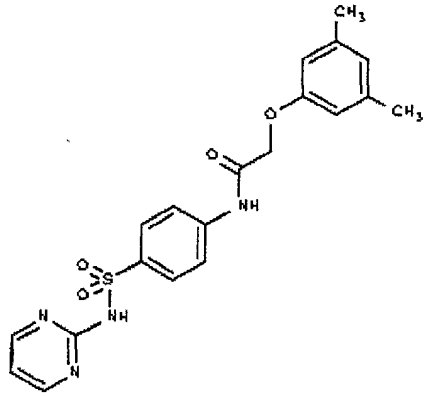
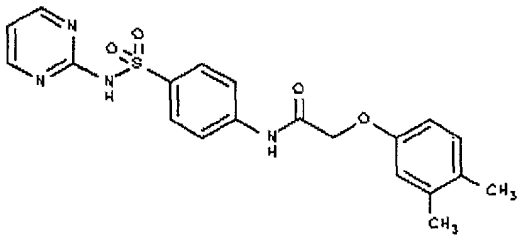
202	
203	
204	
205	

Figure 1-29

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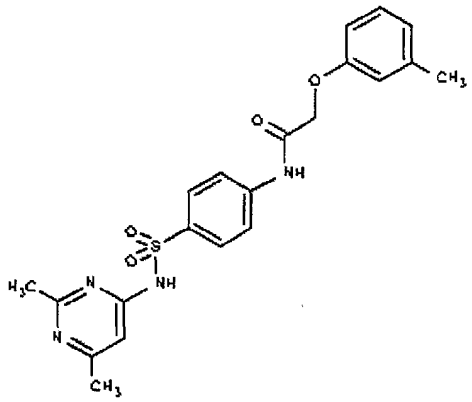
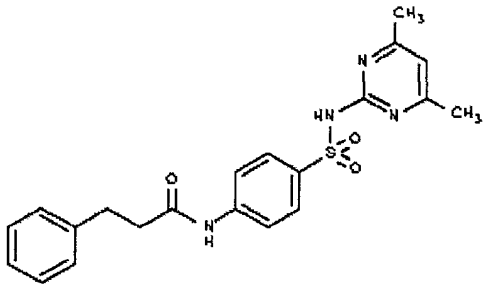
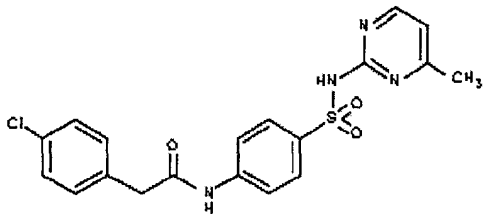
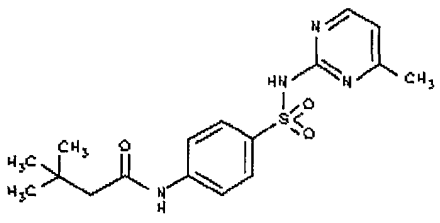
206	
207	
208	
209	

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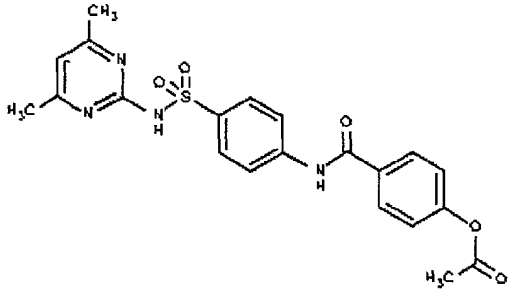
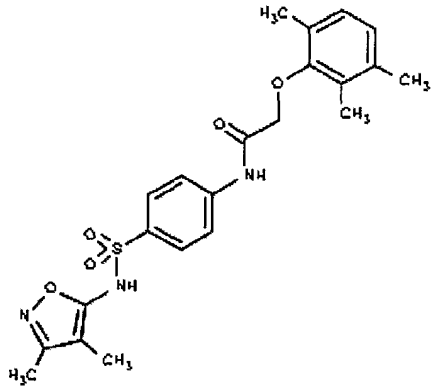
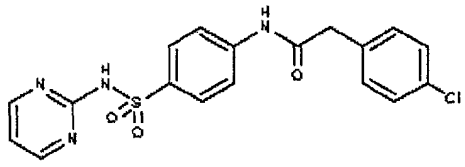
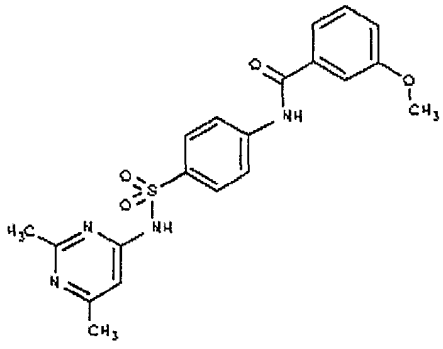
210	
211	
212	
213	

Figure 1-30

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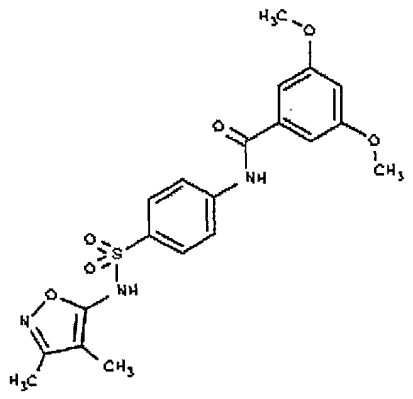
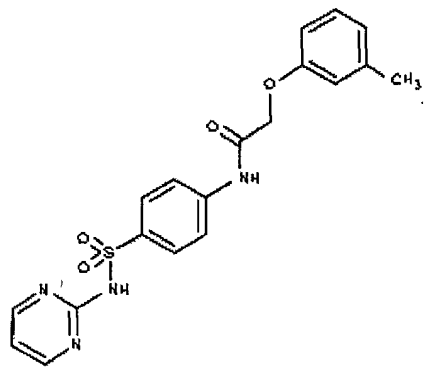
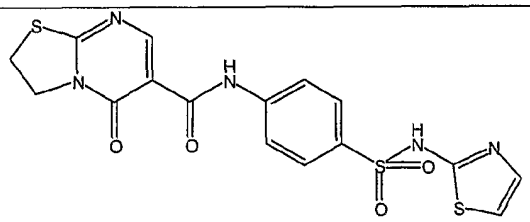
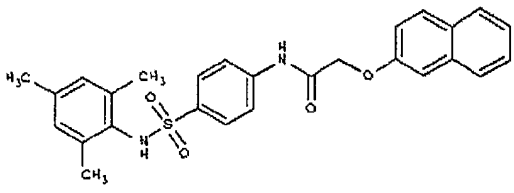
214	
215	
216	
217	

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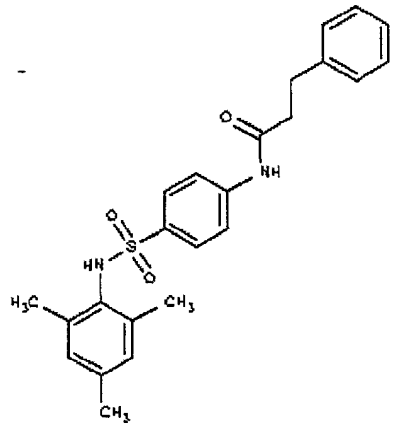
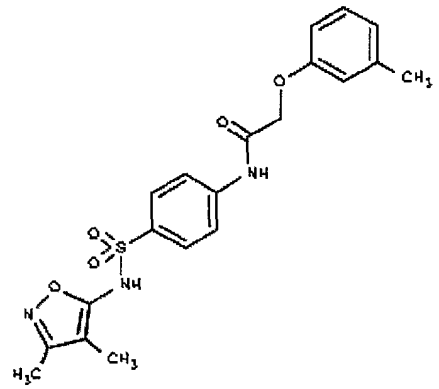
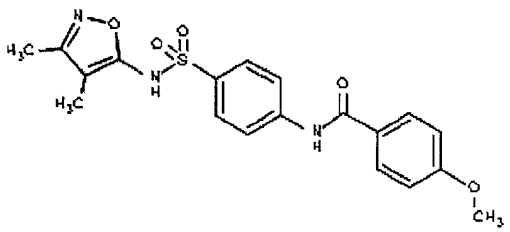
218	
219	
220	

Figure 1-31

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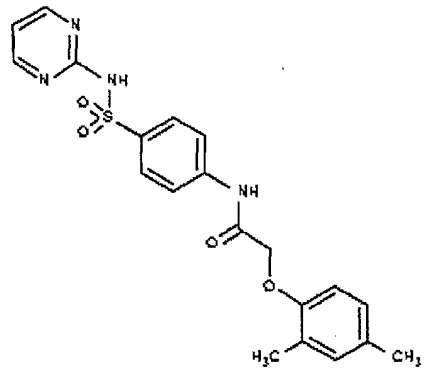
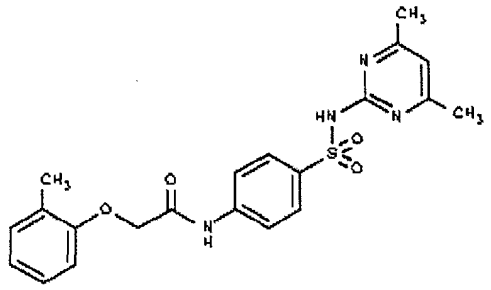
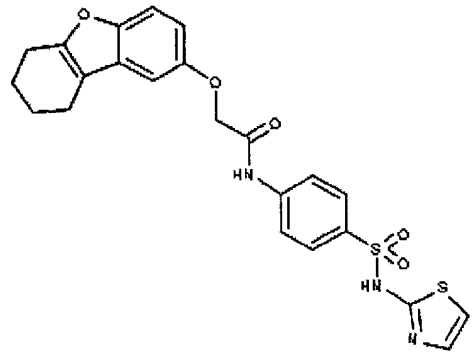
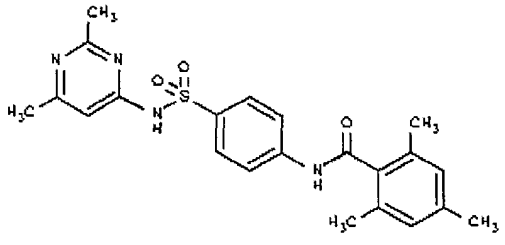
221	
222	
223	
224	

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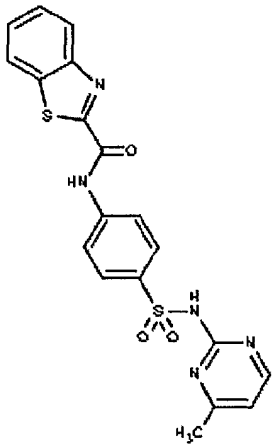
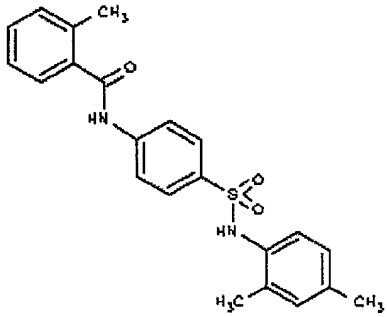
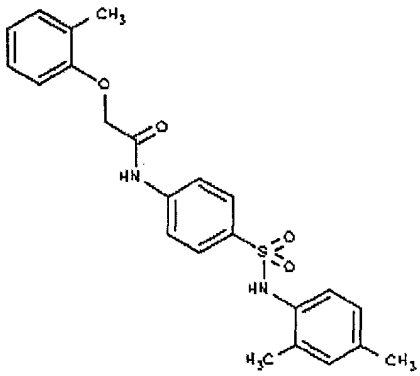
225	
226	
227	

Figure 1-32

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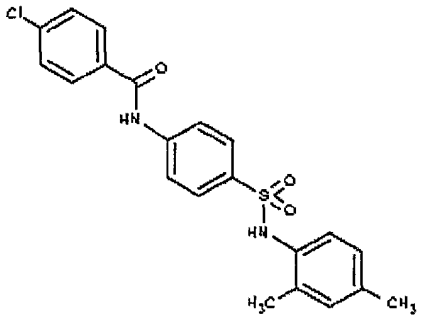
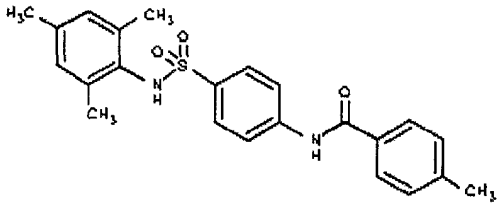
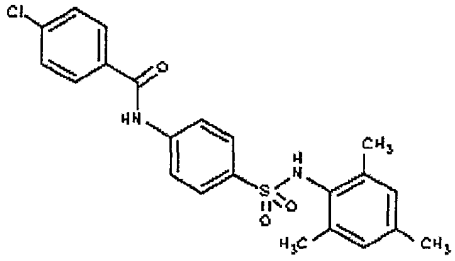
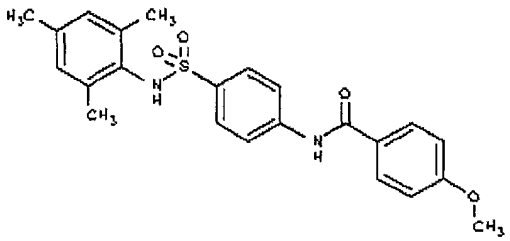
228	
229	
230	
231	

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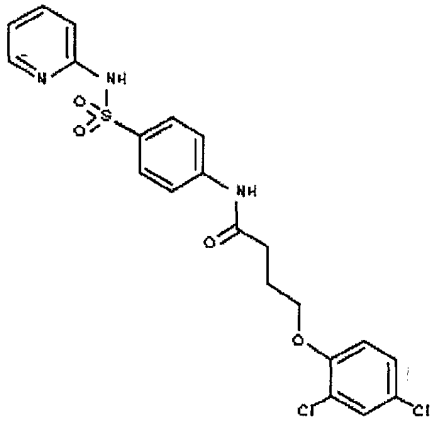
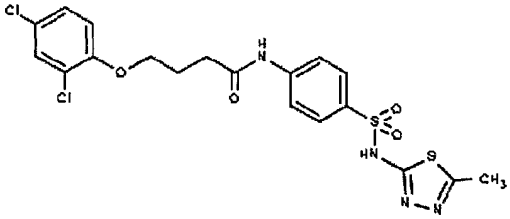
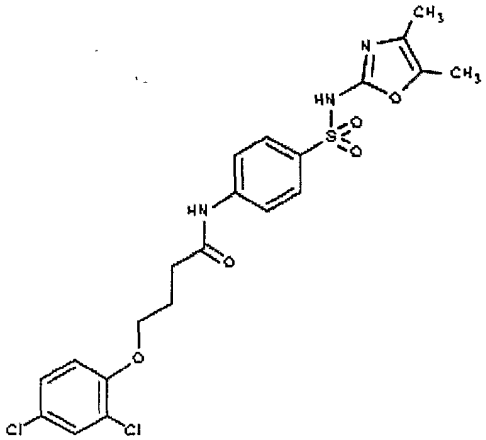
232	
233	
234	

Figure 1-33

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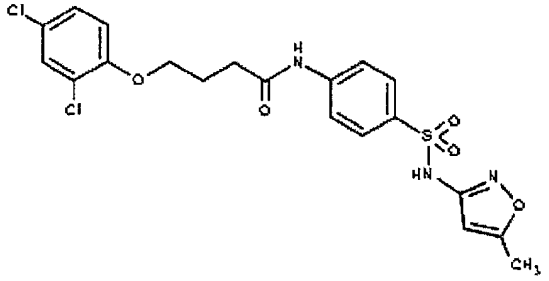
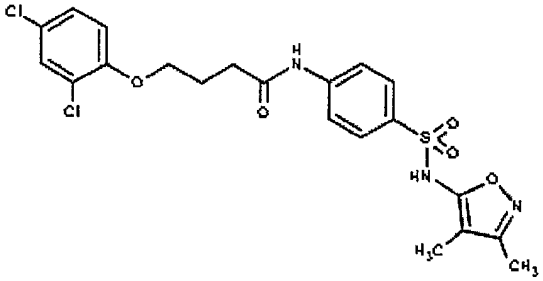
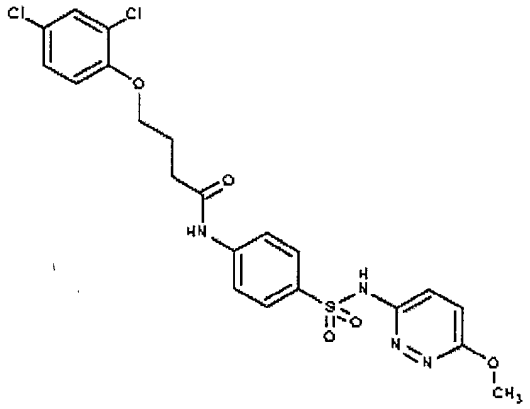
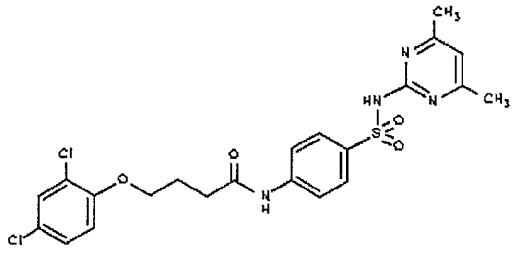
235	
236	
237	
238	

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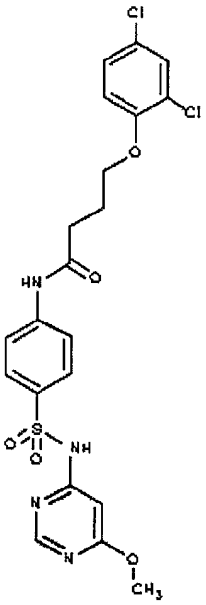
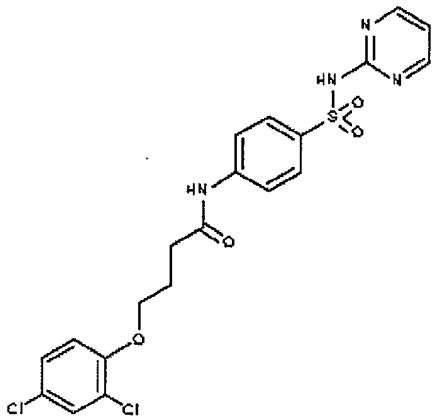
239	
240	

Figure 1-34

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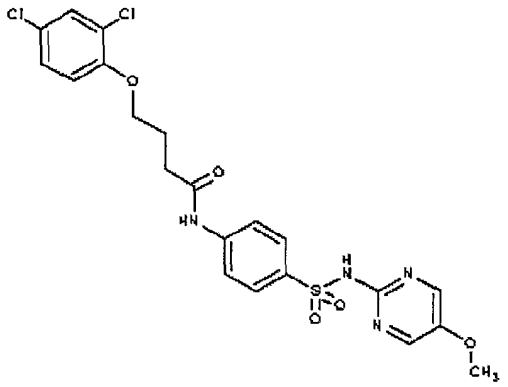
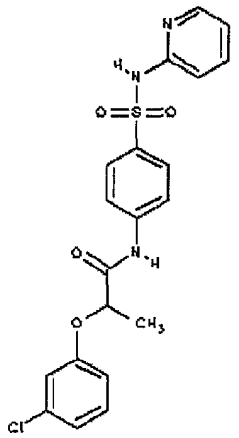
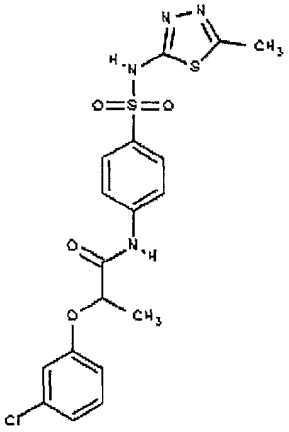
241	
242	
243	

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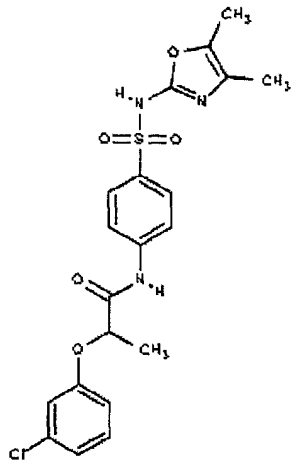
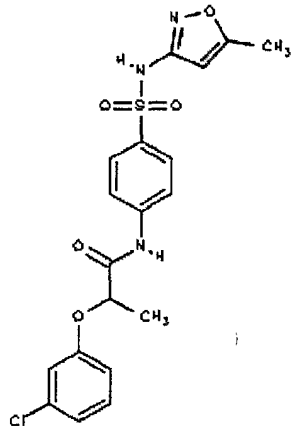
244	
245	

Figure 1-35

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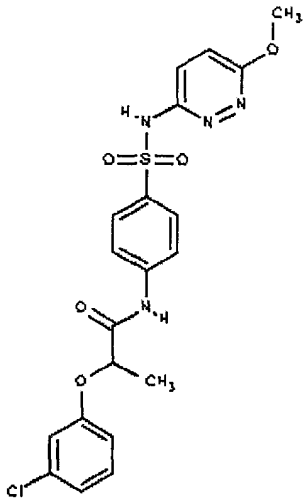
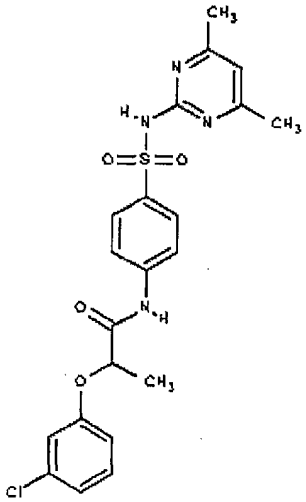
246	
247	

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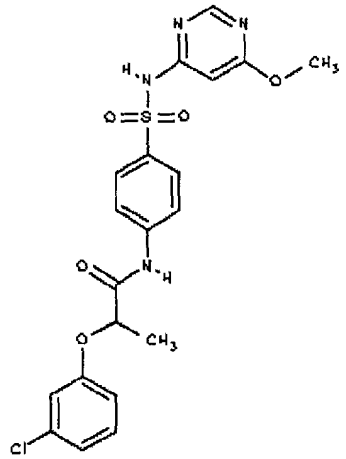
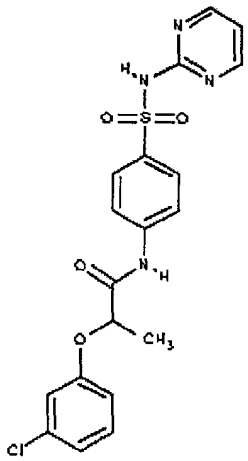
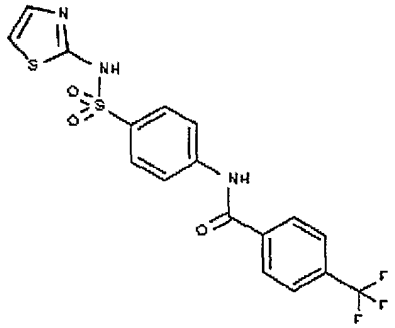
248	
249	
250	

Figure 1-36

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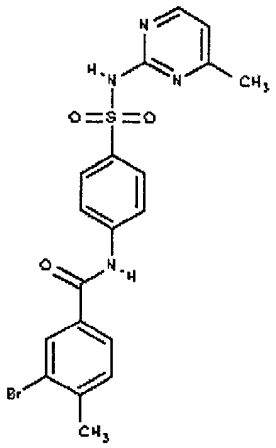
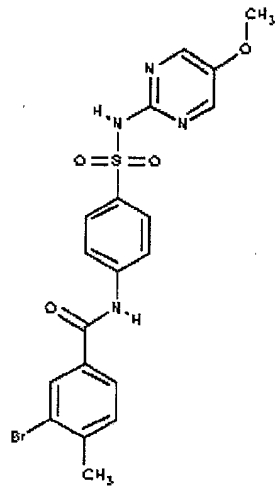
251	
252	

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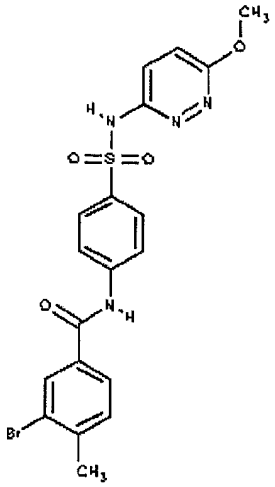
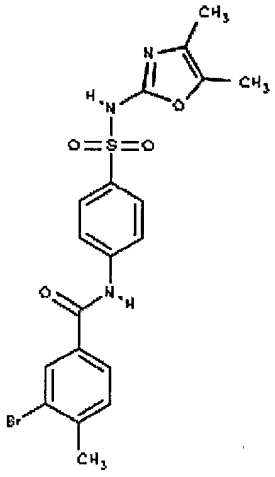
253	
254	

Figure 1-37

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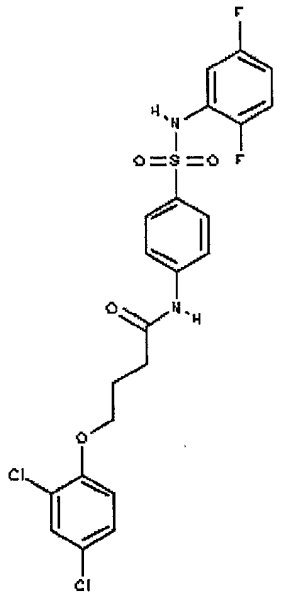
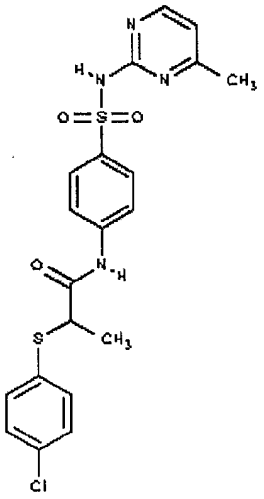
255	
256	

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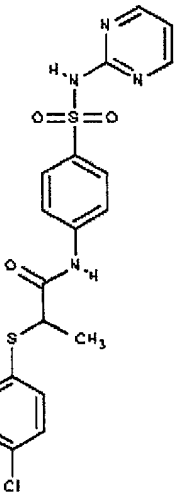
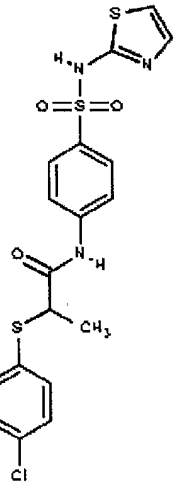
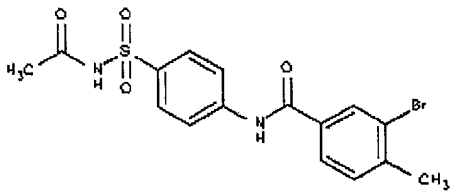
257	
258	
259	

Figure 1-38

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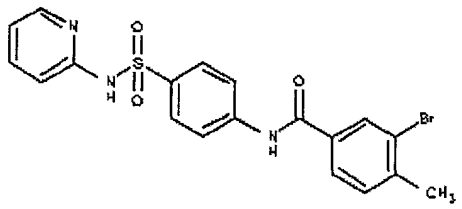
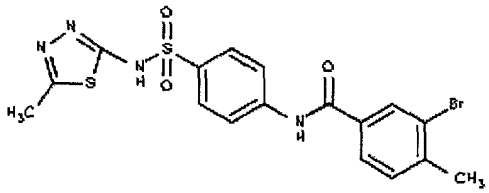
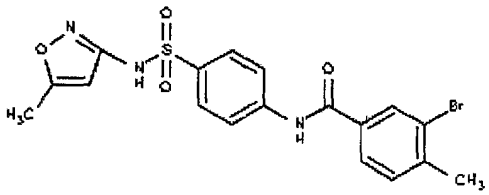
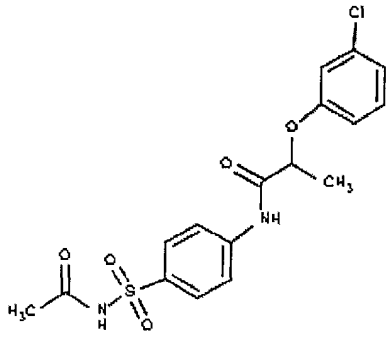
260	
261	
262	
263	

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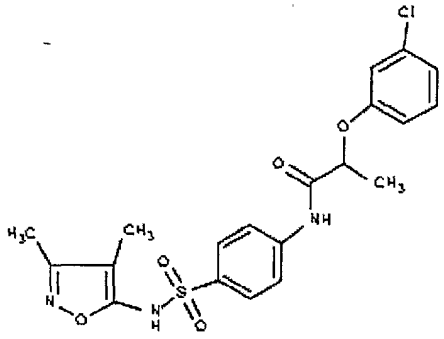
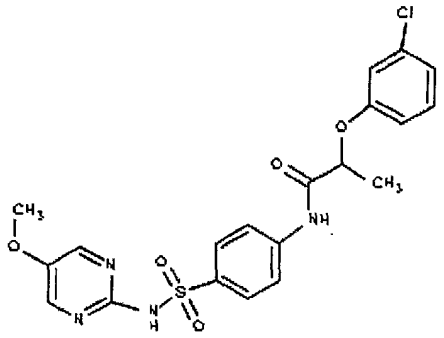
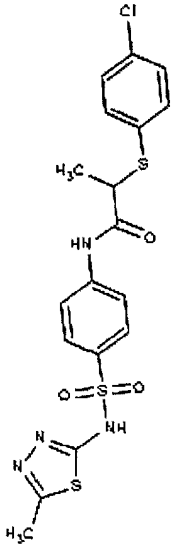
264	
265	
266	

Figure 1-39

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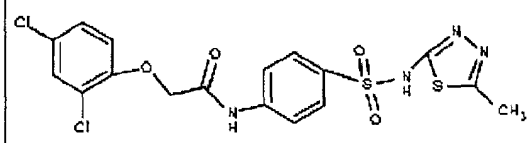
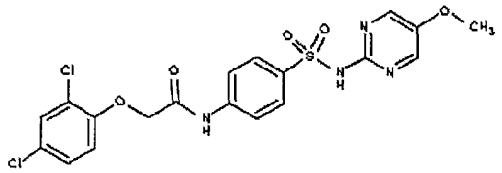
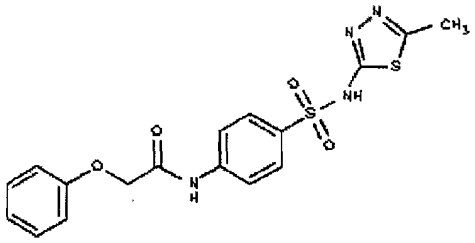
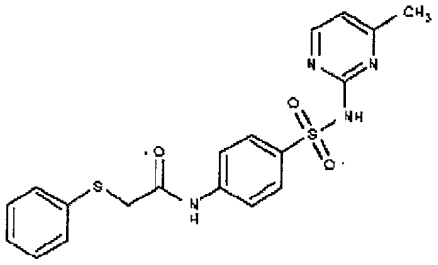
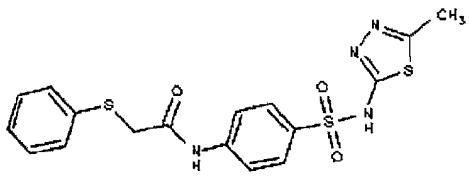
267	
268	
269	
270	
271	

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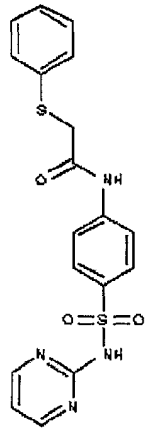
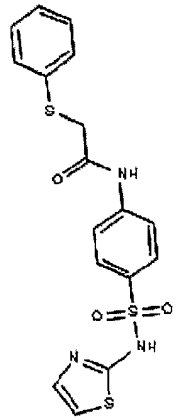
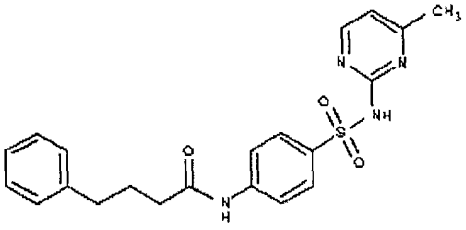
272	
273	
274	

Figure 1-40

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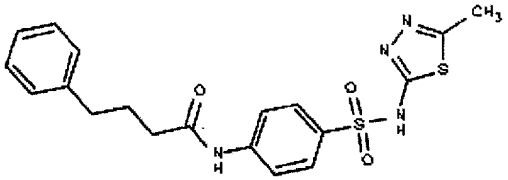
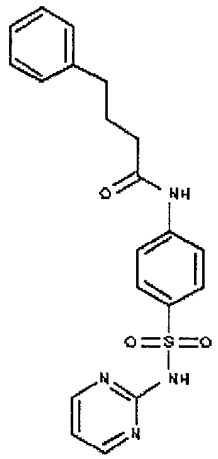
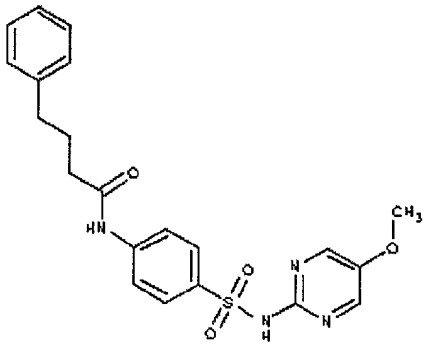
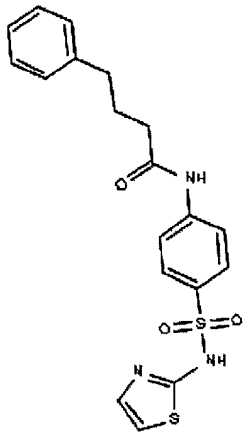
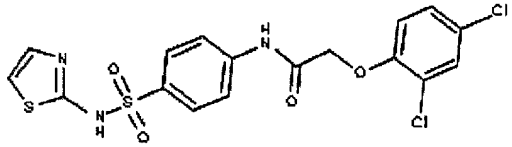
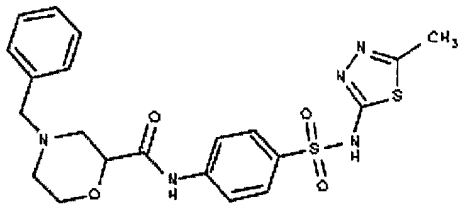
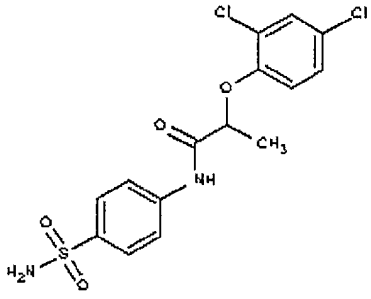
275	
276	
277	
278	
279	
280	
281	

Figure 1-41

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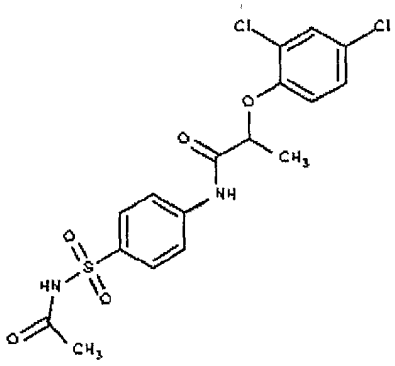
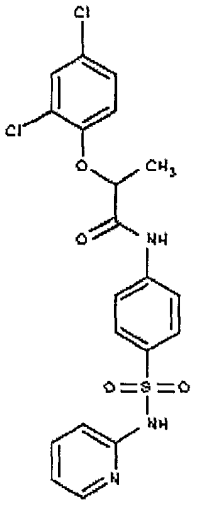
282	
283	

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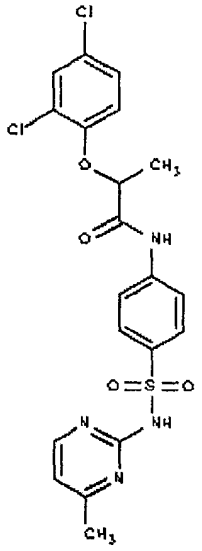
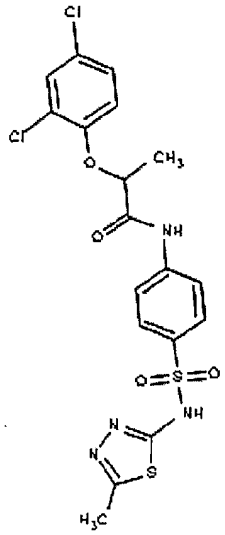
284	
285	

Figure 1-42

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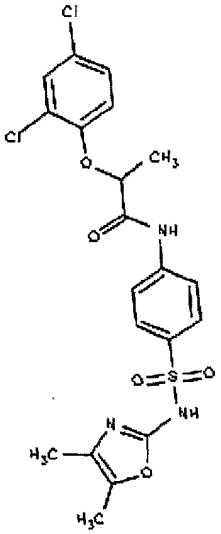
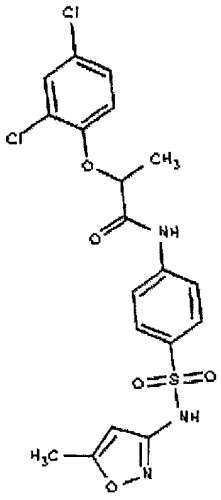
286	
287	

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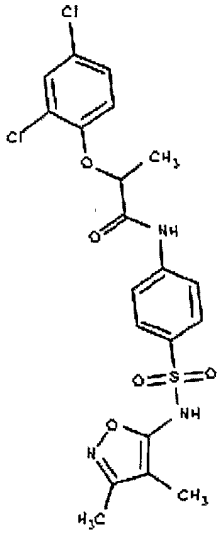
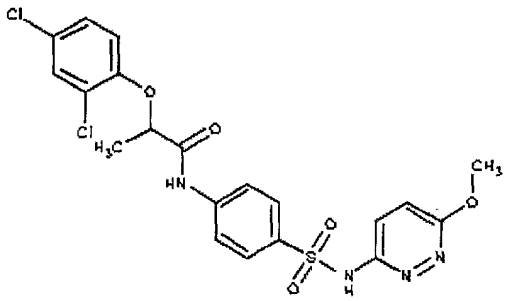
288	
289	

Figure 1-43

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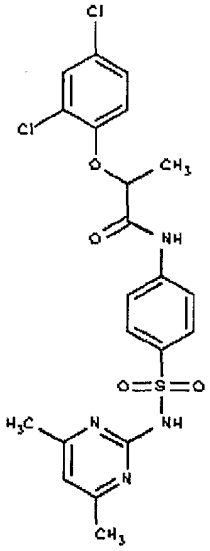
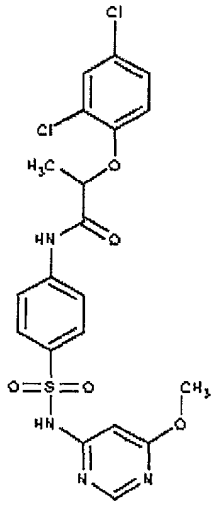
290	
291	

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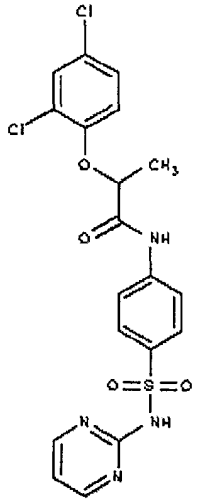
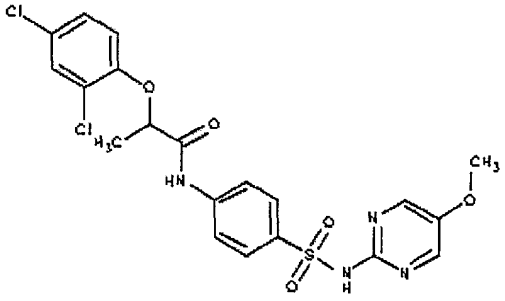
292	
293	

Figure 1-44

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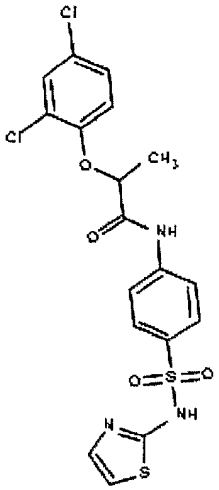
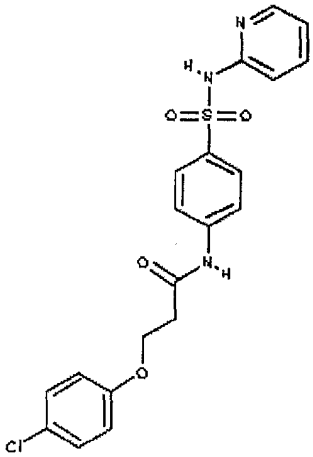
294	
295	

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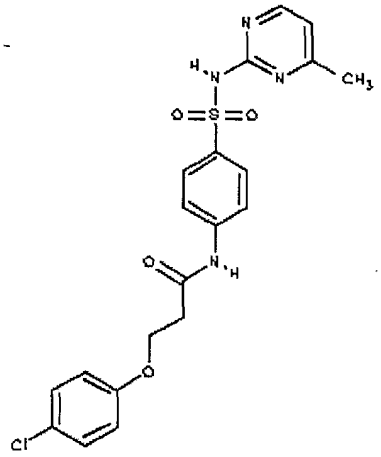
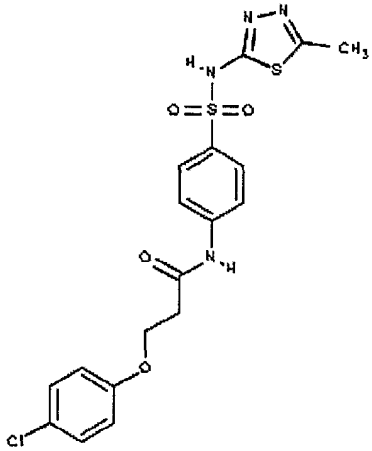
296	
297	

Figure 1-45

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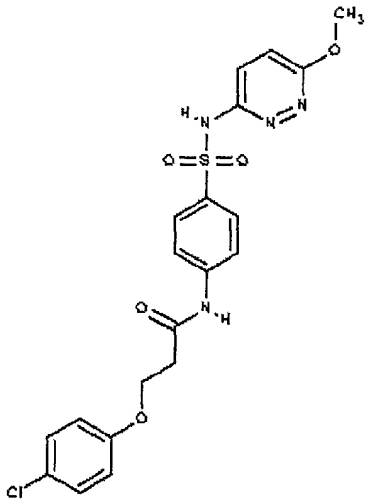
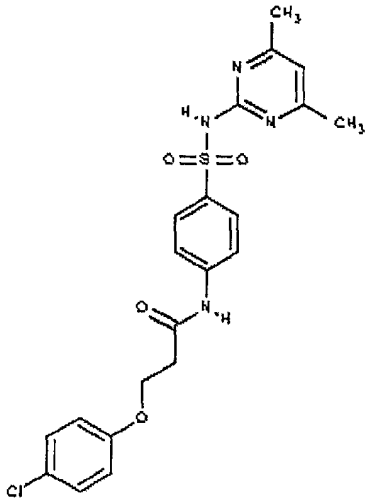
298	
299	

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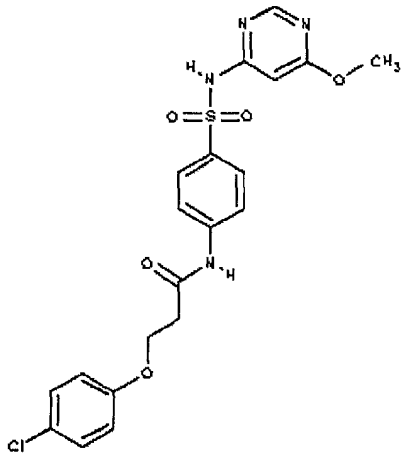
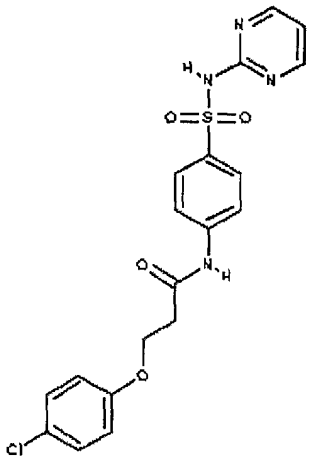
300	
301	

Figure 1-46

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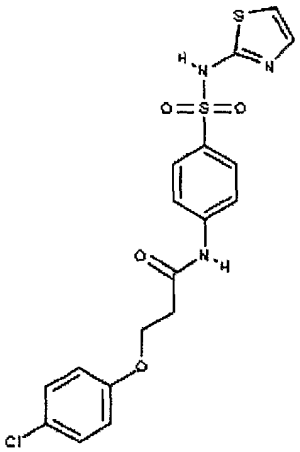
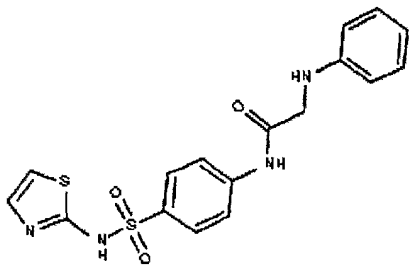
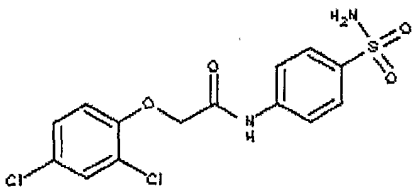
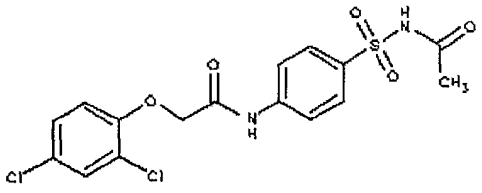
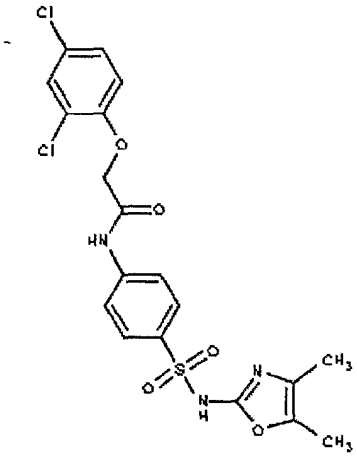
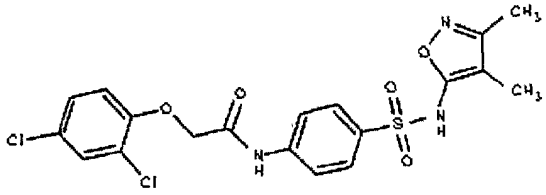
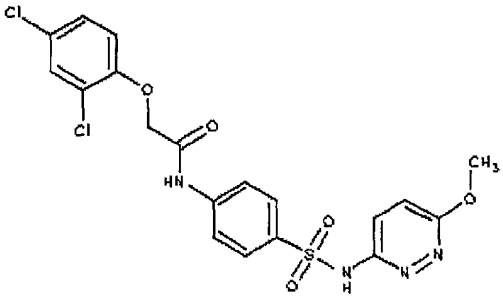
302	
303	
304	
305	
306	
307	
308	

Figure 1-47

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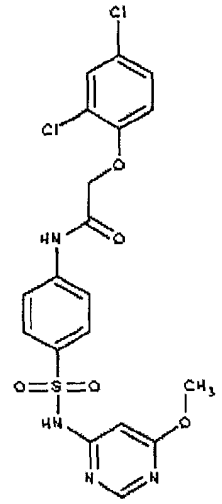
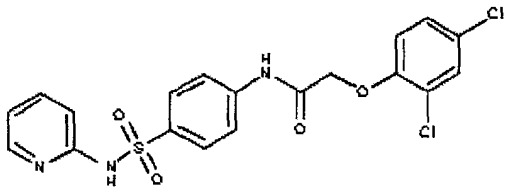
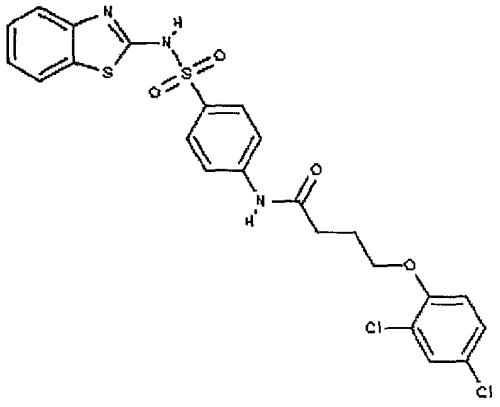
309	
310	
311	

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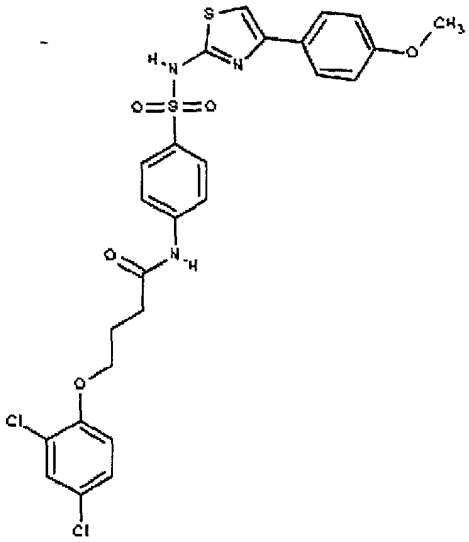
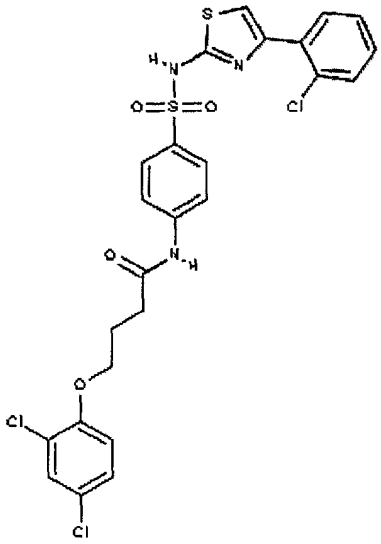
312	
313	

Figure 1-48

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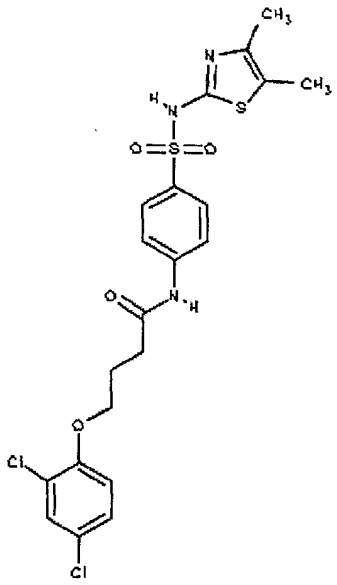
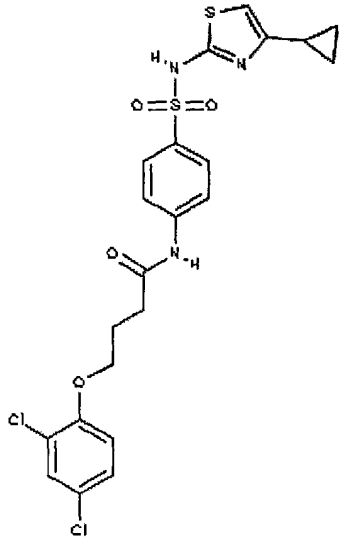
314	
315	

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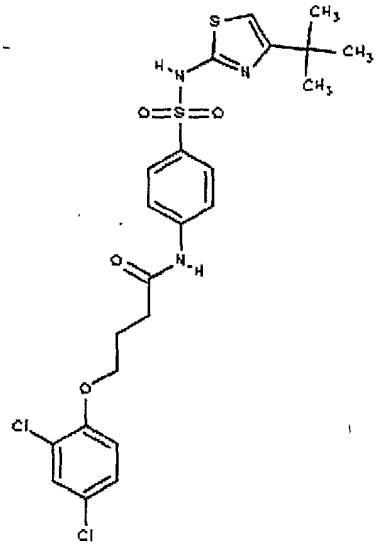
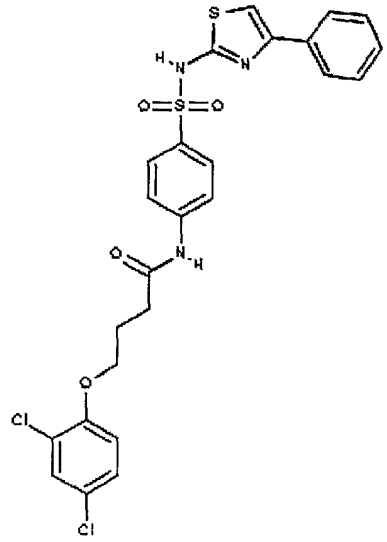
316	
317	

Figure 1-49

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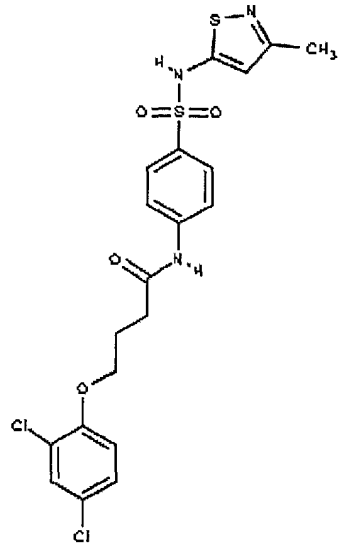
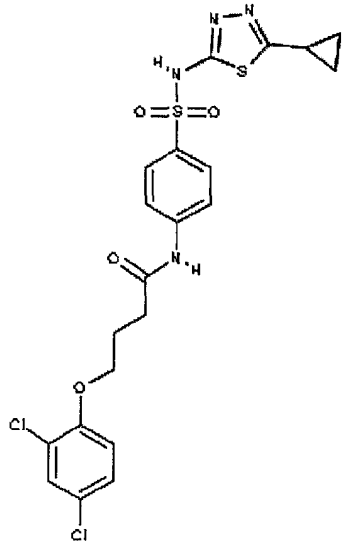
318	
319	

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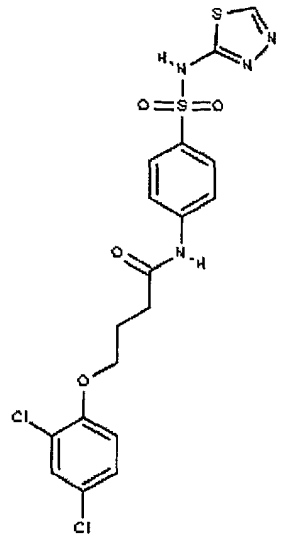
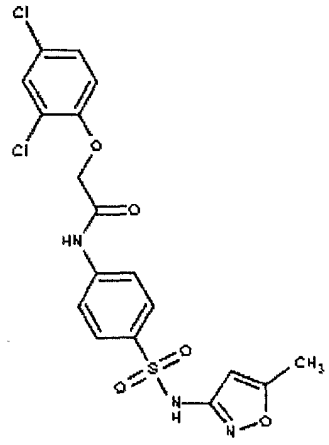
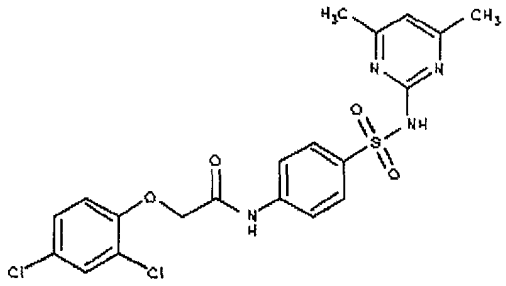
320	
321	
322	

Figure 1-50

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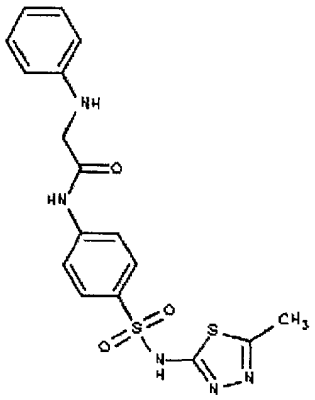
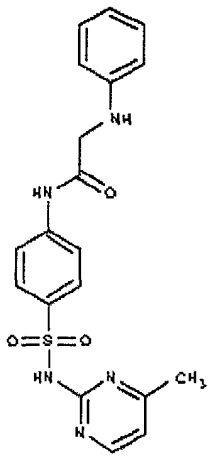
323	
324	

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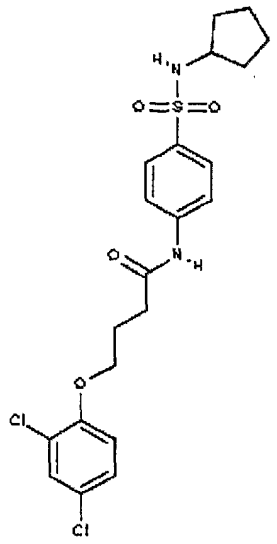
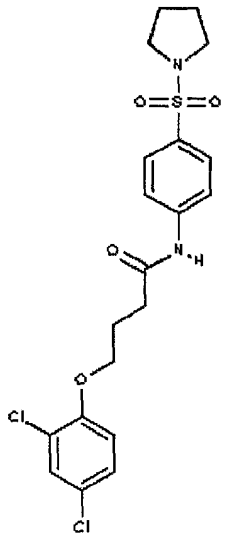
325	
326	

Figure 1-51

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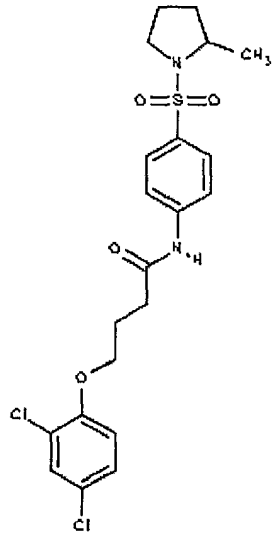
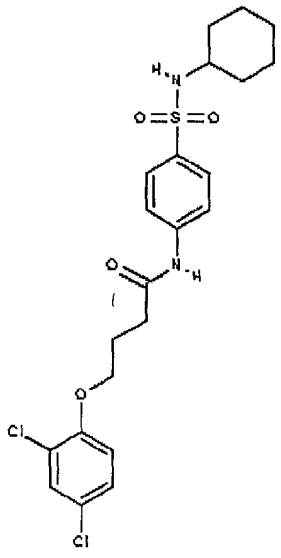
327	
328	

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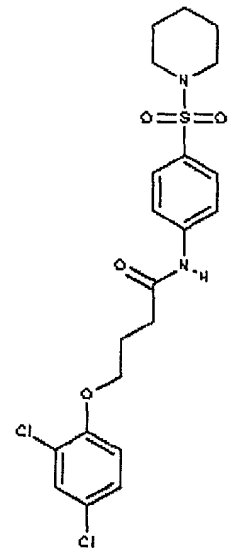
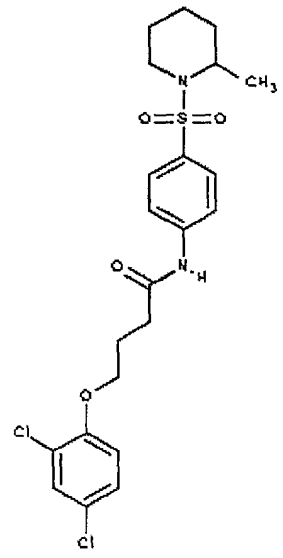
329	
330	

Figure 1-52

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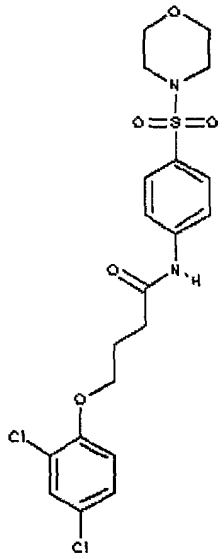
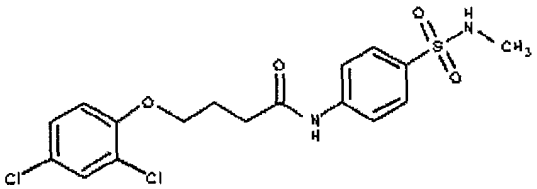
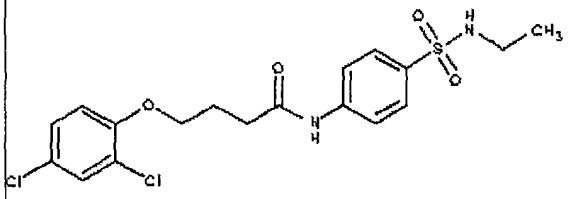
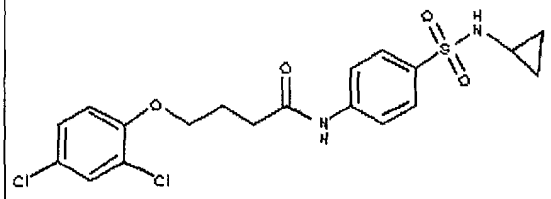
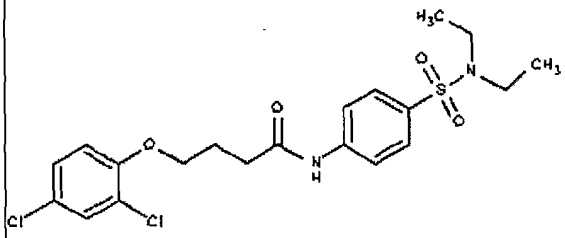
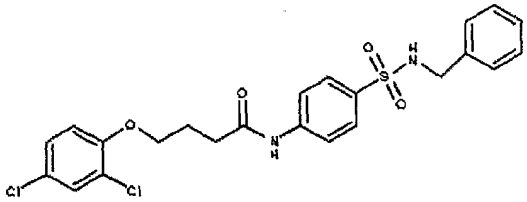
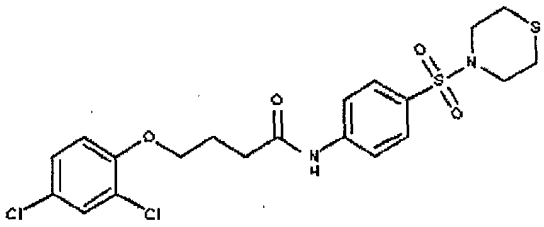
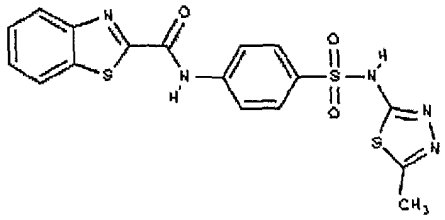
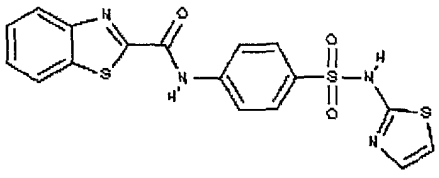
331	
332	
333	
334	
335	
336	
337	
338	
339	

Figure 1-53

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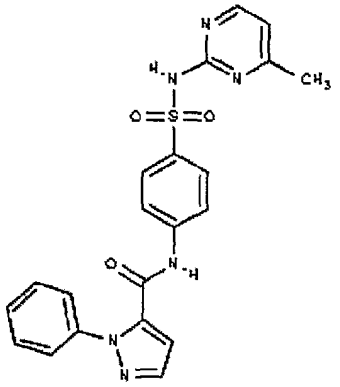
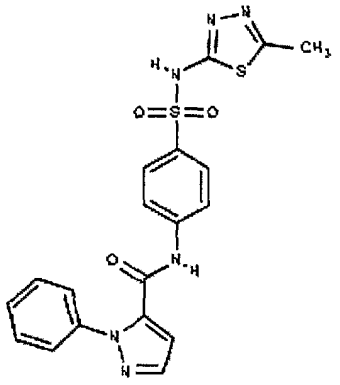
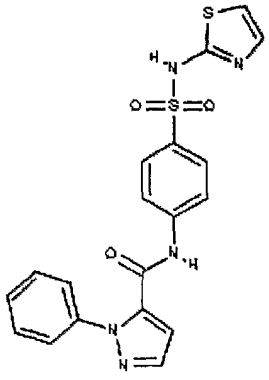
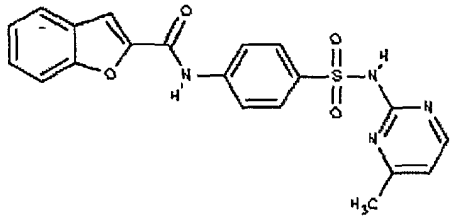
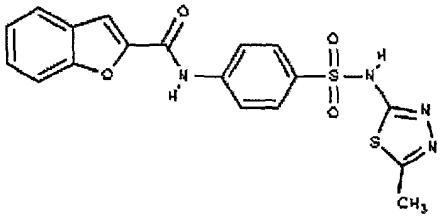
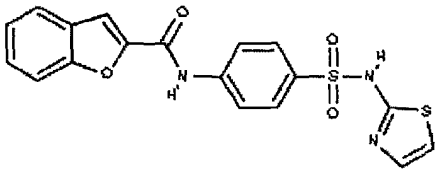
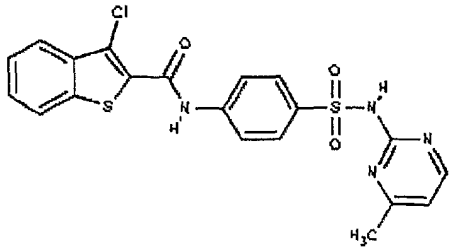
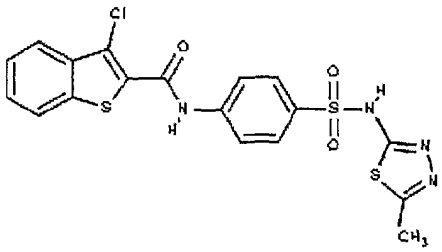
340	
341	
342	
343	
344	
345	
346	
347	

Figure 1-54

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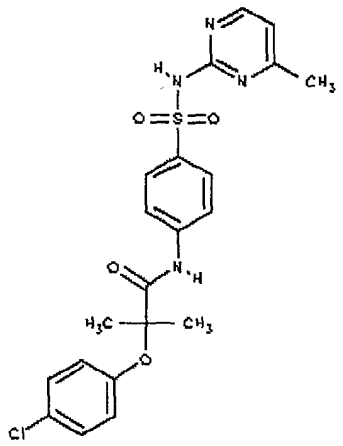
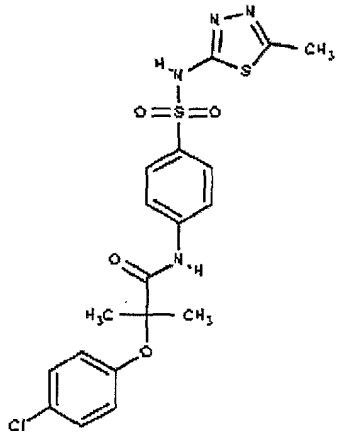
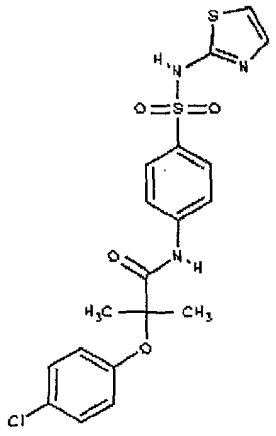
348	
349	
350	

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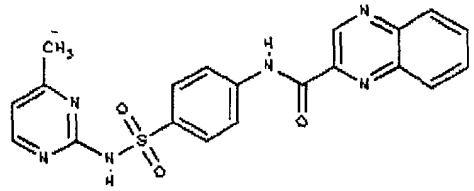
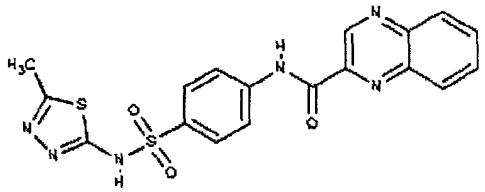
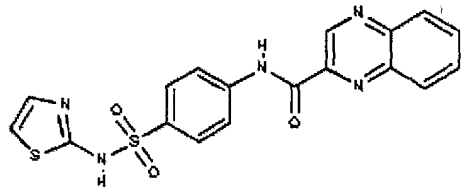
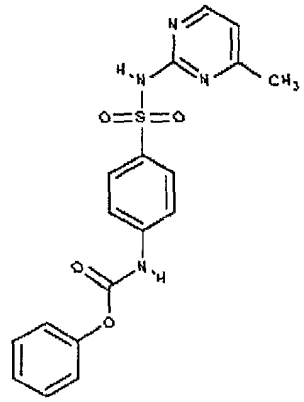
351	
352	
353	
354	

Figure 1-55

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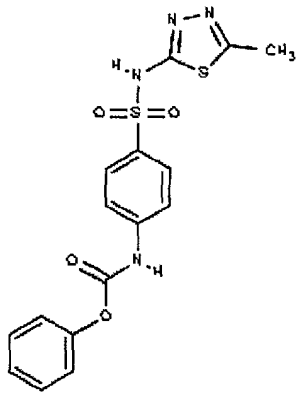
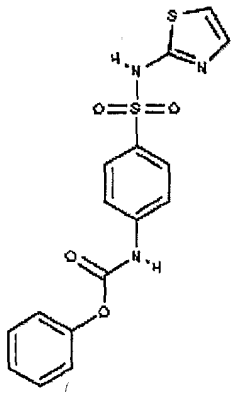
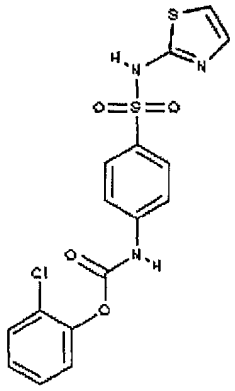
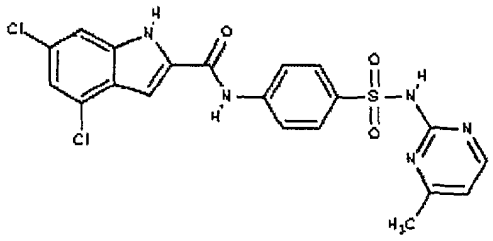
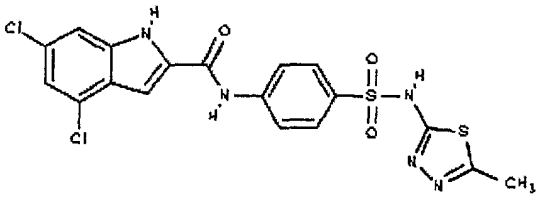
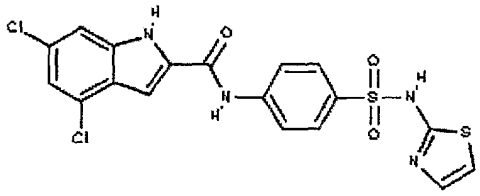
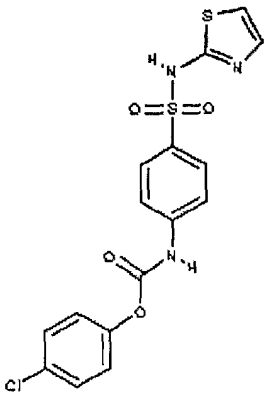
355	
356	
357	
358	
359	
360	
361	

Figure 1-56

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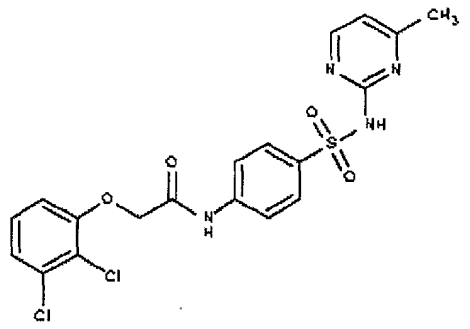
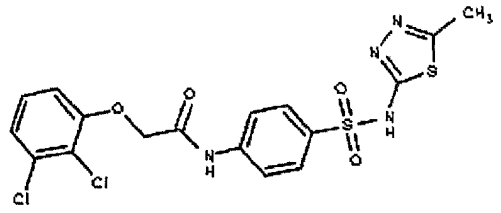
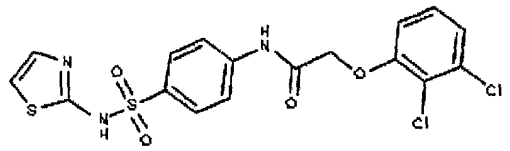
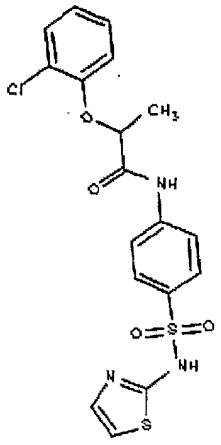
362	
363	
364	
365	

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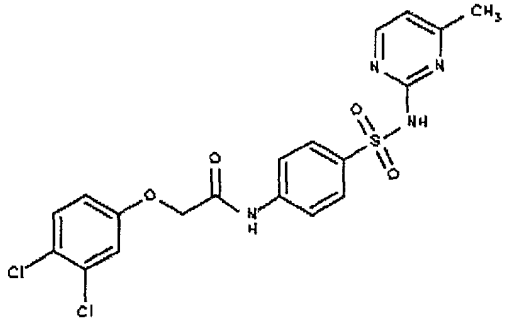
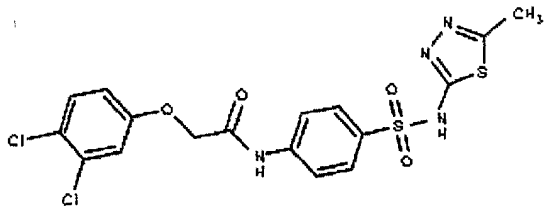
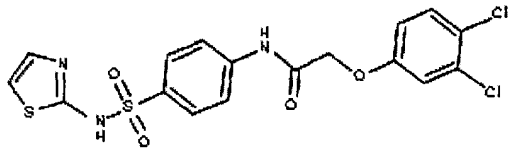
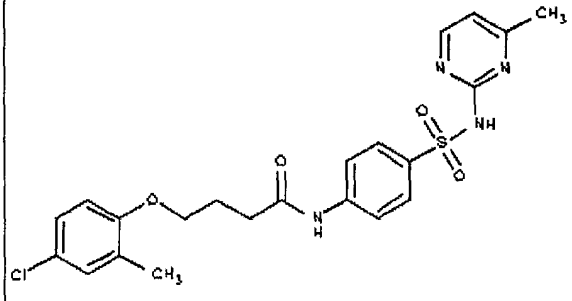
366	
367	
368	
369	

Figure 1-57

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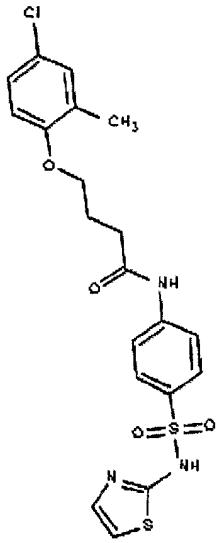
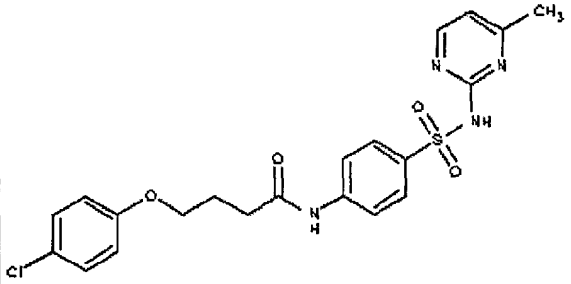
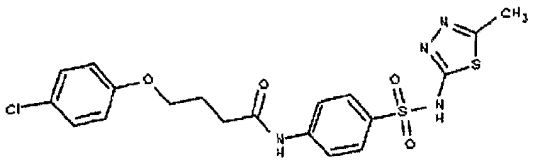
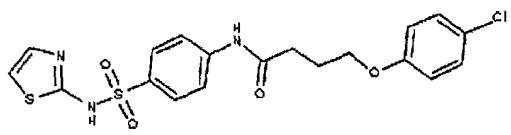
370	
371	
372	
373	

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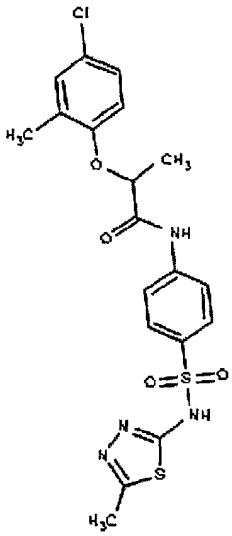
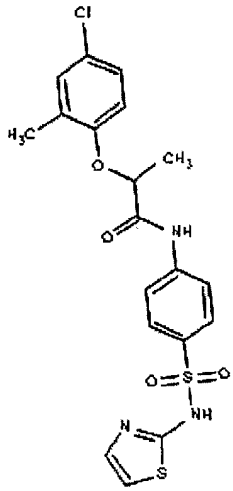
374	
375	

Figure 1-58

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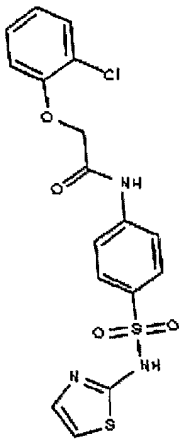
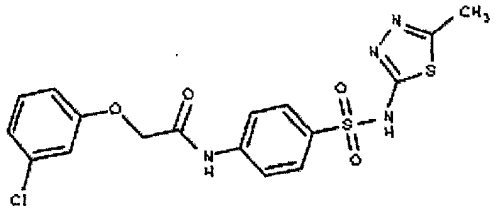
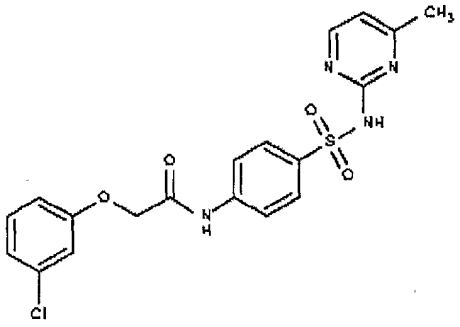
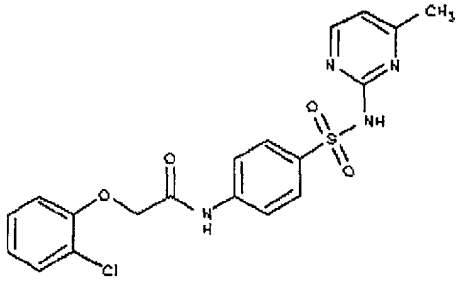
376	
377	
378	
379	

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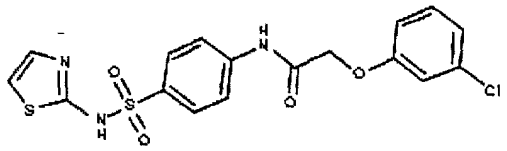
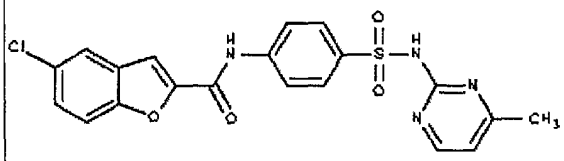
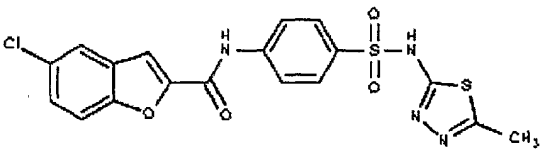
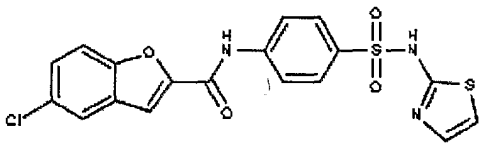
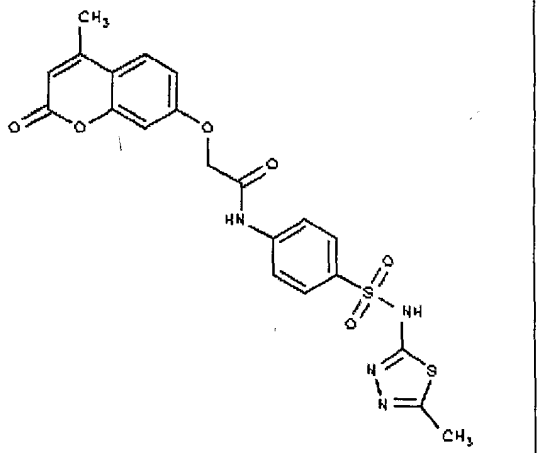
380	
381	
382	
383	
384	

Figure 1-59

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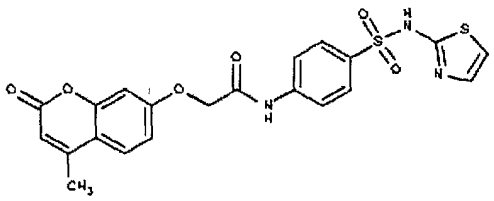
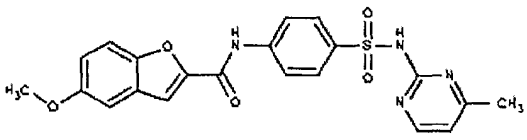
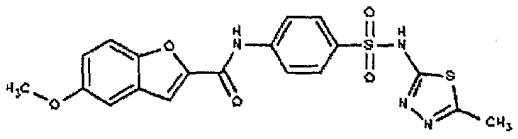
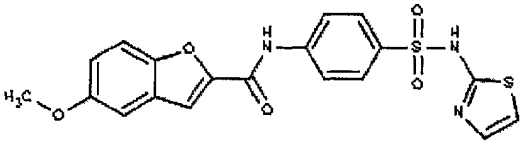
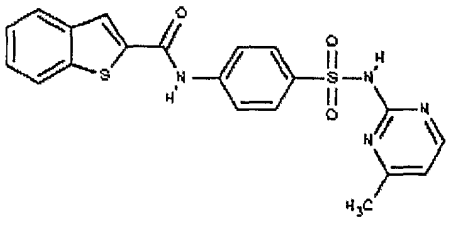
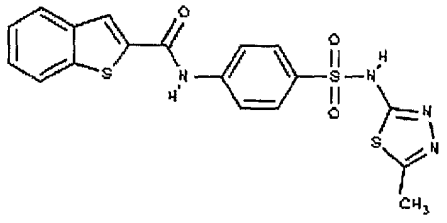
385	
386	
387	
388	
389	
390	

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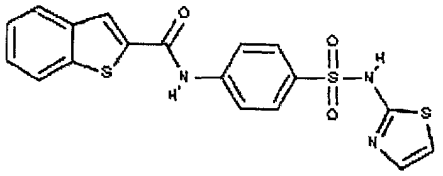
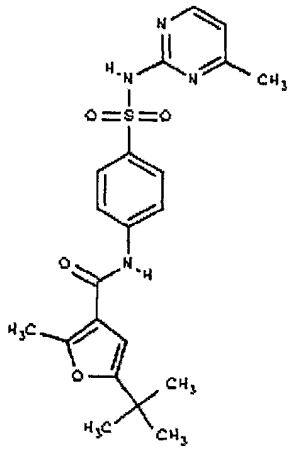
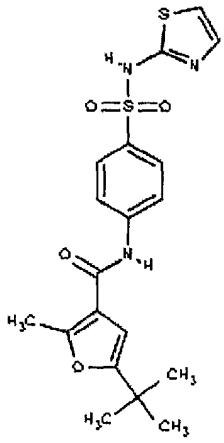
391	
392	
393	

Figure 1-60

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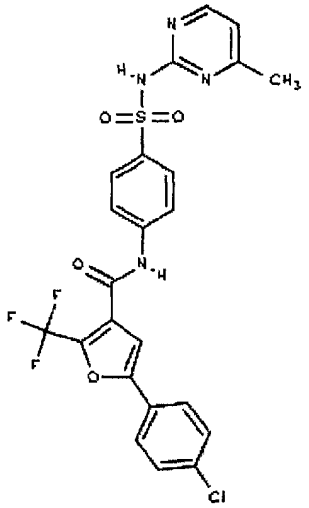
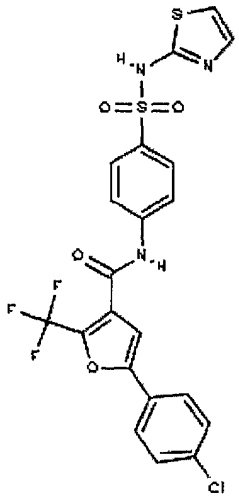
394	
395	

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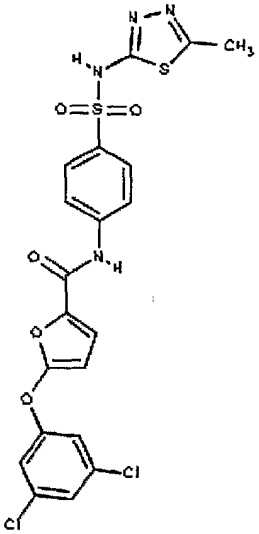
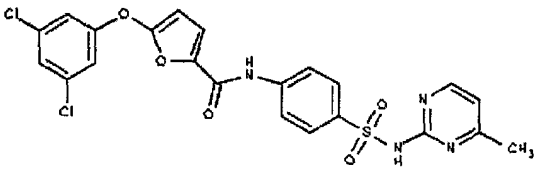
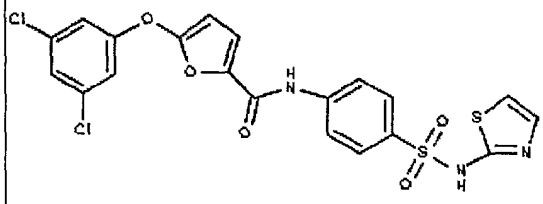
396	
397	
398	

Figure 1-61

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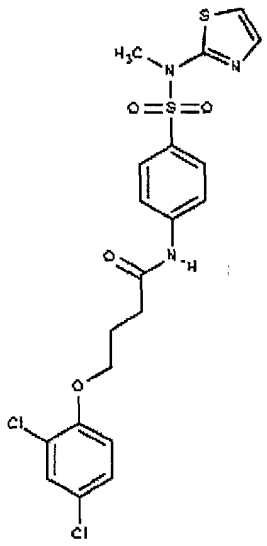
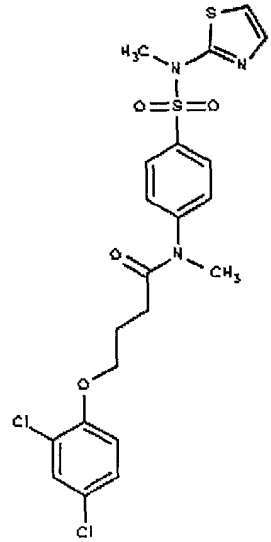
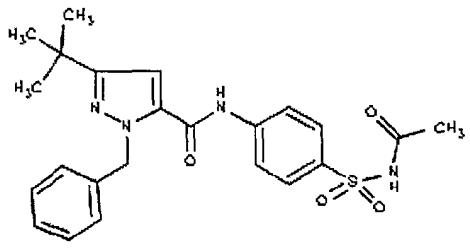
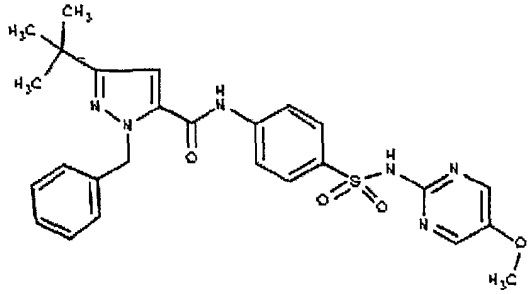
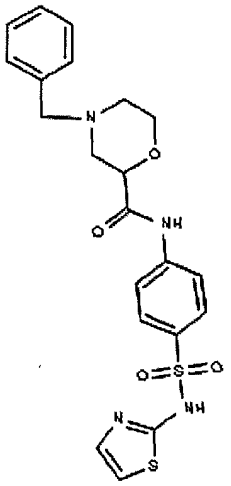
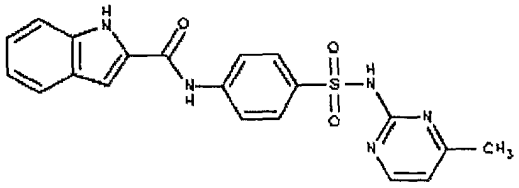
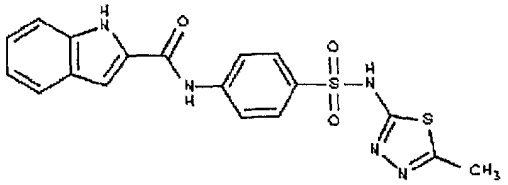
399	
400	
401	
402	
403	
404	
405	

Figure 1-62

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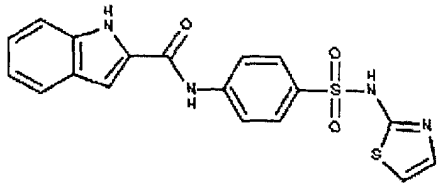
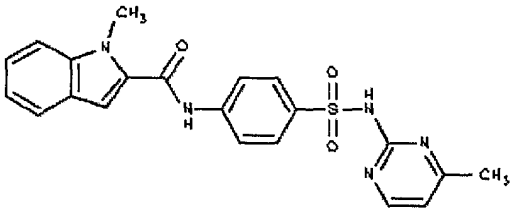
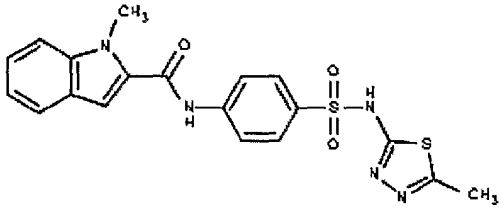
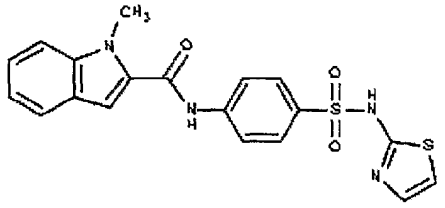
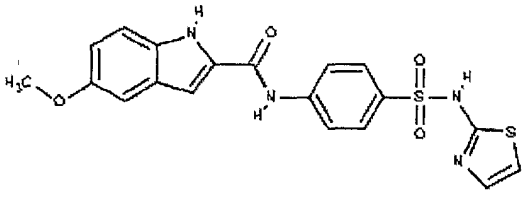
406	
407	
408	
409	
410	

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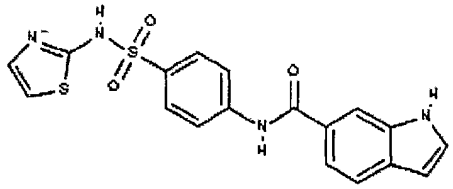
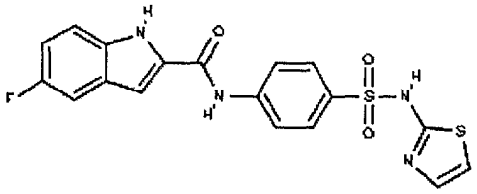
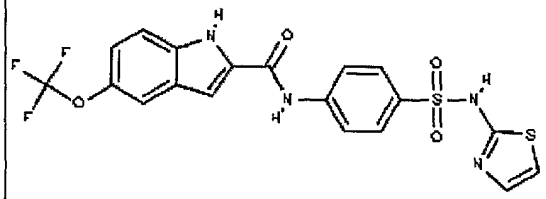
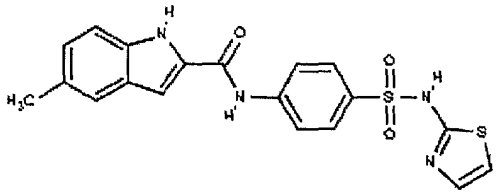
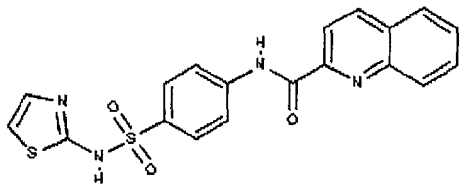
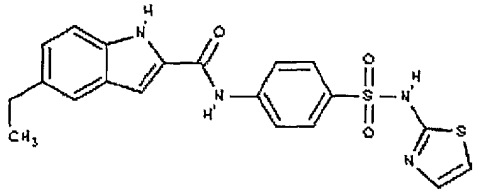
411	
412	
413	
414	
415	
416	

Figure 1-63

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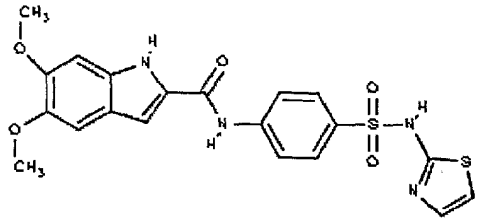
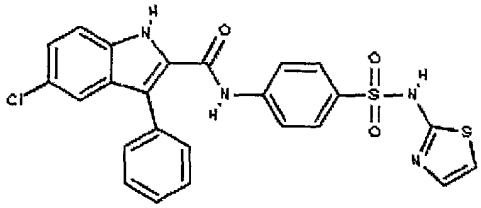
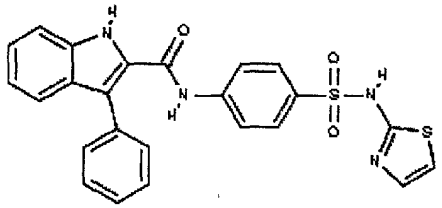
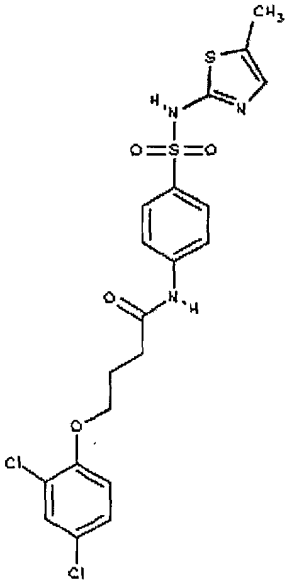
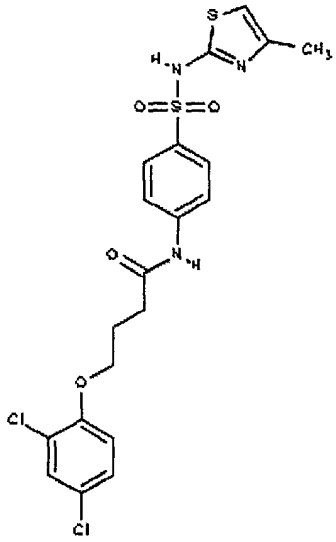
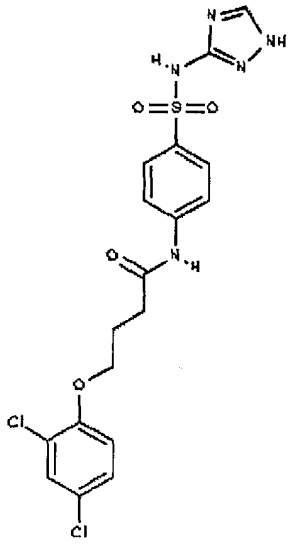
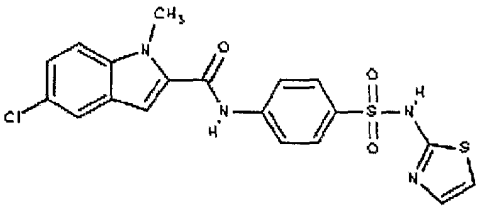
417	
418	
419	
420	
421	
422	
423	

Figure 1-64

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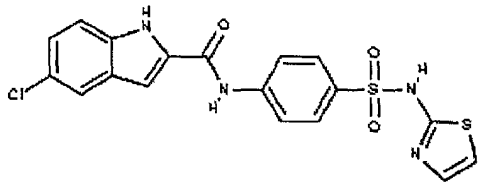
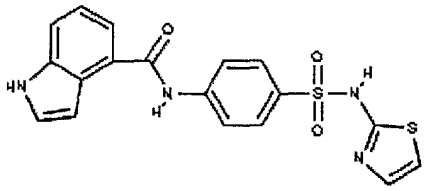
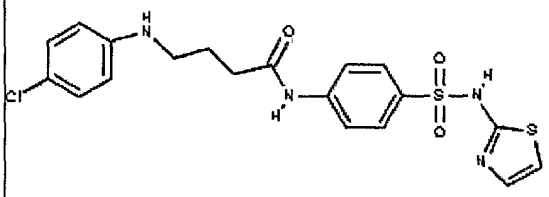
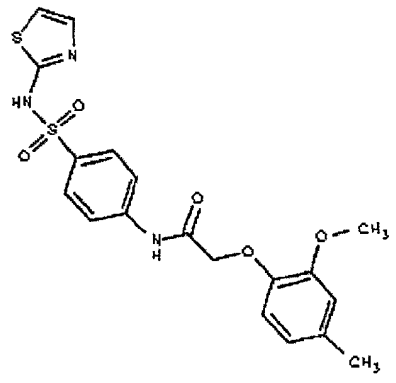
424	
425	
426	
427	

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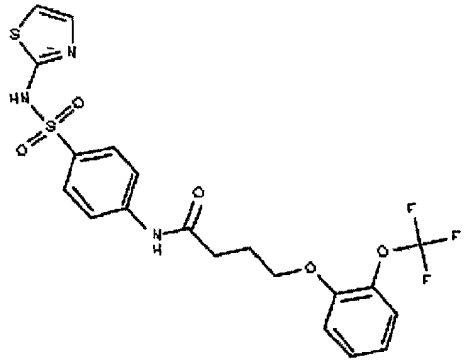
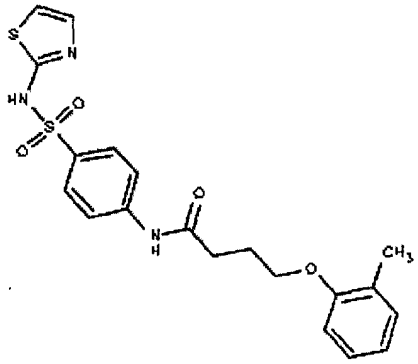
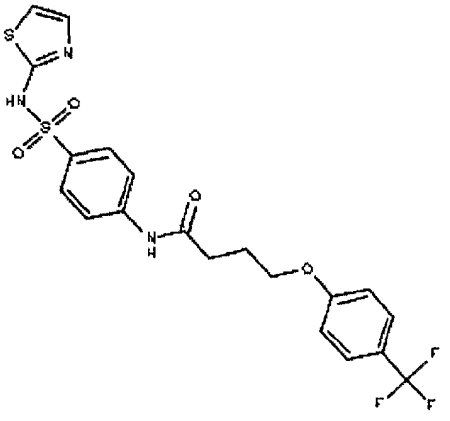
428	
429	
430	

Figure 1-65

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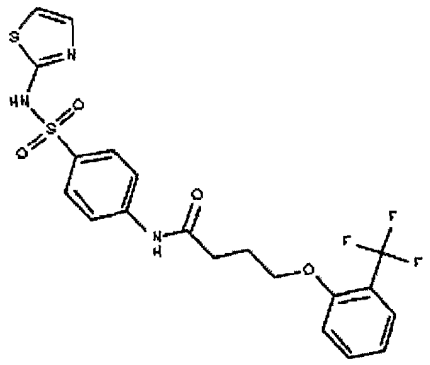
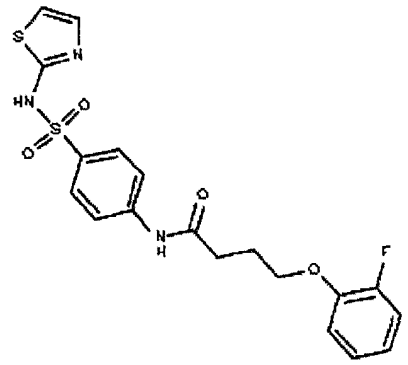
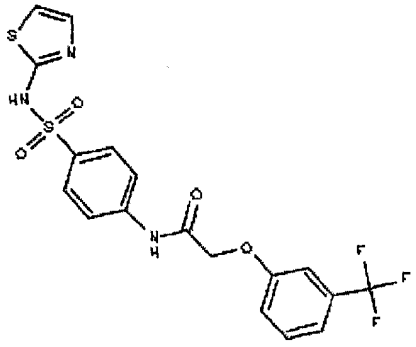
431	
432	
433	

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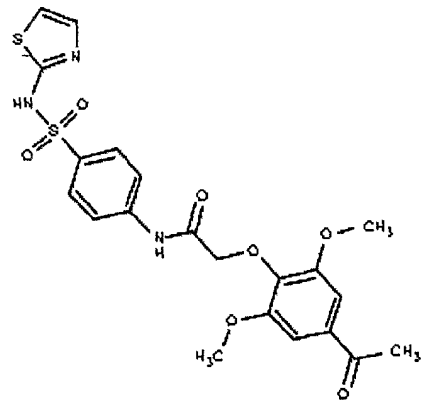
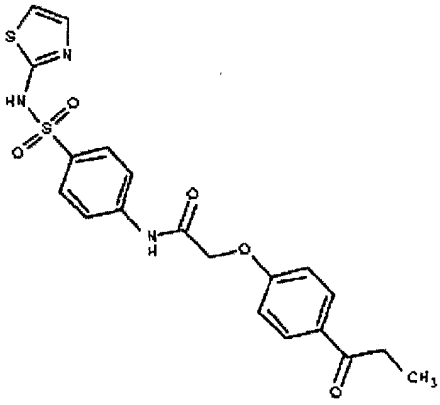
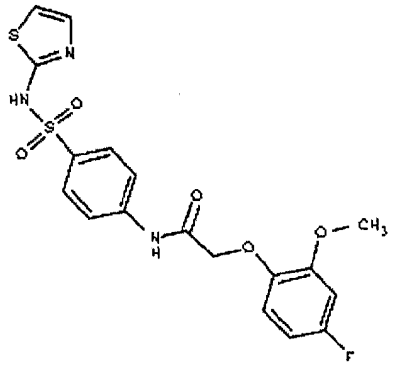
434	
435	
436	

Figure 1-66

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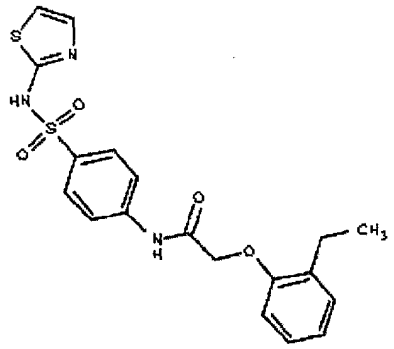
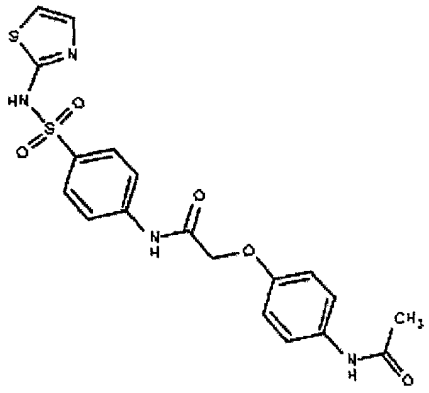
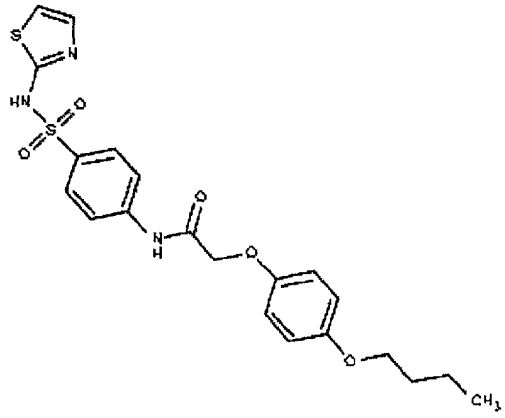
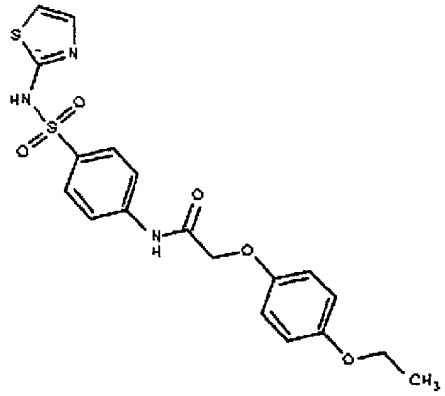
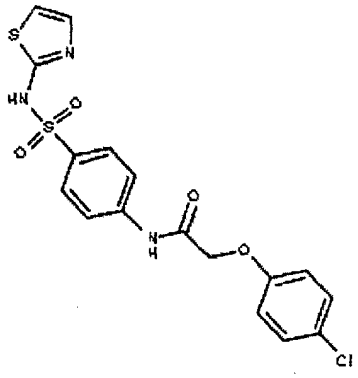
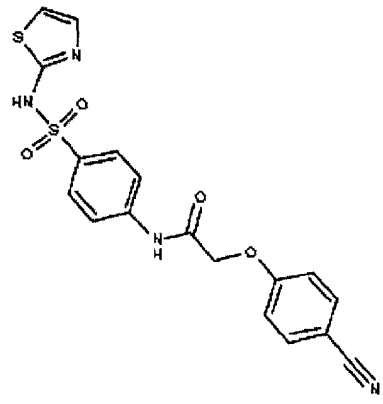
437	
438	
439	
440	
441	
442	

Figure 1-67

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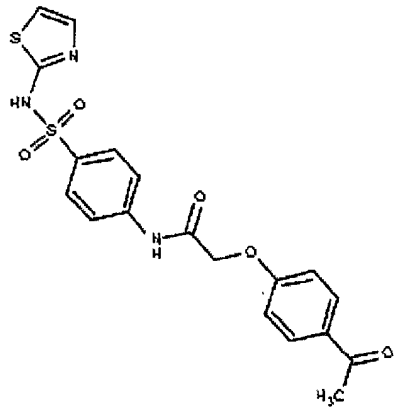
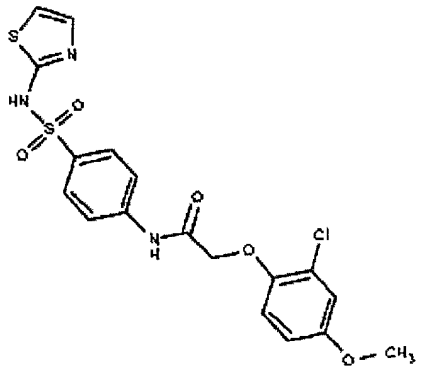
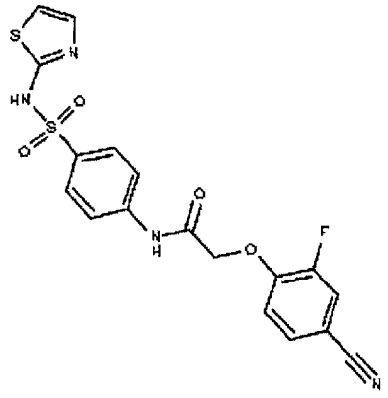
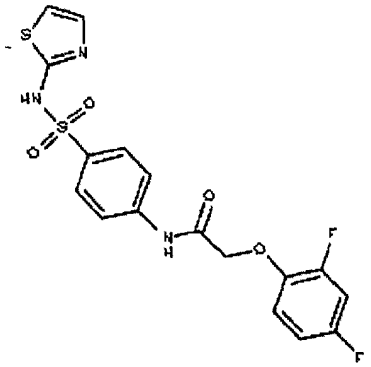
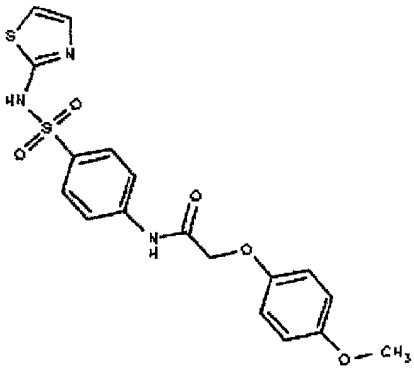
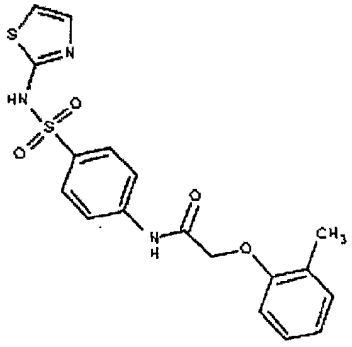
443	
444	
445	
446	
447	
448	

Figure 1-68

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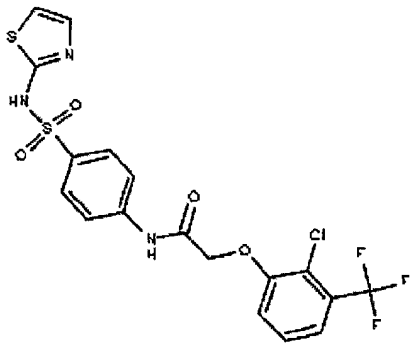
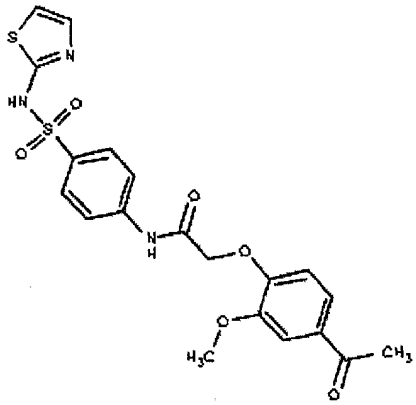
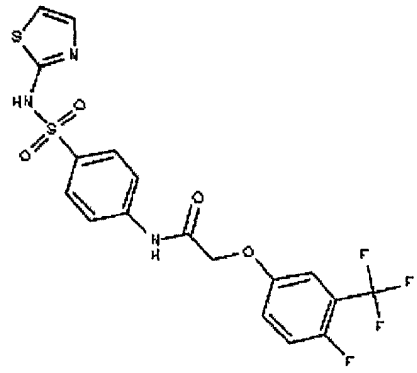
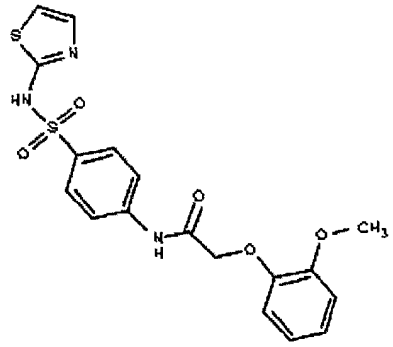
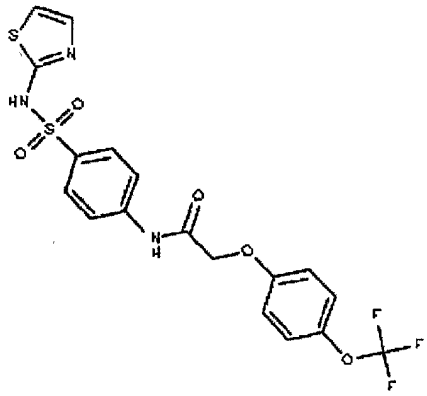
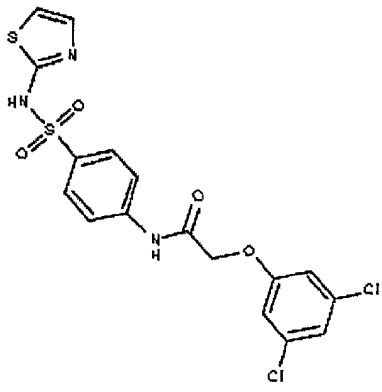
449	
450	
451	
452	
453	
454	

Figure 1-69

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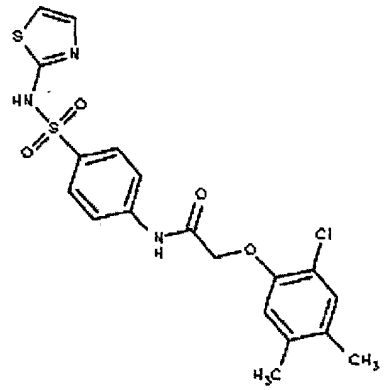
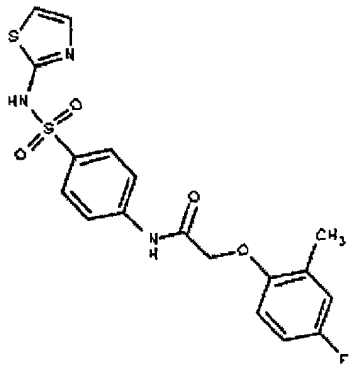
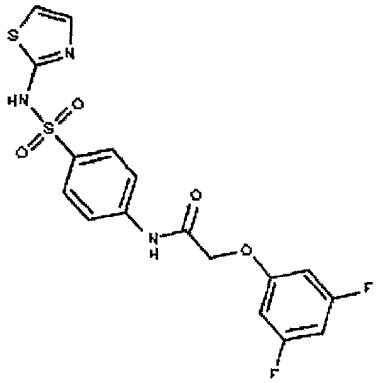
455	
456	
457	

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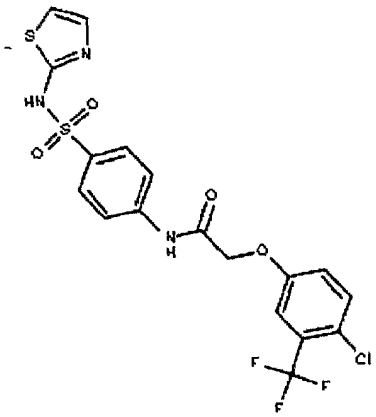
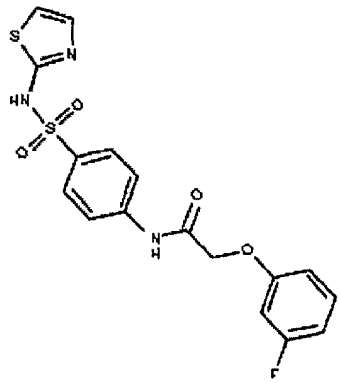
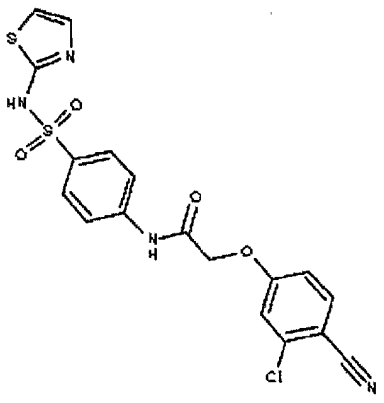
458	
459	
460	

Figure 1-70

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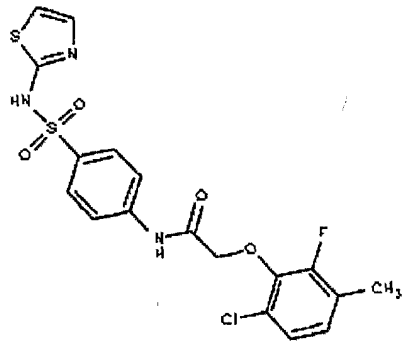
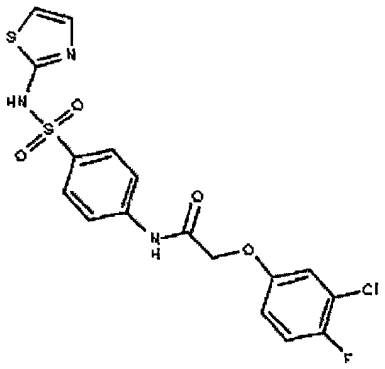
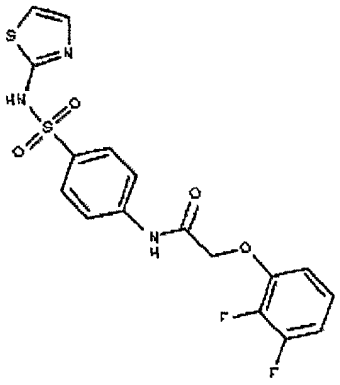
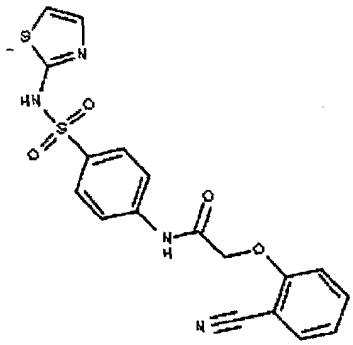
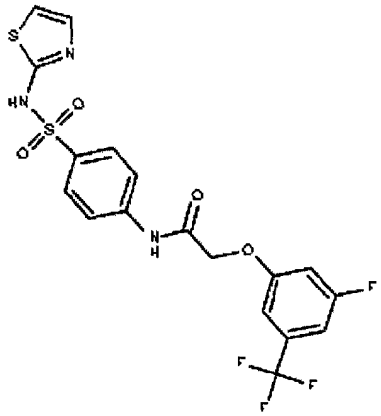
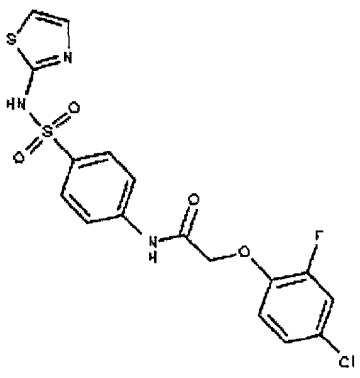
461	
462	
463	
464	
465	
466	

Figure 1-71

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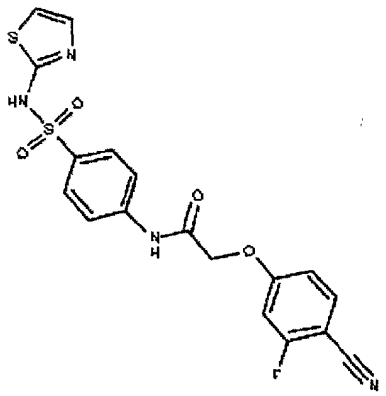
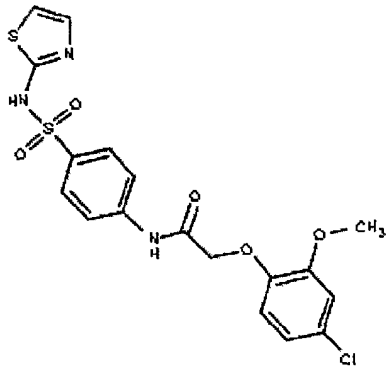
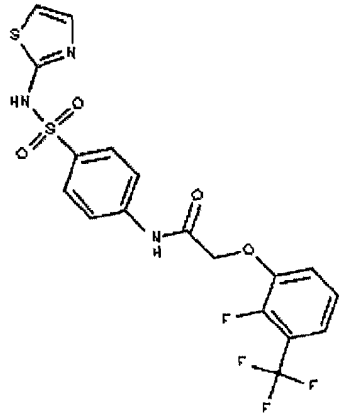
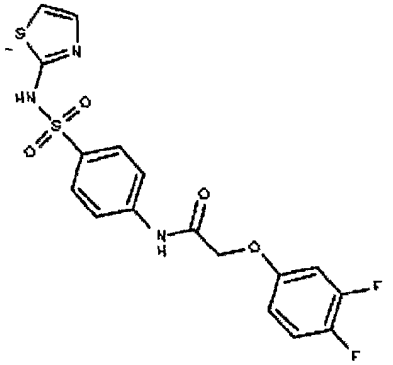
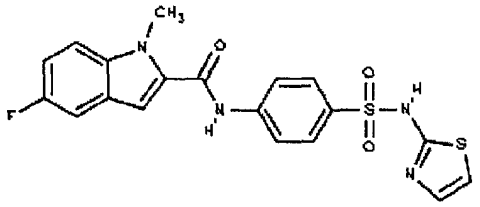
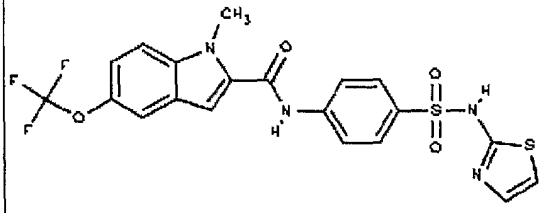
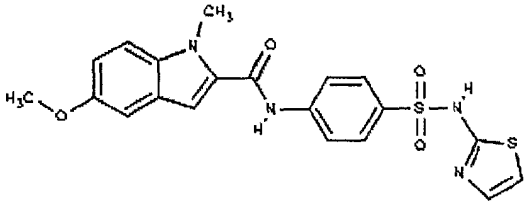
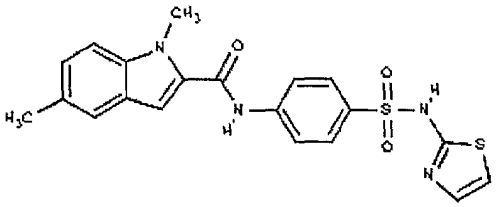
467	
468	
469	
470	
471	
472	
473	
474	

Figure 1-72

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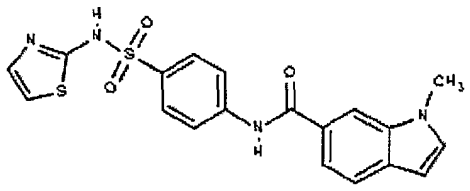
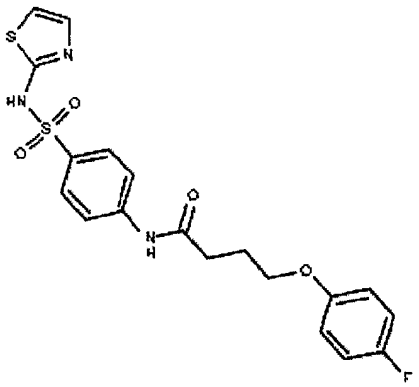
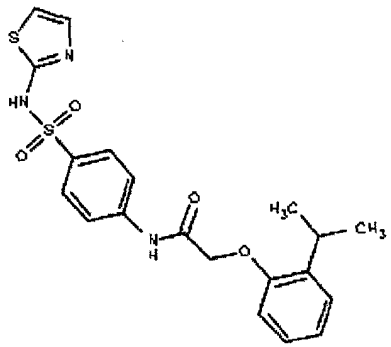
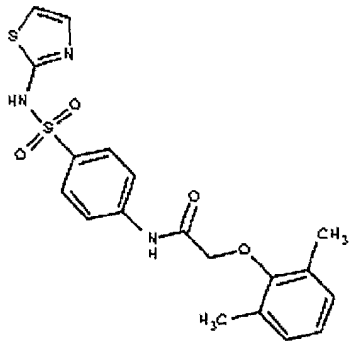
475	
476	
477	
478	

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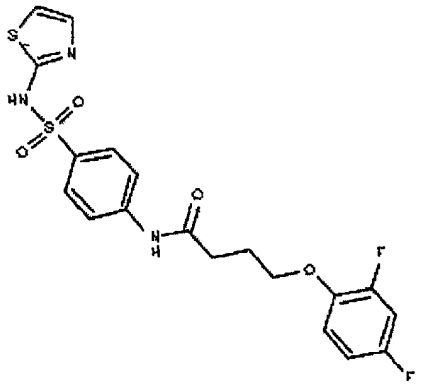
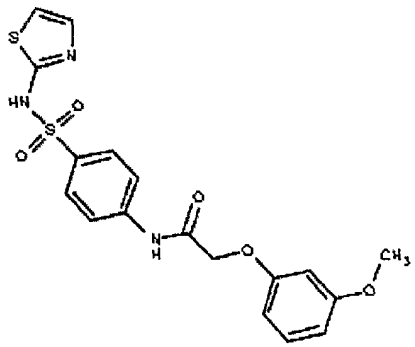
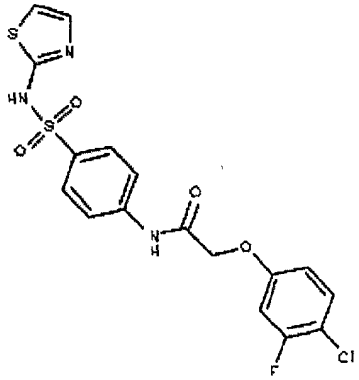
479	
480	
481	

Figure 1-73

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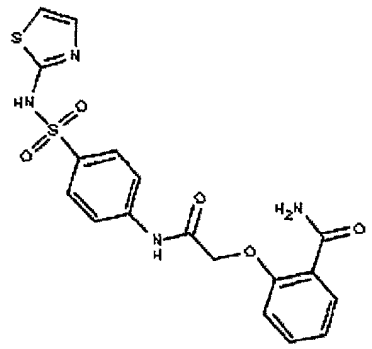
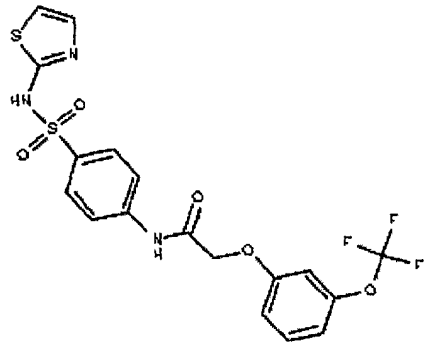
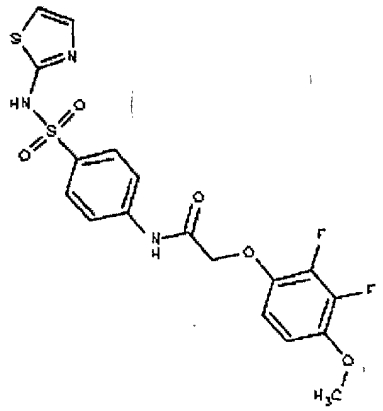
482	
483	
484	

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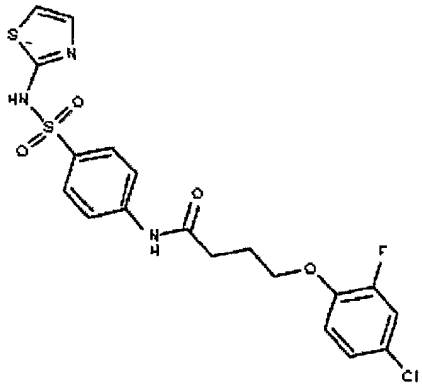
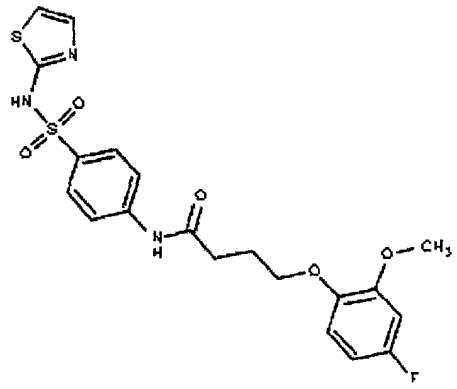
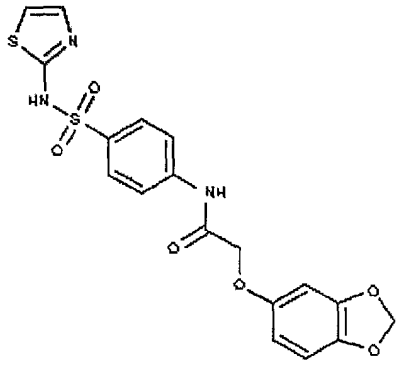
485	
486	
487	

Figure 1-74

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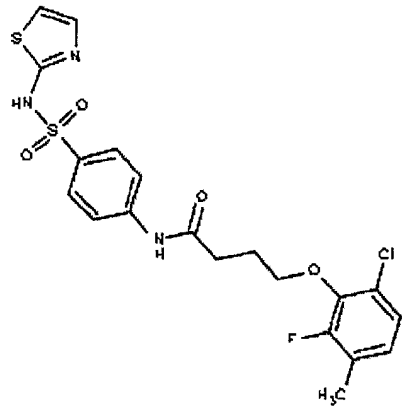
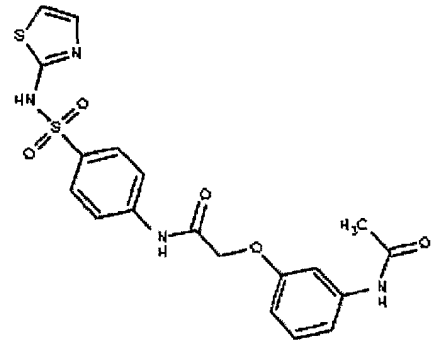
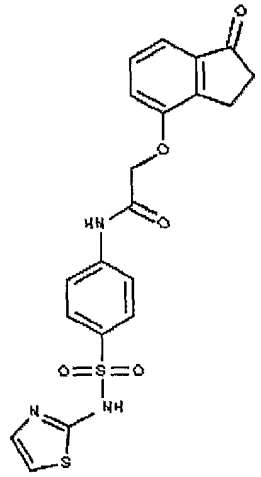
488	
489	
490	

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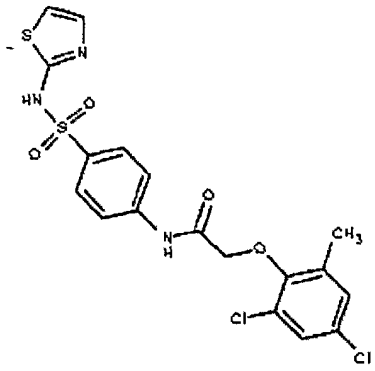
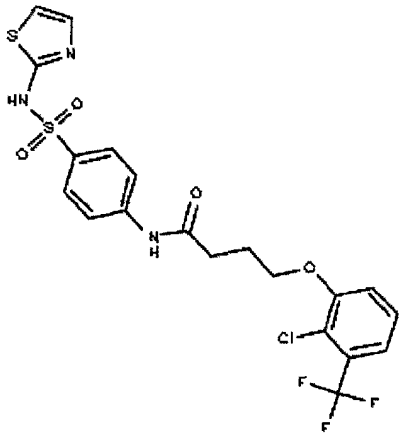
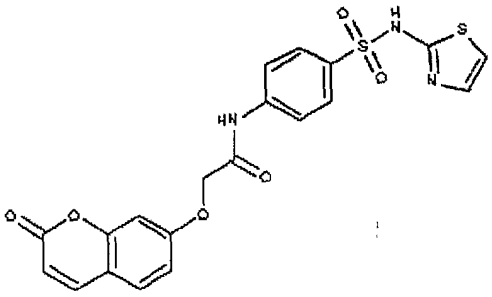
491	
492	
493	

Figure 1-75

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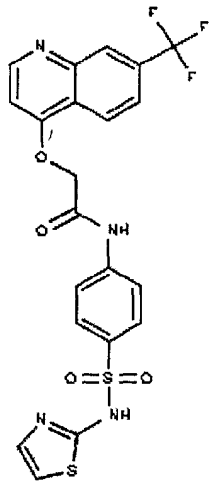
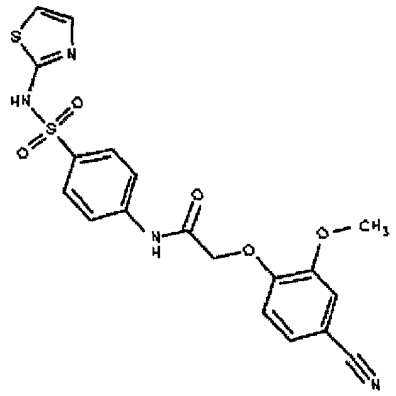
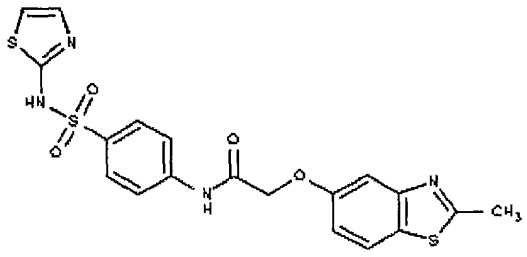
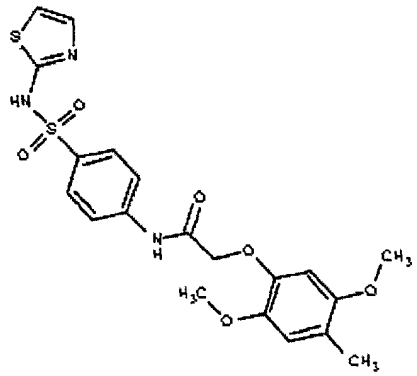
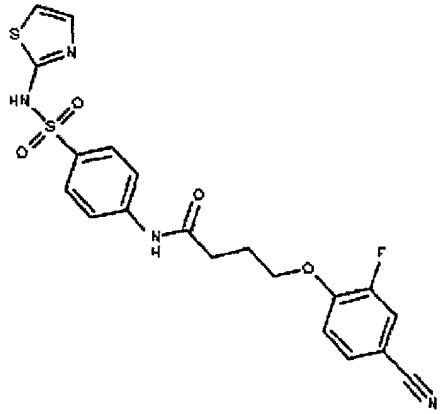
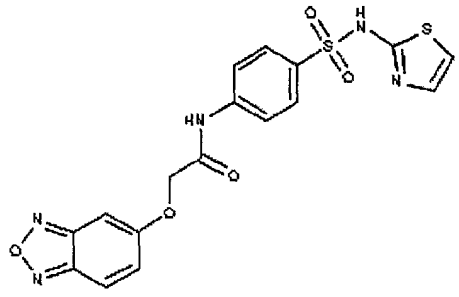
494	
495	
496	
497	
498	
499	

Figure 1-76

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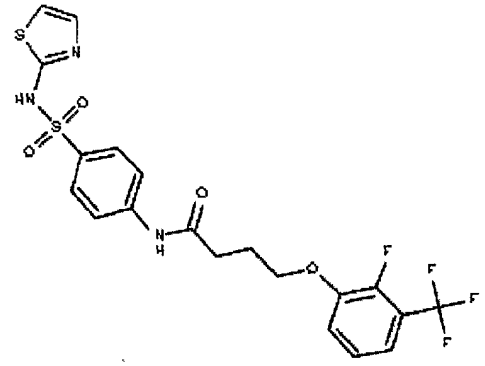
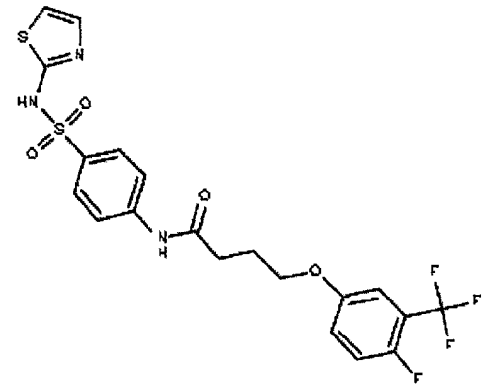
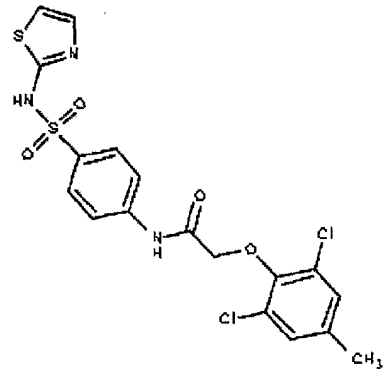
500	
501	
502	

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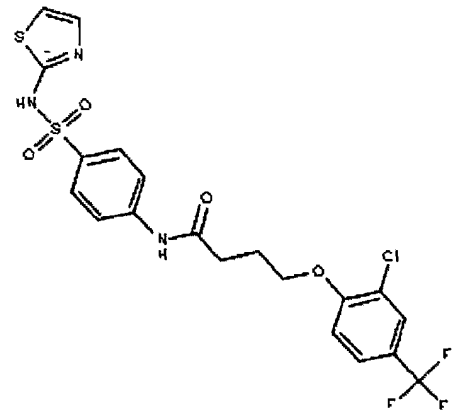
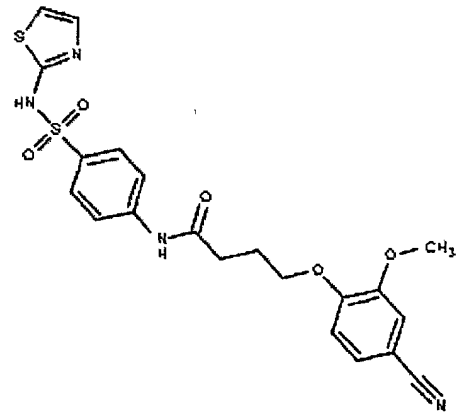
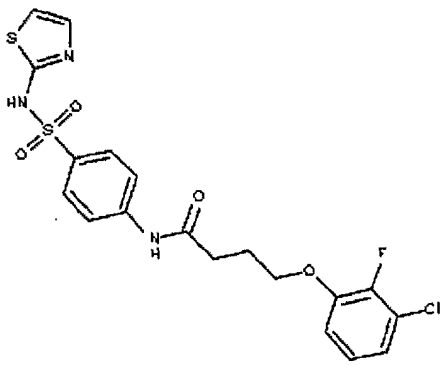
503	
504	
505	

Figure 1-77

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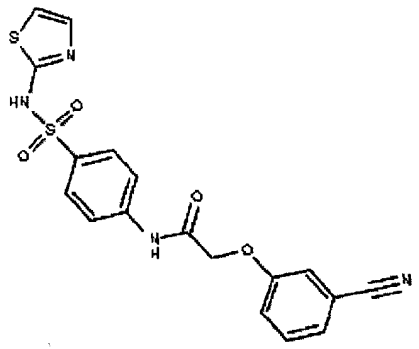
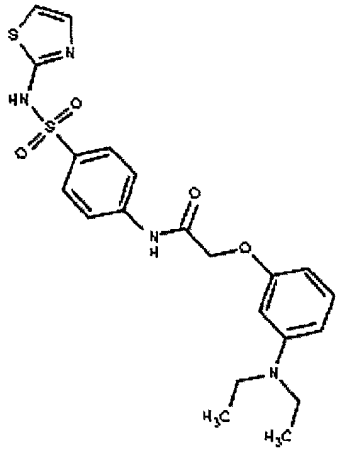
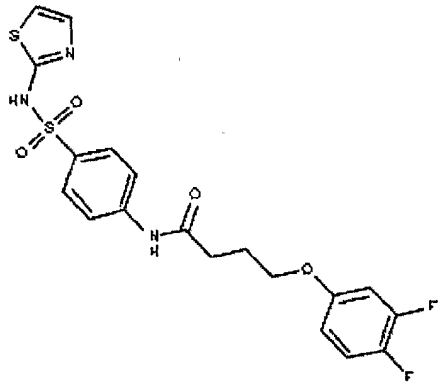
506	
507	
508	

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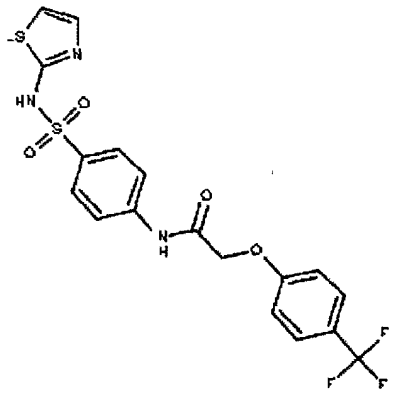
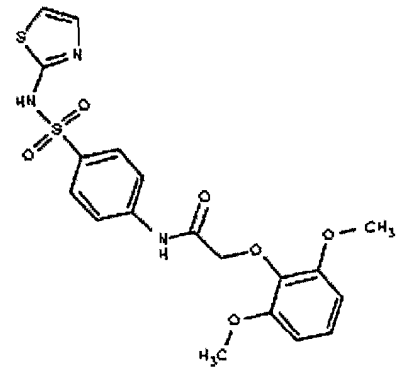
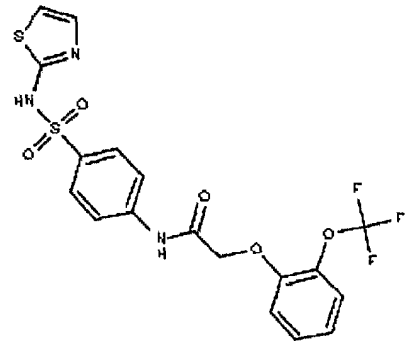
509	
510	
511	

Figure 1-78

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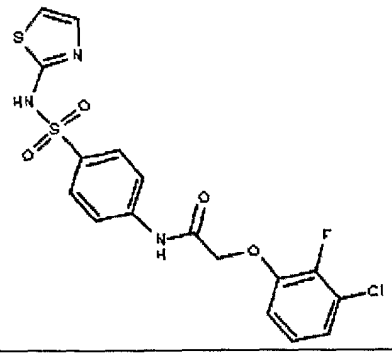
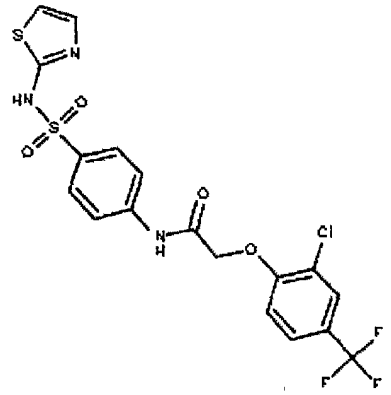
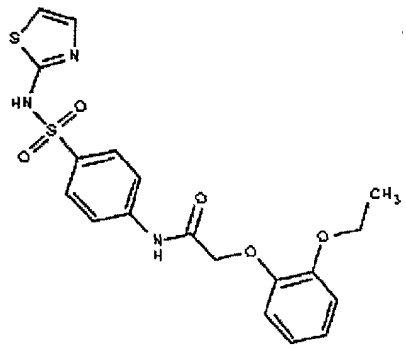
512	
513	
514	

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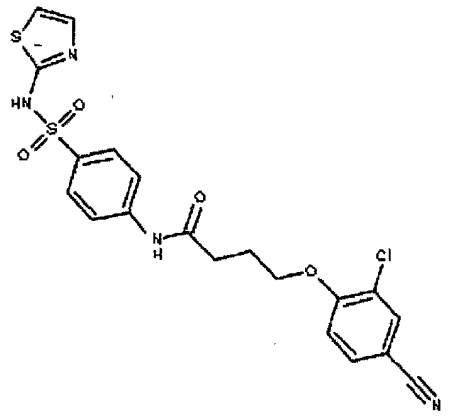
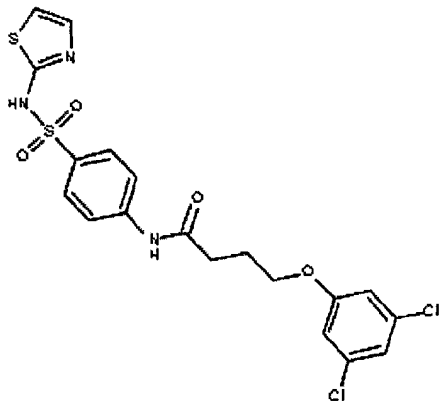
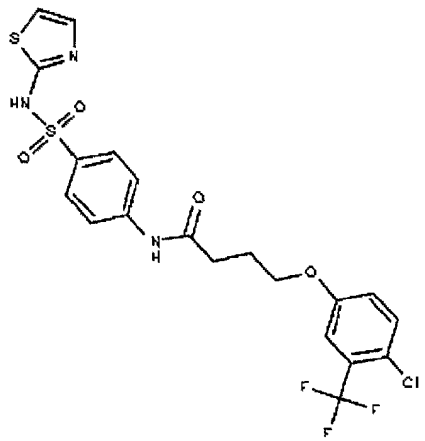
515	
516	
517	

Figure 1-79

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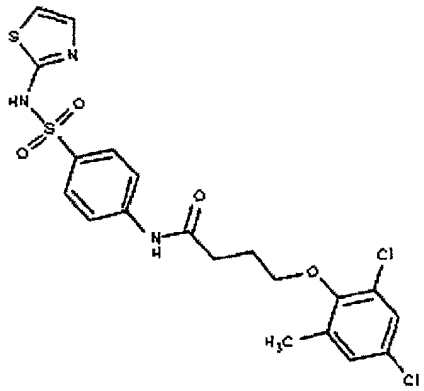
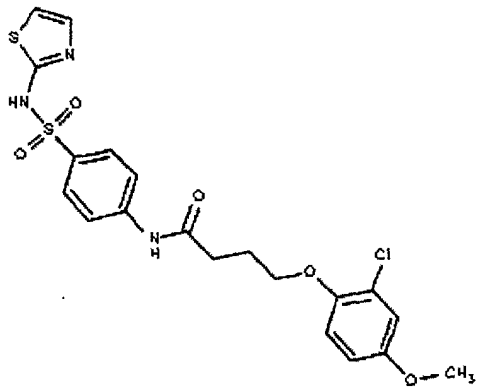
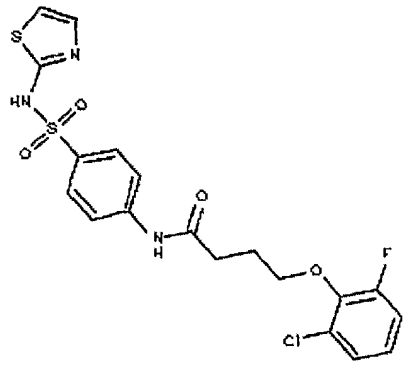
518	
519	
520	

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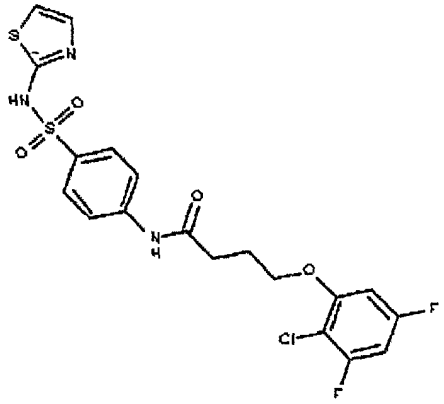
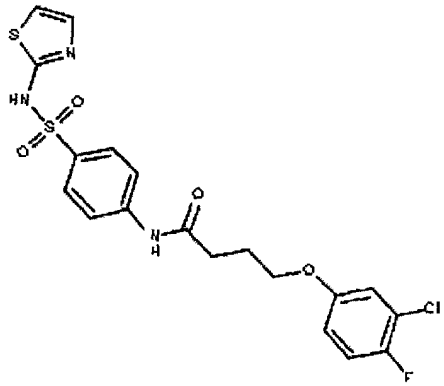
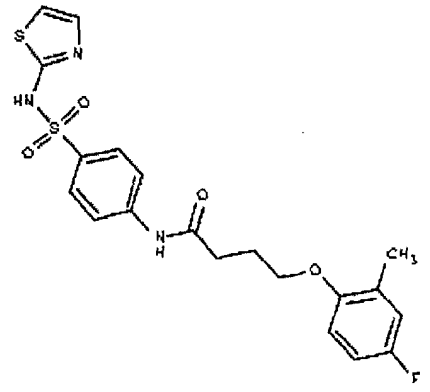
521	
522	
523	

Figure 1-80

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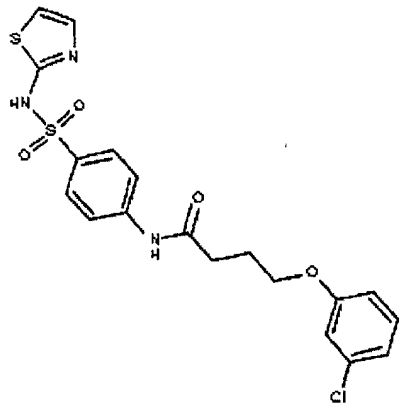
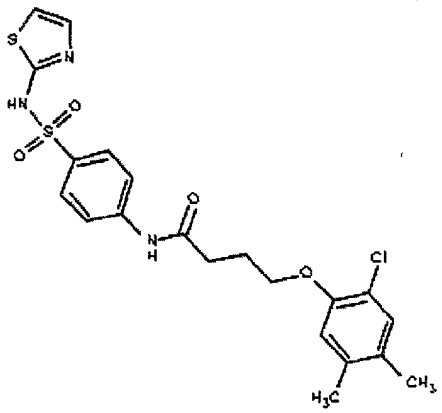
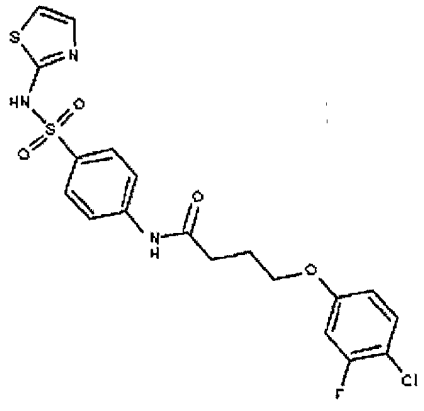
524	
525	
526	

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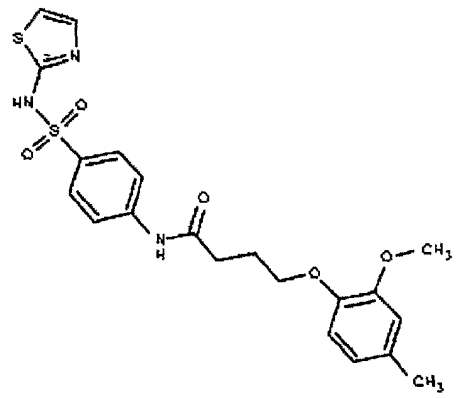
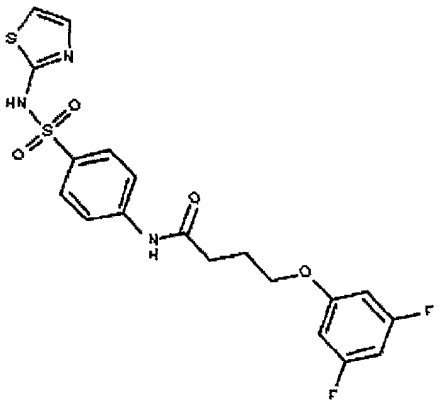
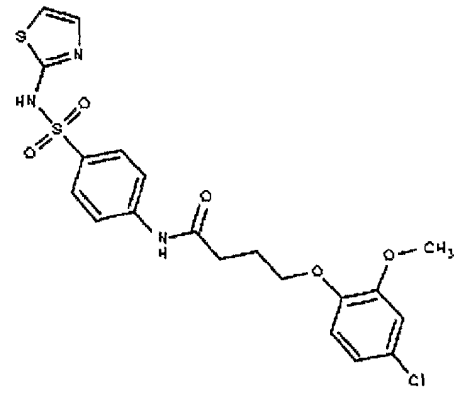
527	
528	
529	

Figure 1-81

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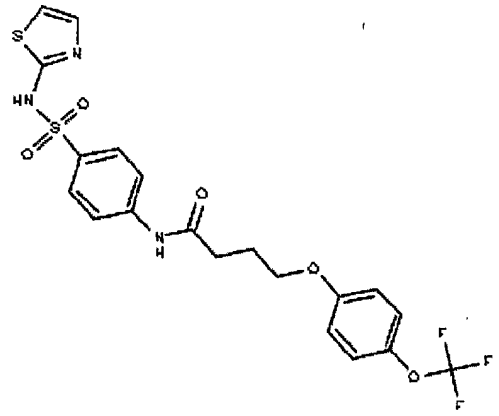
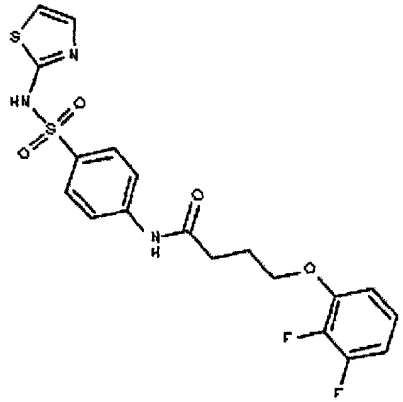
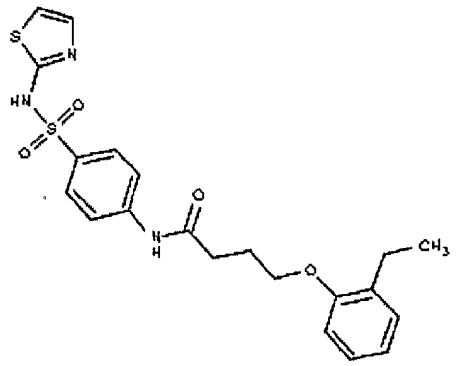
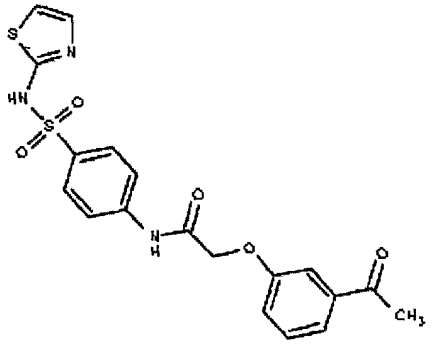
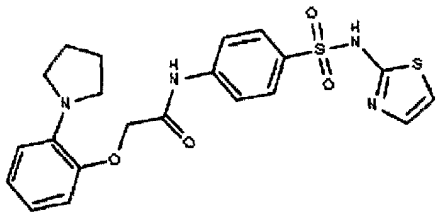
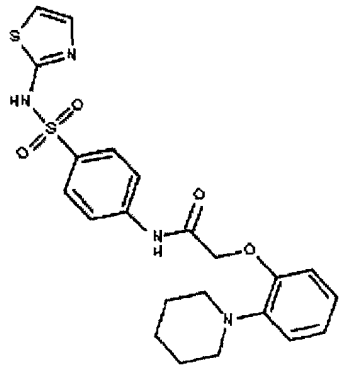
530	
531	
532	
533	
534	
535	

Figure 1-82

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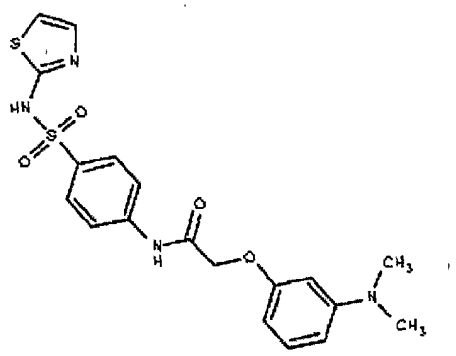
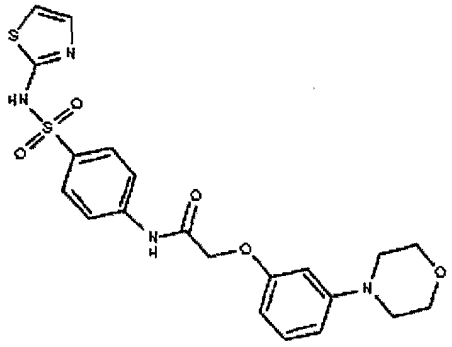
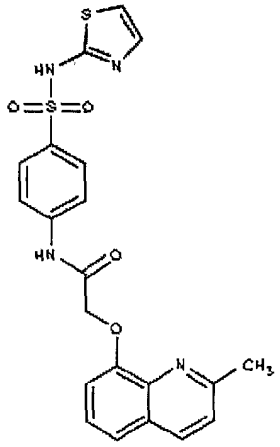
536	
537	
538	

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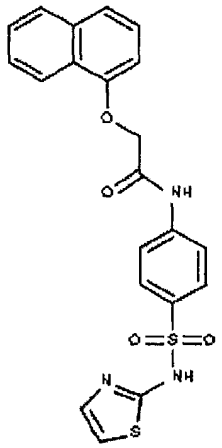
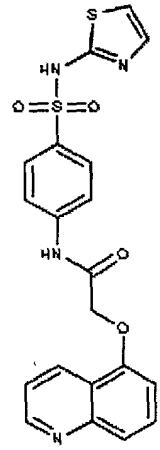
539	
540	

Figure 1-83

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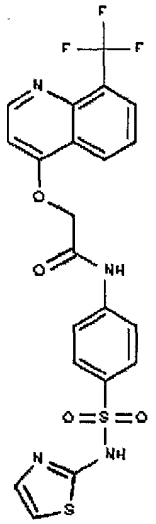
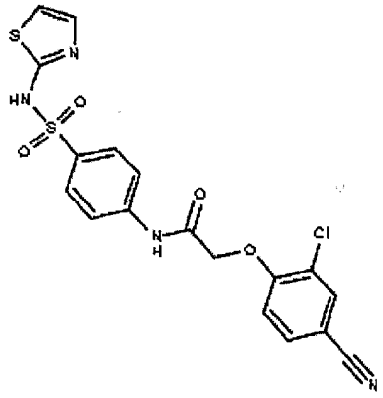
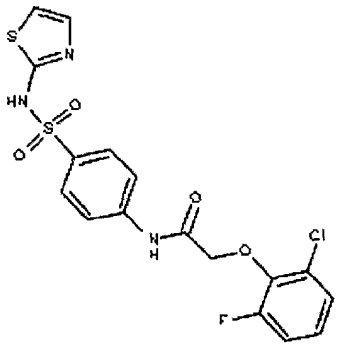
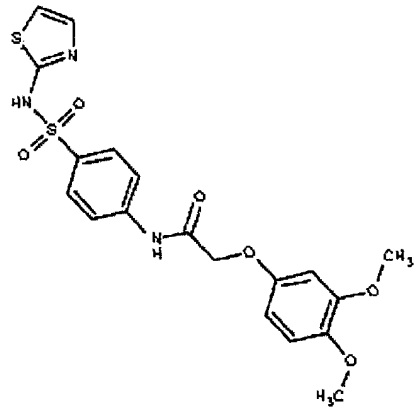
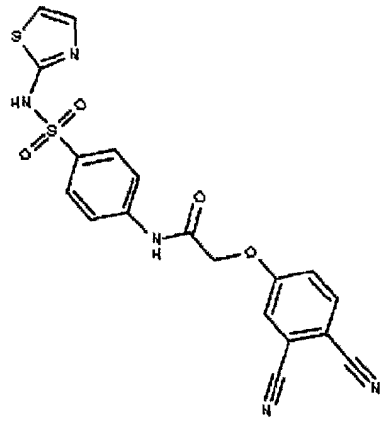
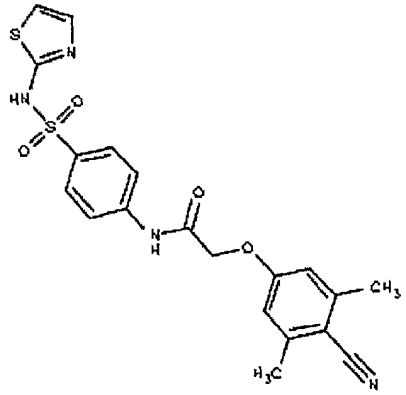
541	
542	
543	
544	
545	
546	

Figure 1-84

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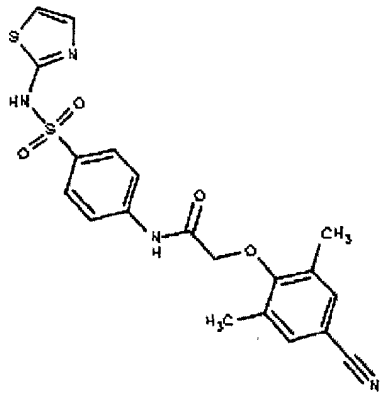
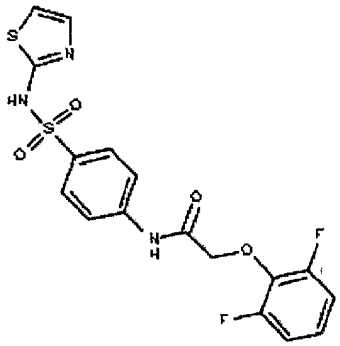
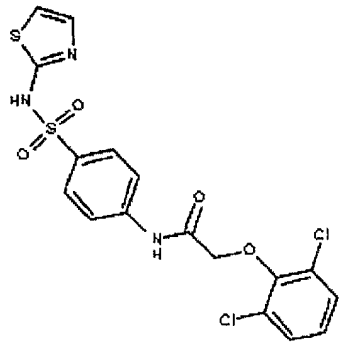
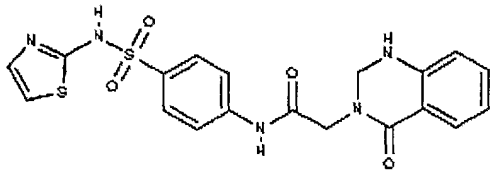
547	
548	
549	
550	

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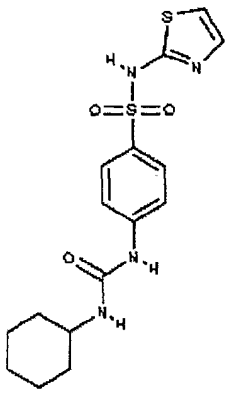
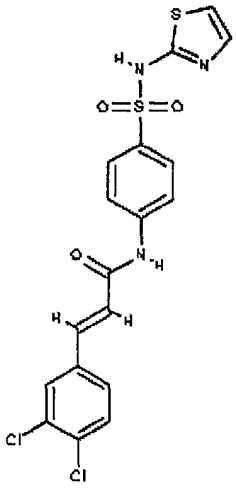
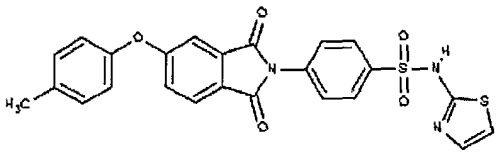
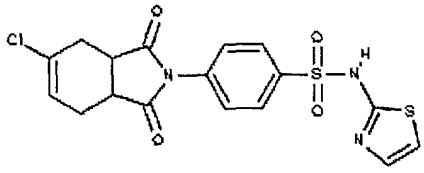
551	
552	
553	
554	

Figure 1-85

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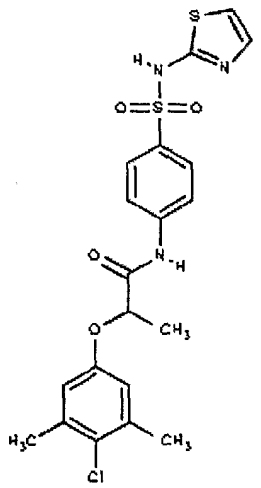
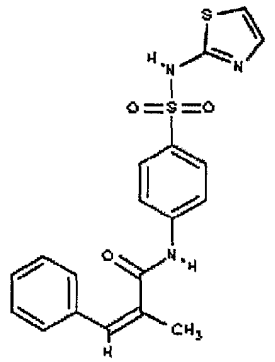
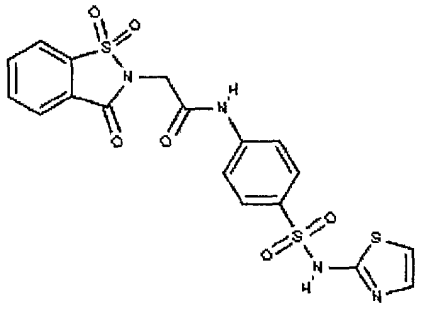
555	
556	
557	

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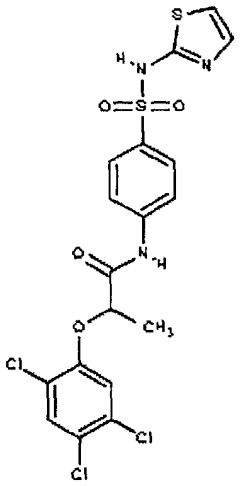
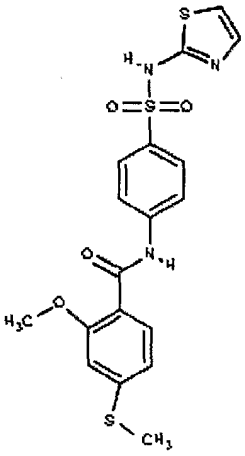
558	
559	

Figure 1-86

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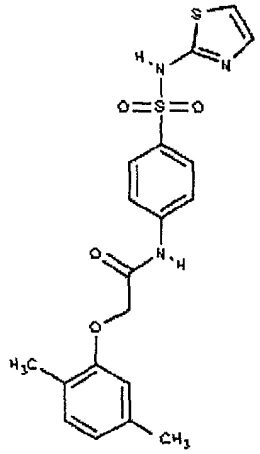
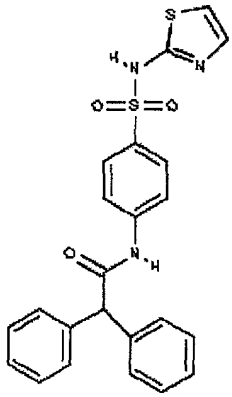
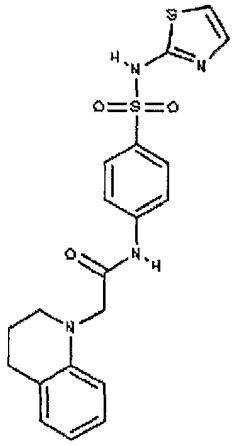
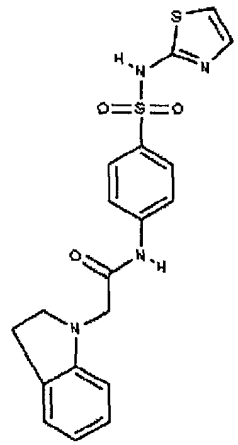
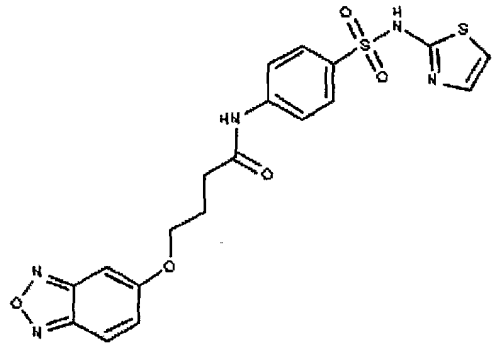
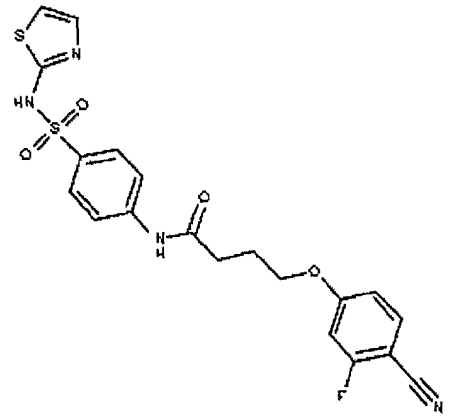
560	
561	
562	
563	
564	
565	

Figure 1-87

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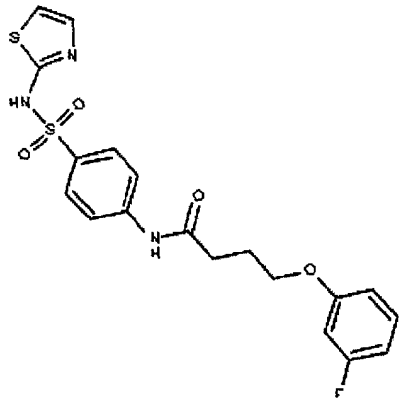
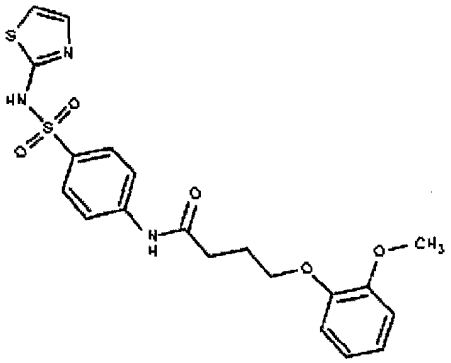
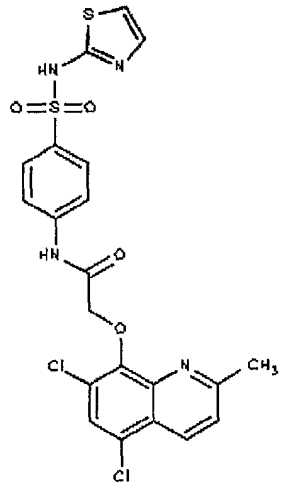
566	
567	
568	

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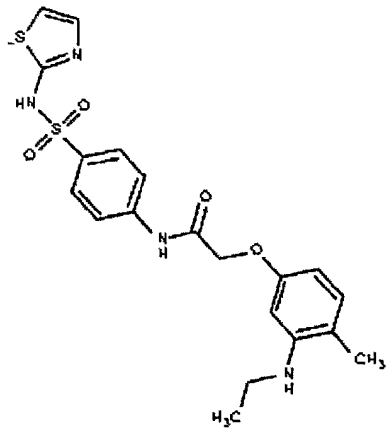
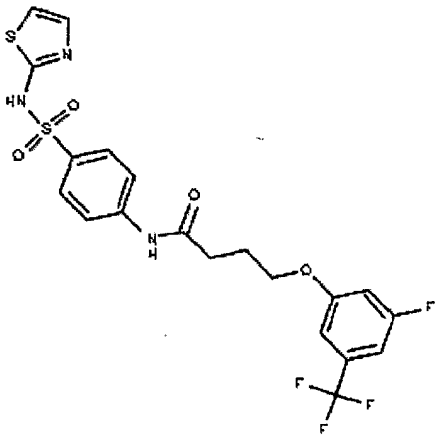
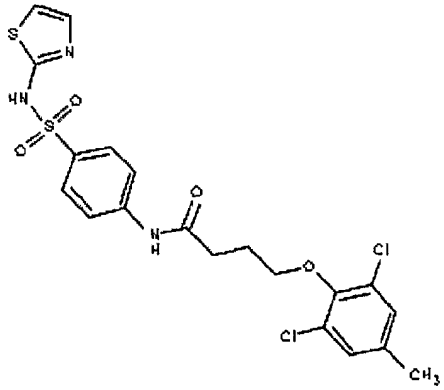
569	
570	
571	

Figure 1-88

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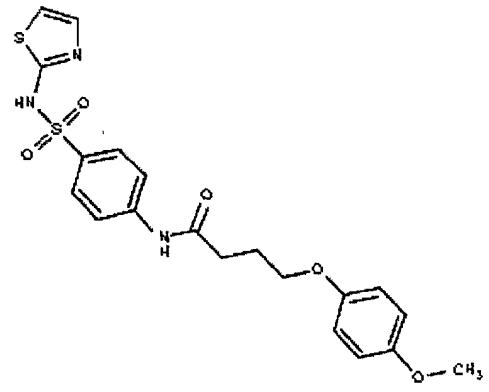
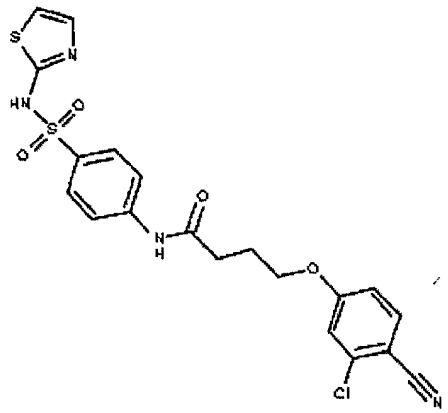
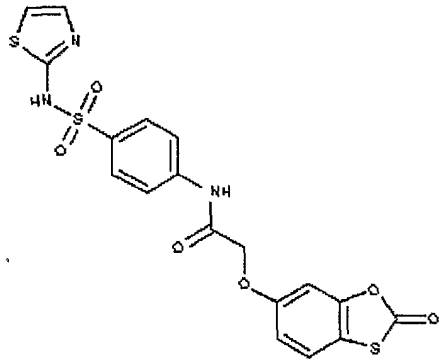
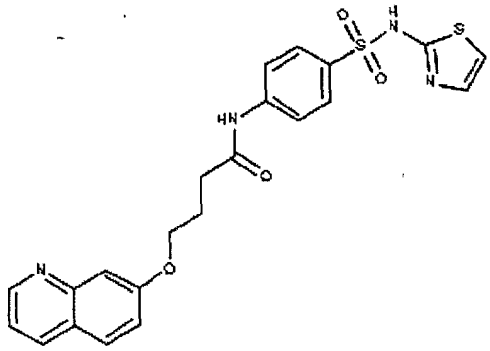
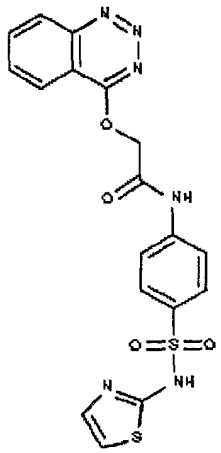
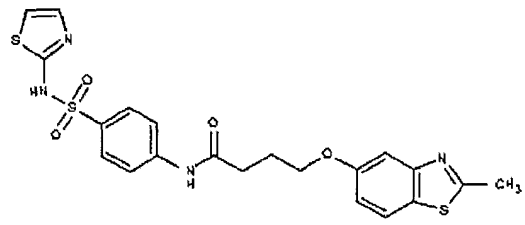
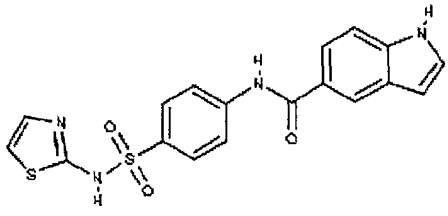
572	
573	
574	
575	
576	
577	
578	

Figure 1-89

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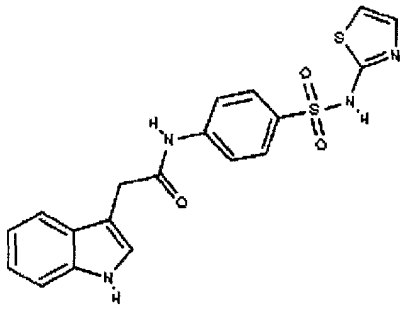
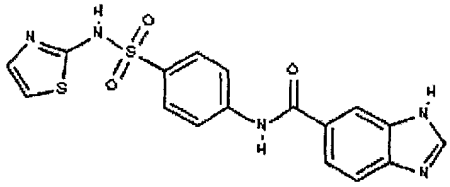
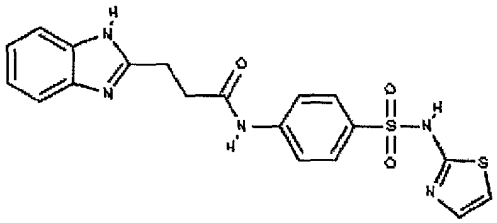
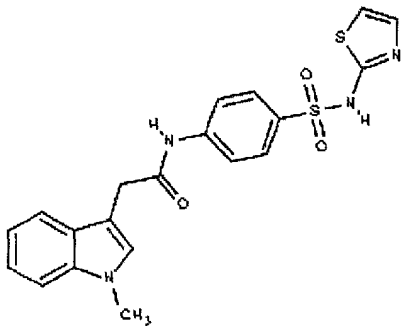
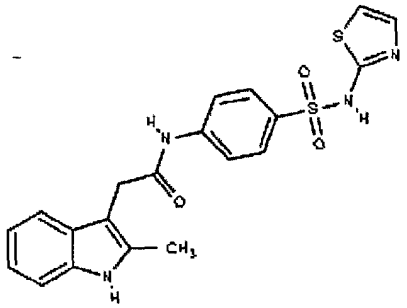
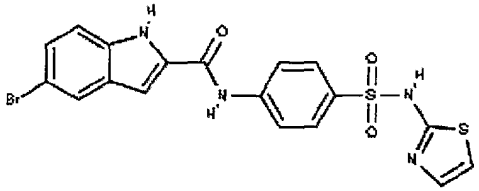
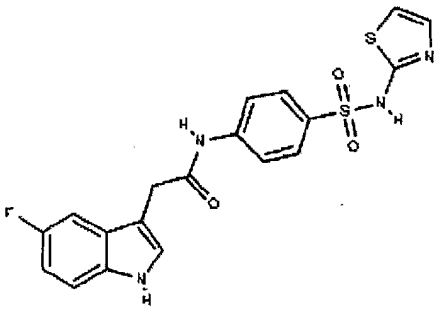
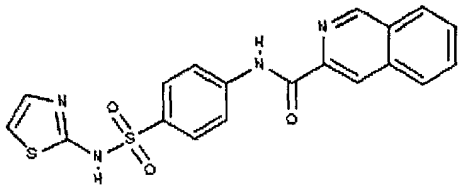
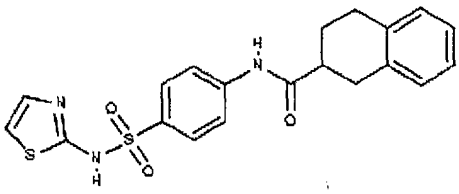
579	
580	
581	
582	
583	
584	
585	
586	
587	

Figure 1-90

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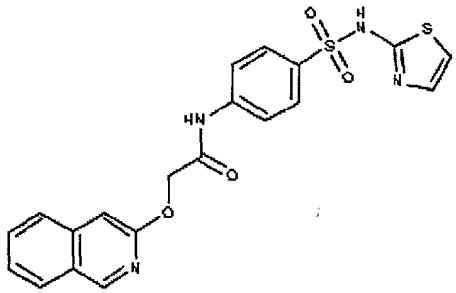
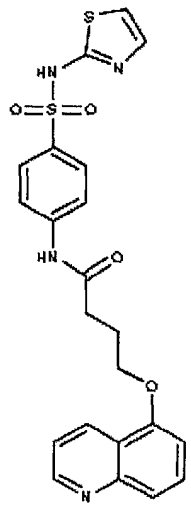
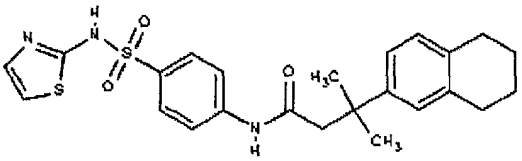
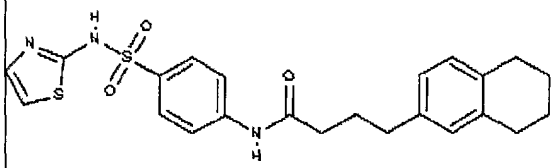
588	
589	
590	
591	

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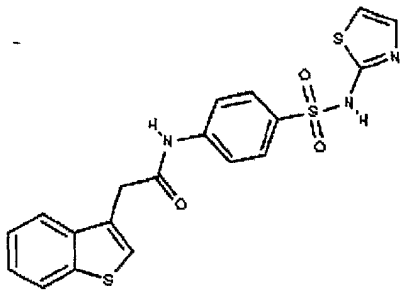
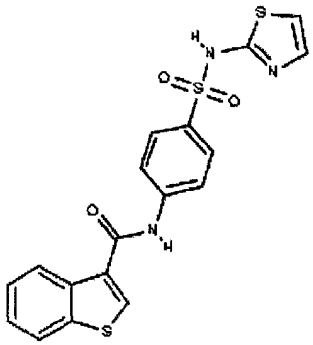
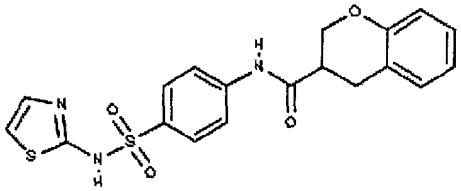
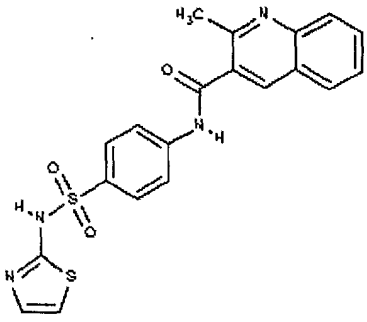
592	
593	
594	
595	

Figure 1-91

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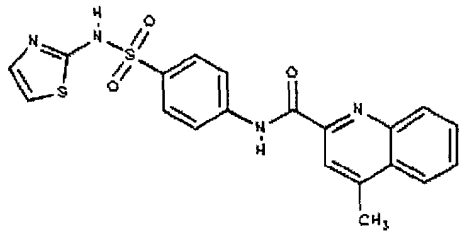
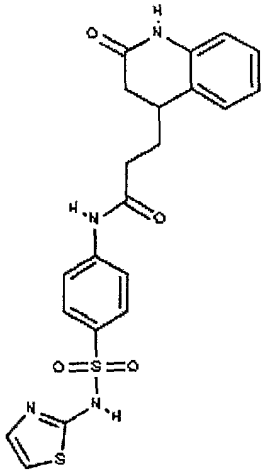
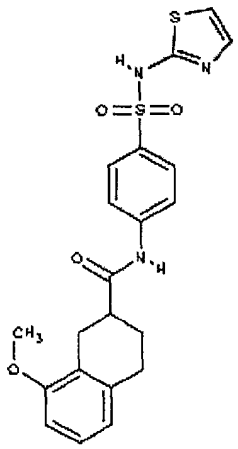
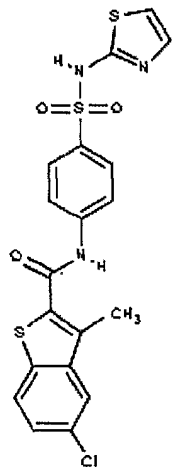
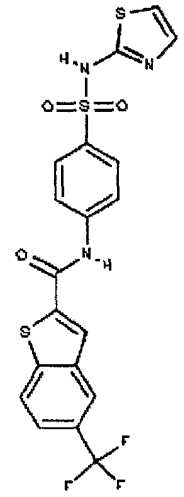
596	
597	
598	
599	
600	

Figure 1-92

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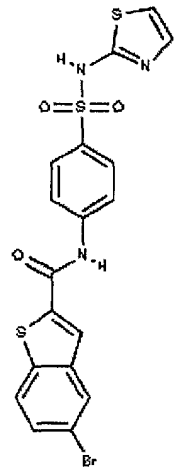
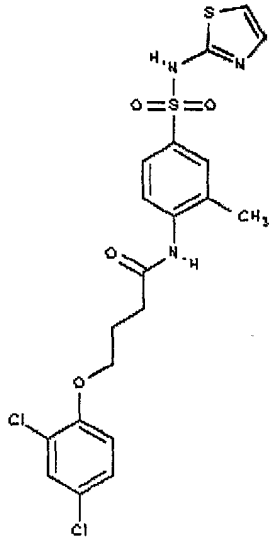
601	
602	

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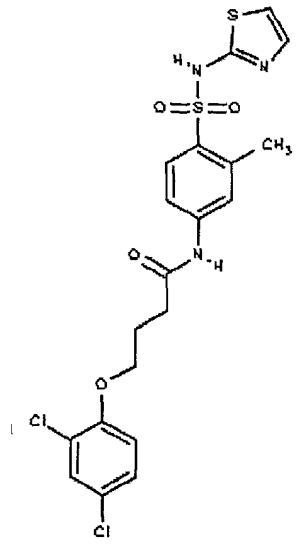
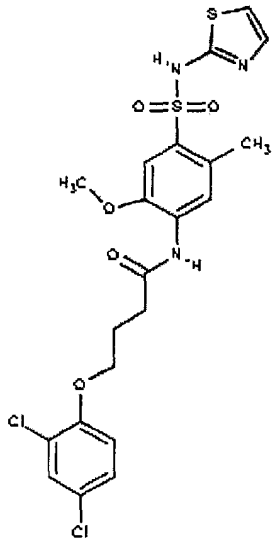
603	
604	

Figure 1-93

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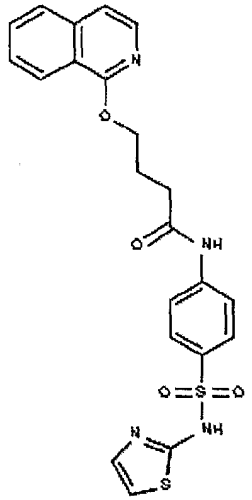
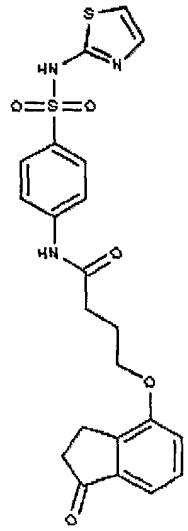
605	
606	

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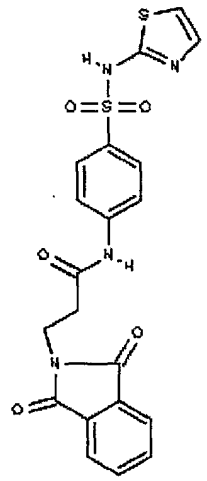
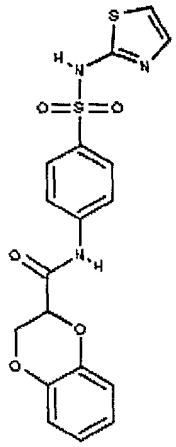
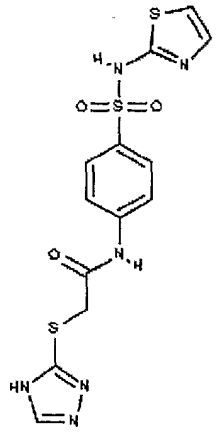
607	
608	
609	

Figure 1-94

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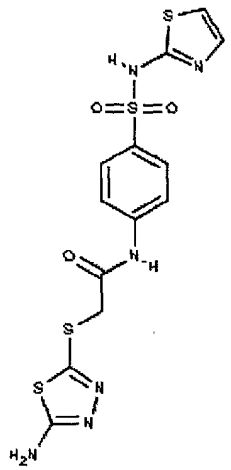
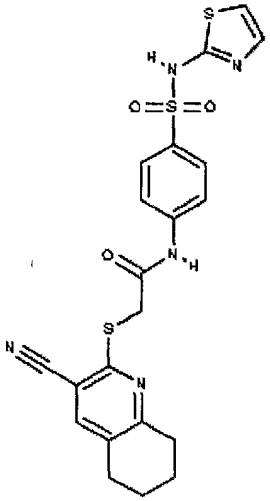
610	
611	

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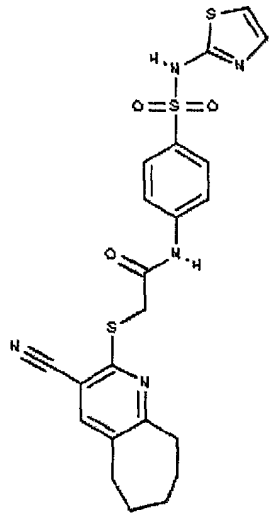
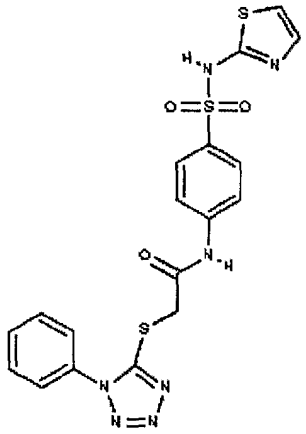
612	
613	

Figure 1-95

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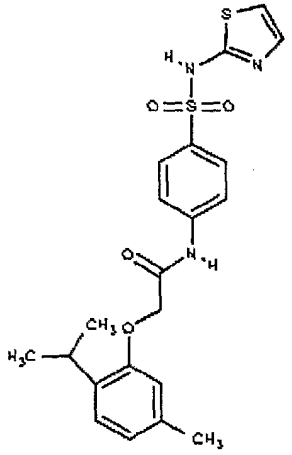
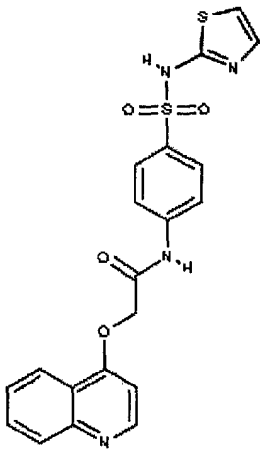
614	
615	

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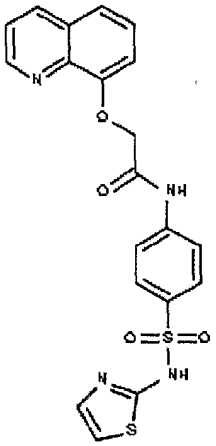
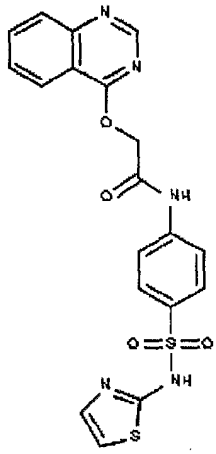
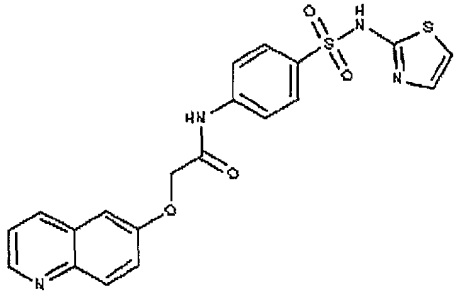
616	
617	
618	

Figure 1-96

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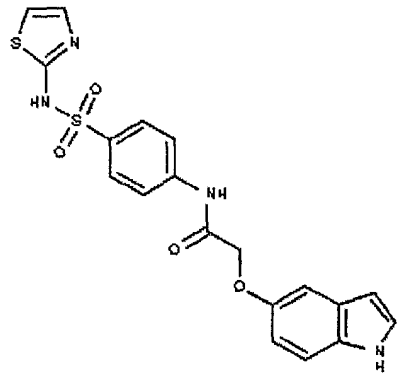
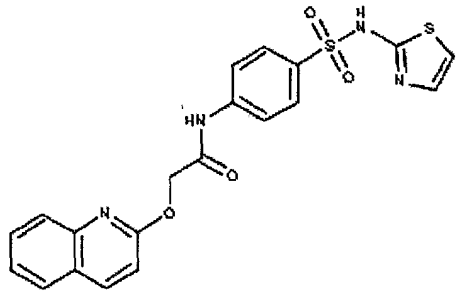
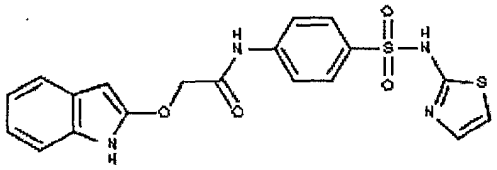
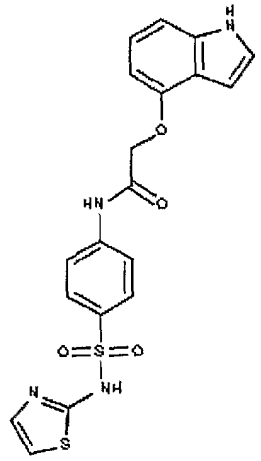
619	
620	
621	
622	

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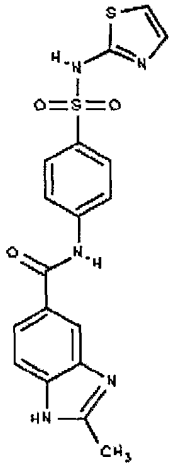
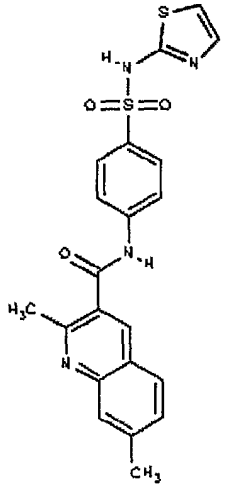
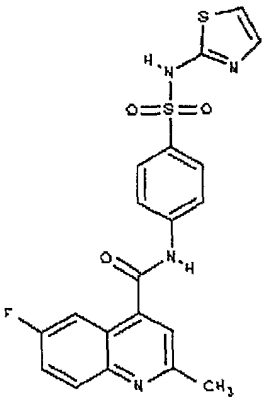
623	
624	
625	

Figure 1-97

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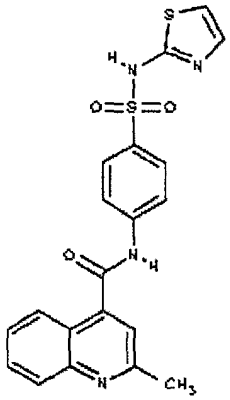
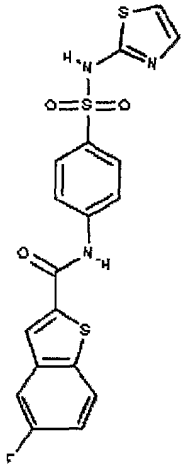
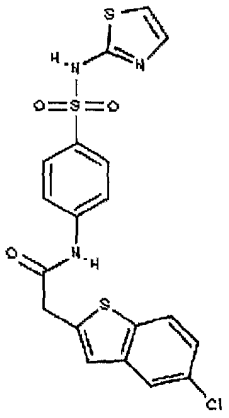
626	
627	
628	

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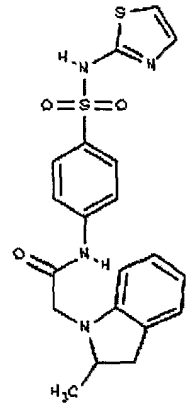
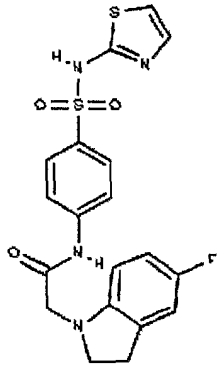
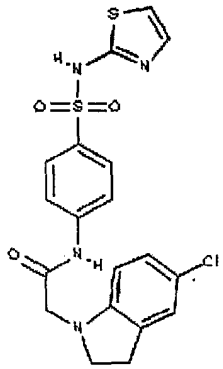
629	
630	
631	

Figure 1-98

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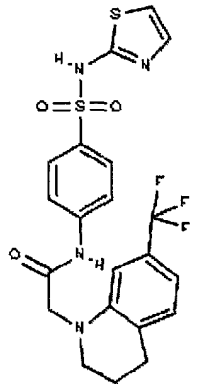
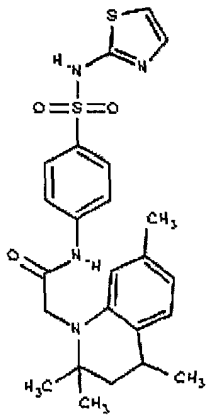
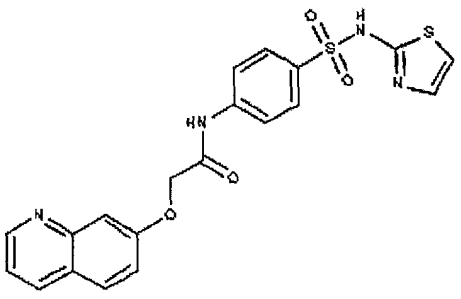
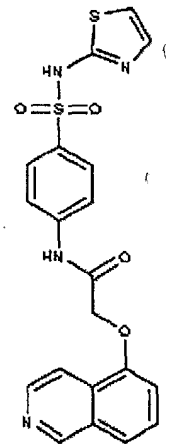
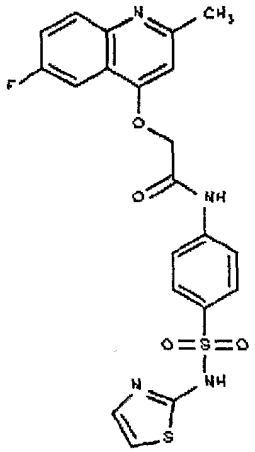
632	
633	
634	
635	
636	

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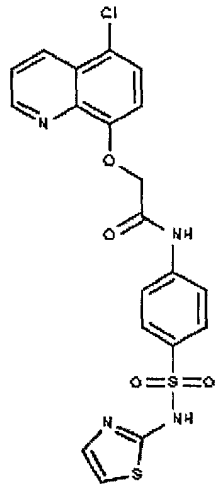
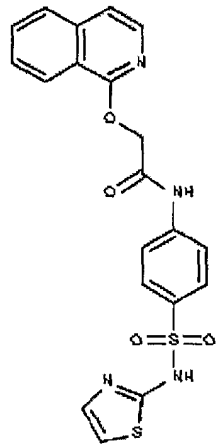
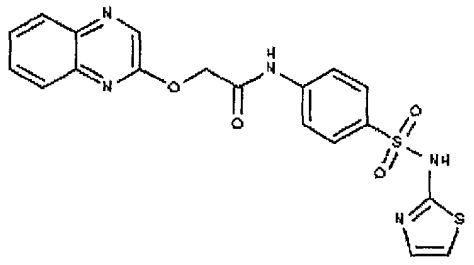
637	
638	
639	

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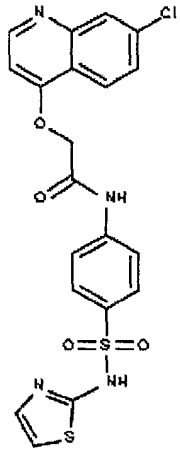
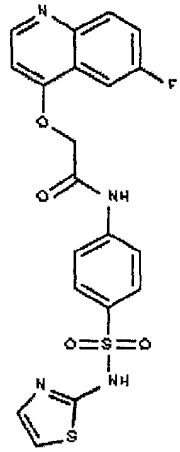
640	
641	

Figure 1-100

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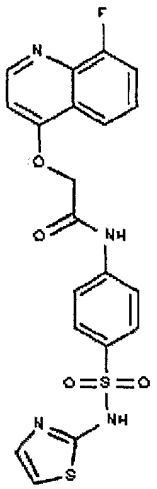
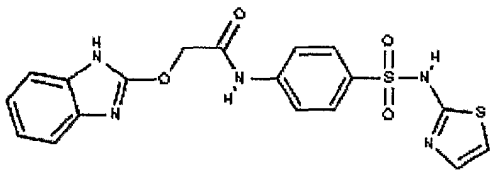
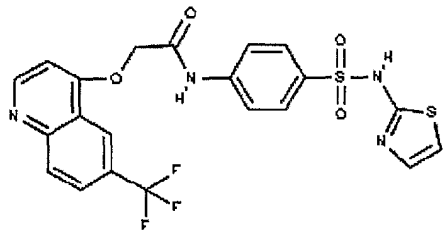
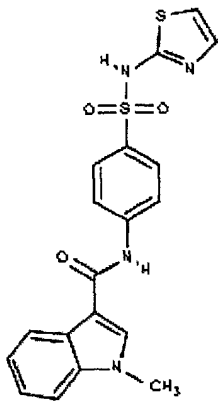
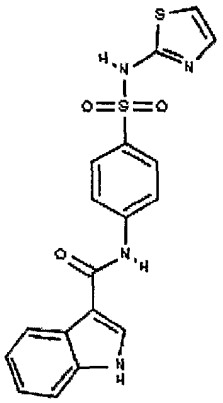
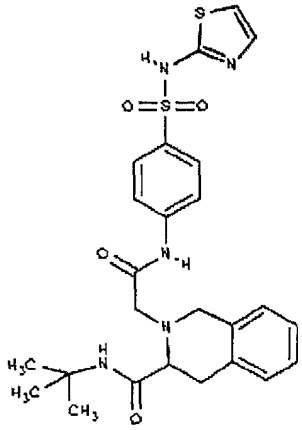
642	
643	
644	
645	
646	
647	

Figure 1-101

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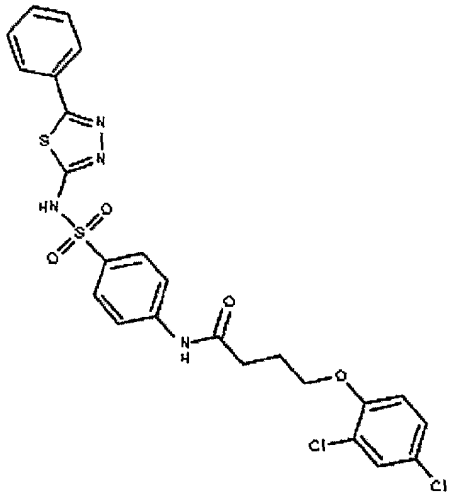
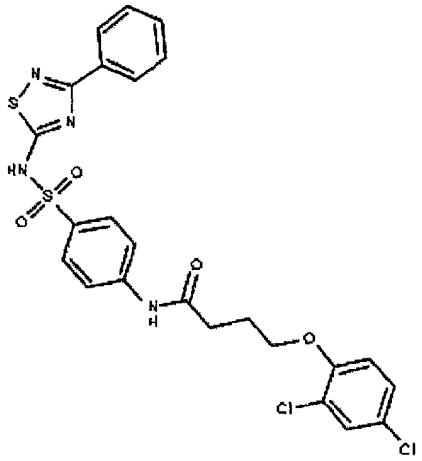
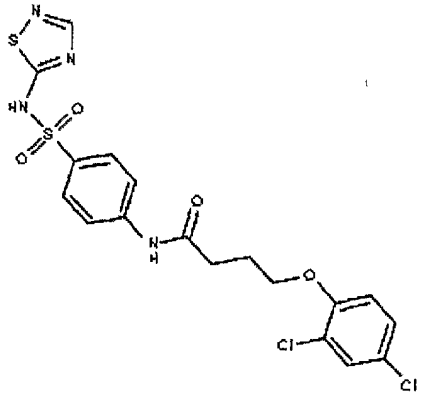
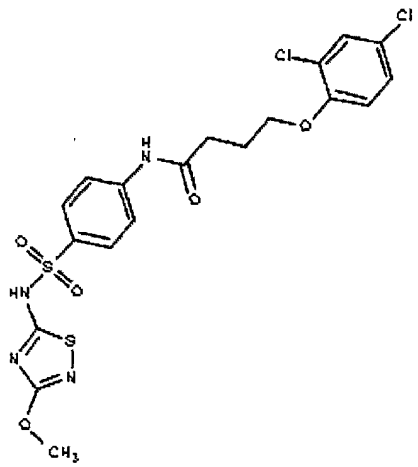
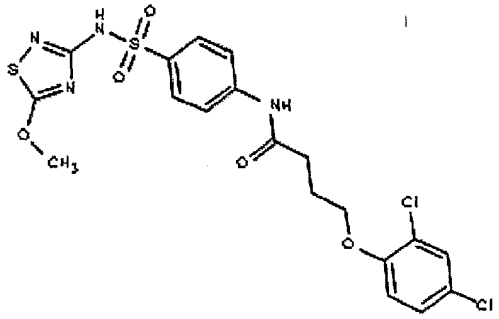
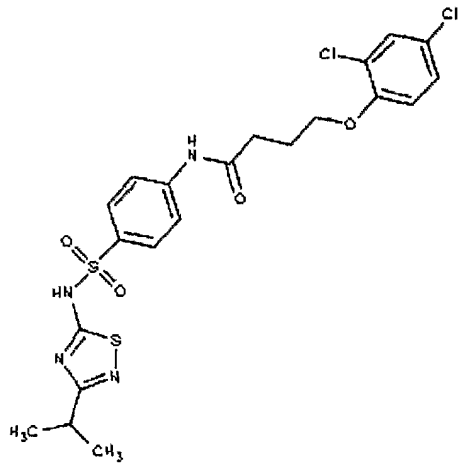
648	
649	
650	
651	
652	
653	

Figure 1-102

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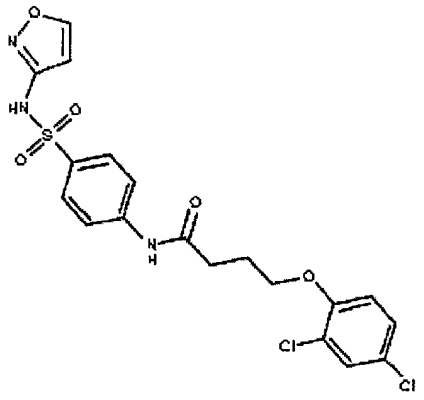
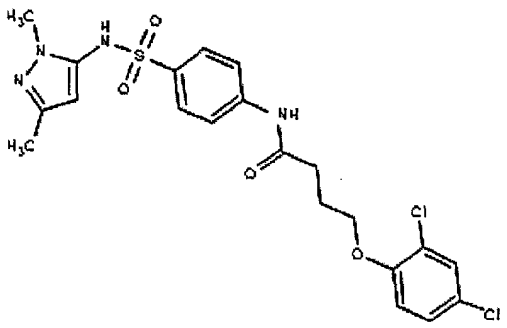
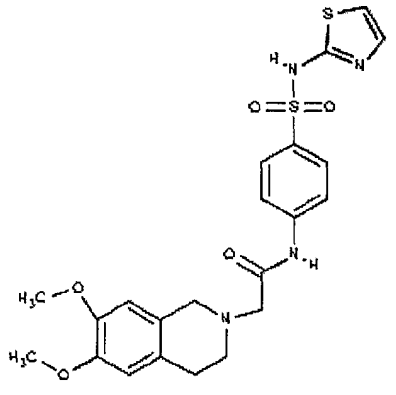
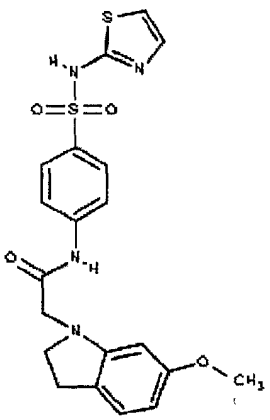
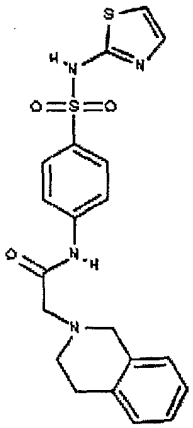
654	
655	
656	
657	
658	

Figure 1-103

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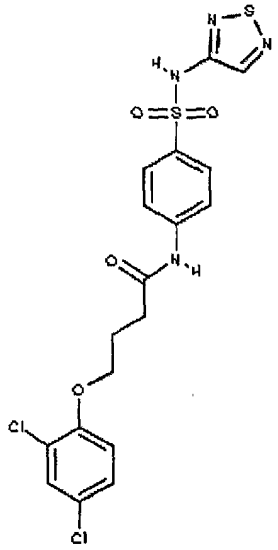
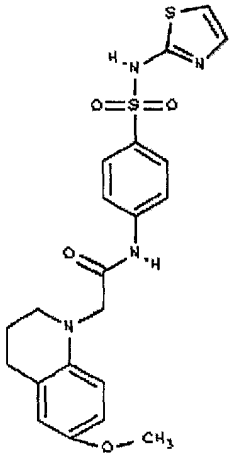
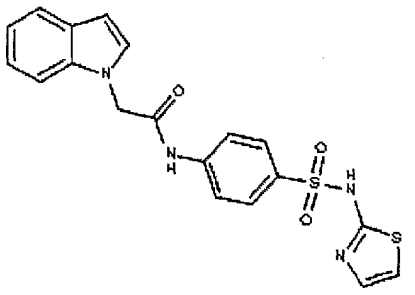
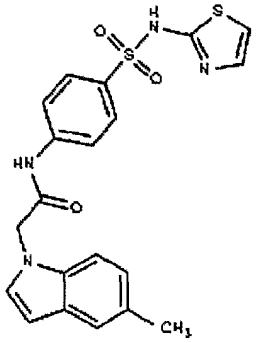
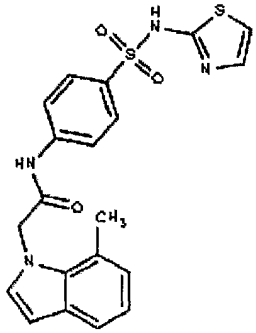
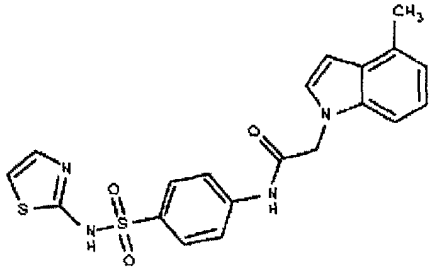
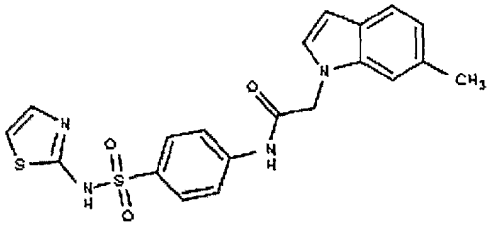
659	
660	
661	
662	
663	
664	
665	

Figure 1-104

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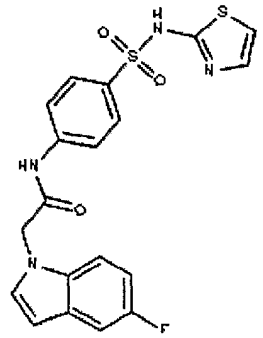
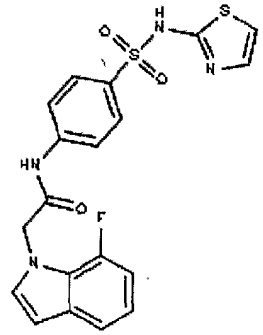
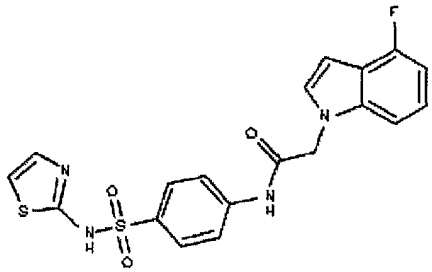
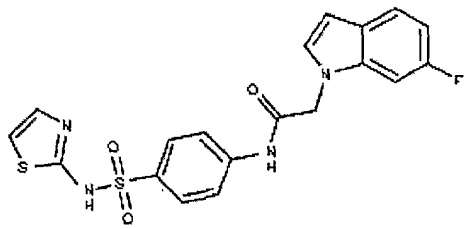
666	
667	
668	
669	

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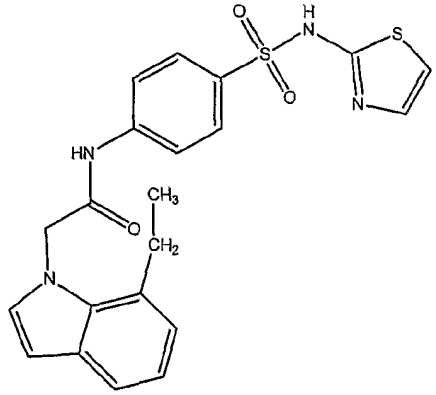
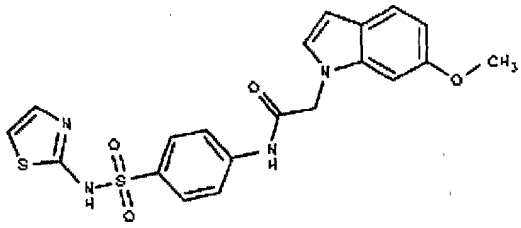
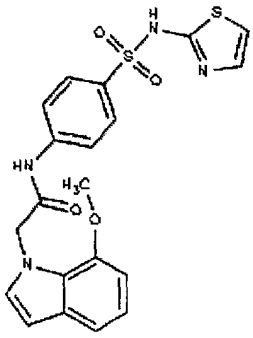
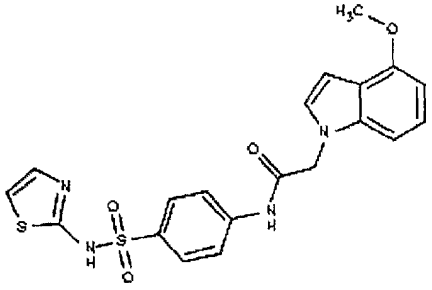
670	
671	
672	
673	

Figure 1-105

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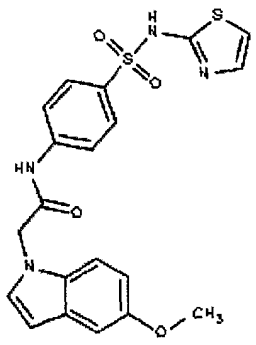
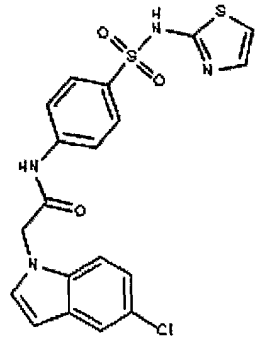
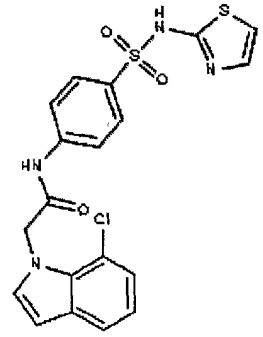
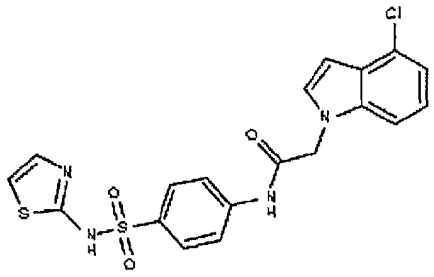
674	
675	
676	
677	

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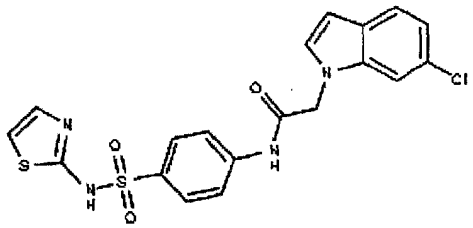
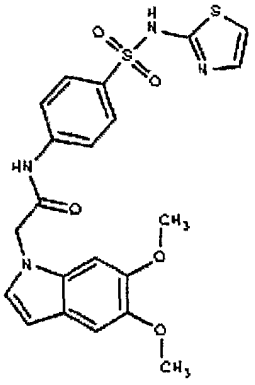
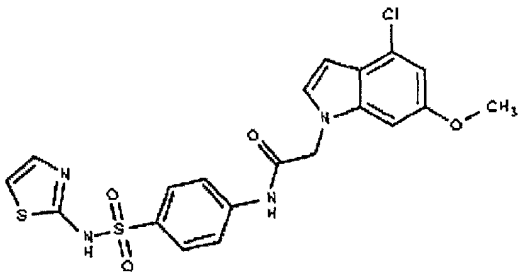
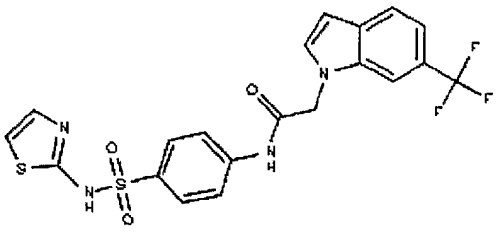
678	
679	
680	
681	

Figure 1-106

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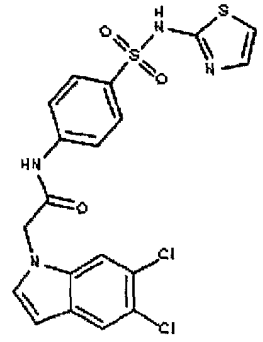
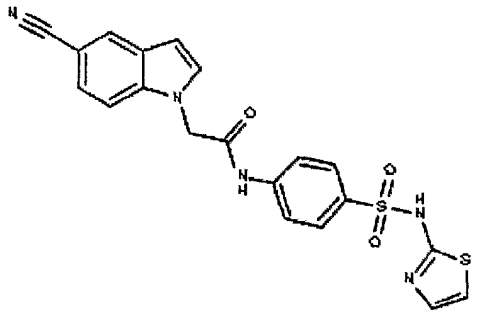
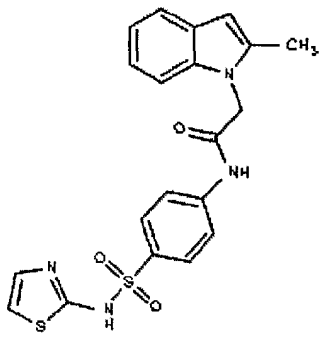
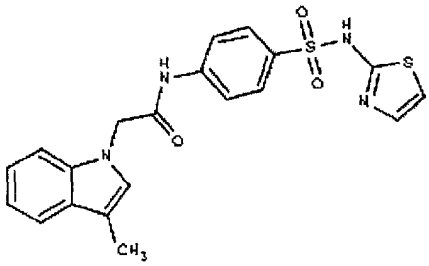
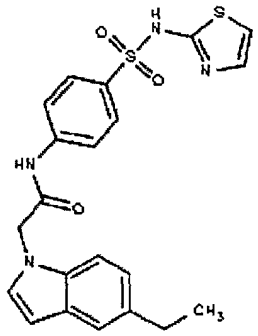
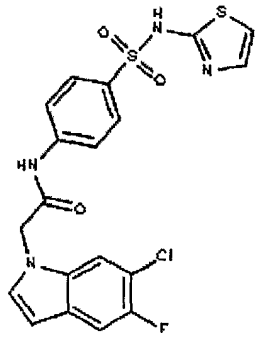
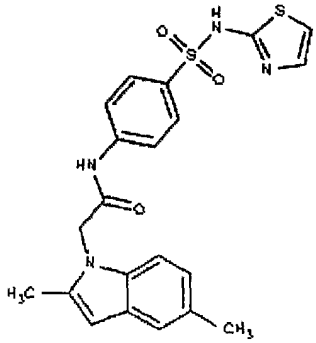
682	
683	
684	
685	
686	
687	
688	

Figure 1-107

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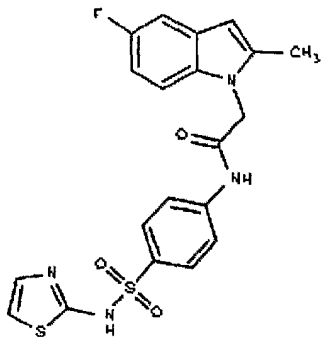
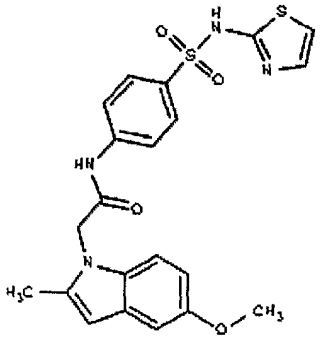
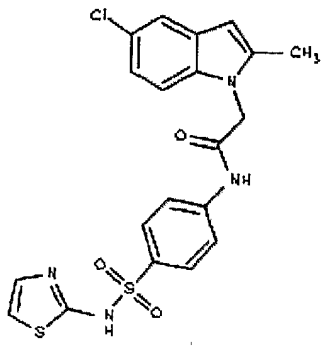
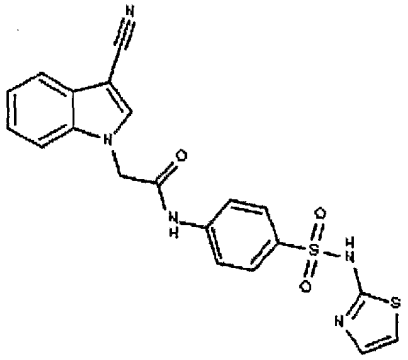
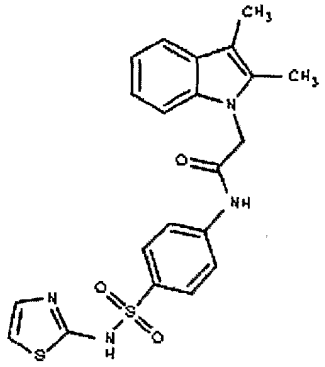
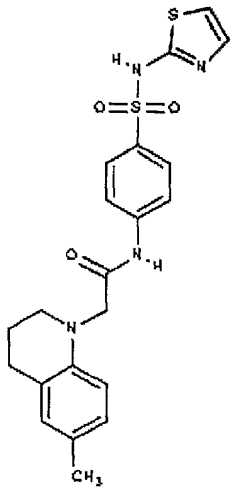
689	
690	
691	
692	
693	
694	

Figure 1-108

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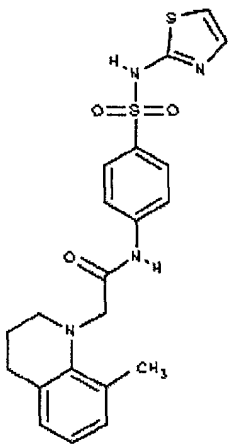
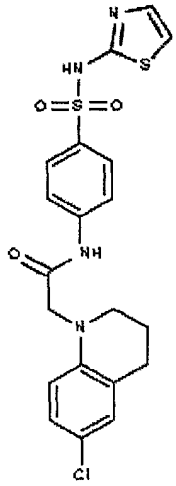
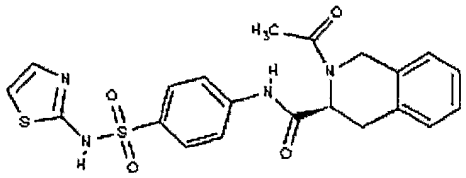
695	
696	
697	

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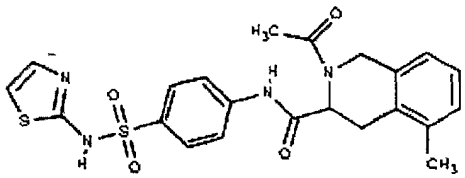
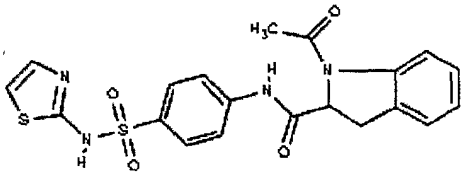
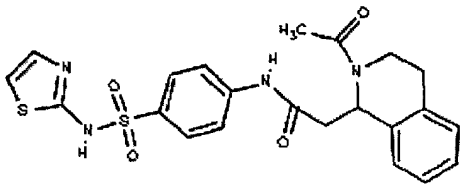
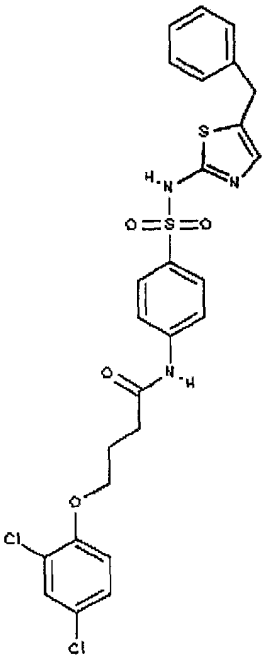
698	
699	
700	
701	

Figure 1-109

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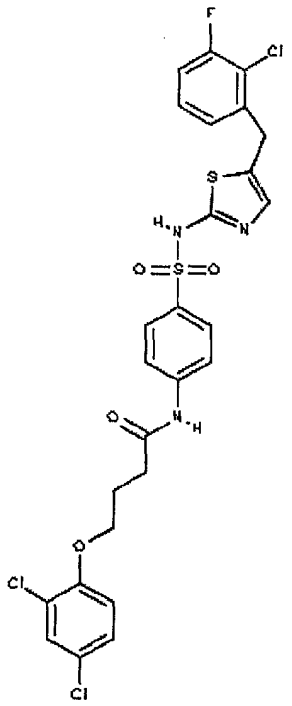
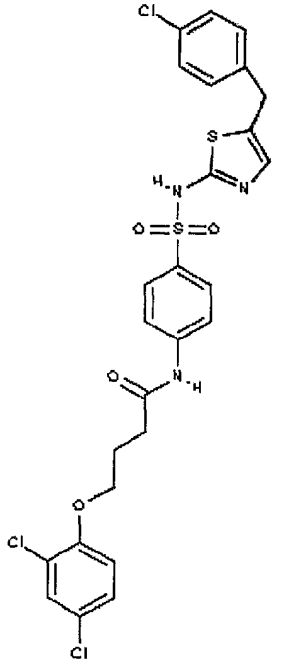
702	
703	

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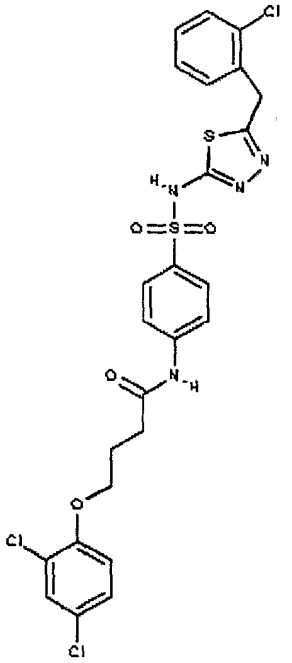
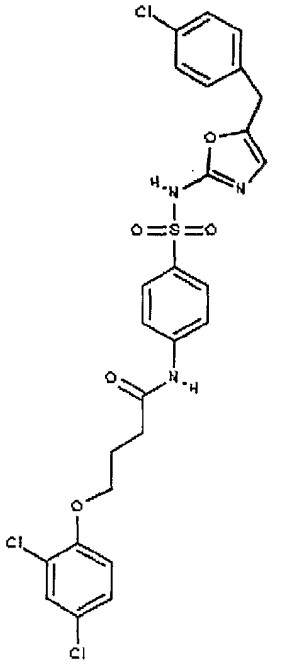
704	
705	

Figure 1-110

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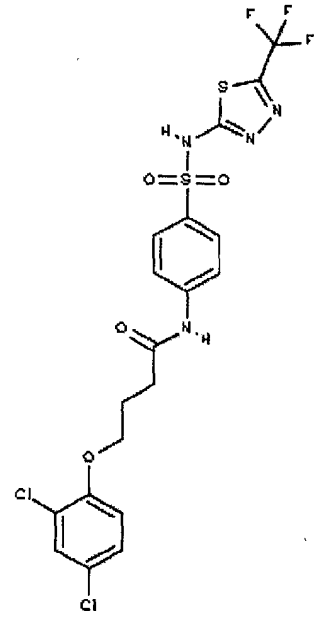
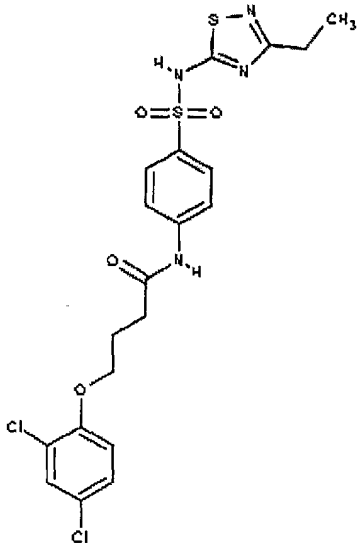
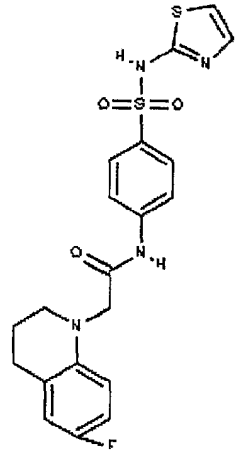
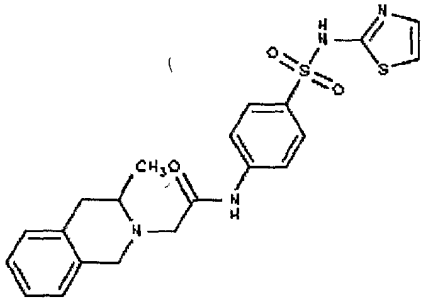
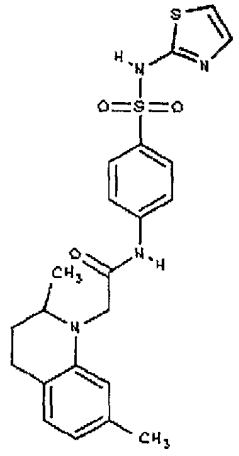
706	
707	
708	
709	
710	

Figure 1-111

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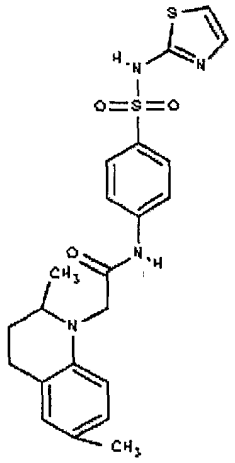
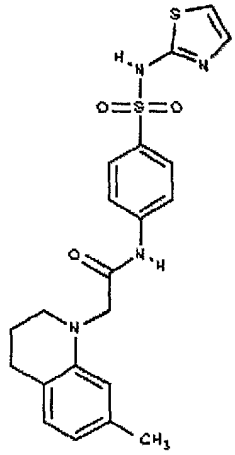
711	
712	

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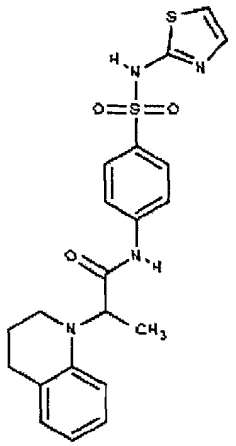
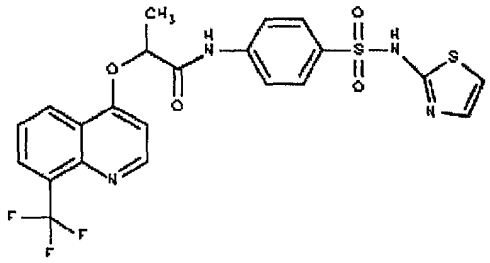
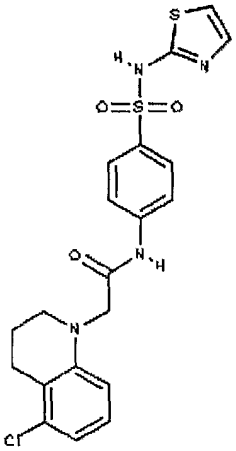
713	
714	
715	

Figure 1-112

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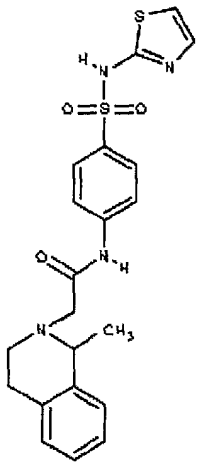
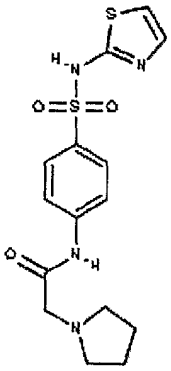
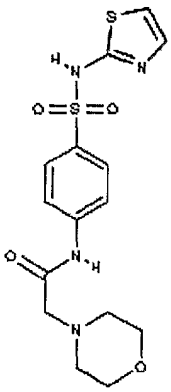
716	
717	
718	

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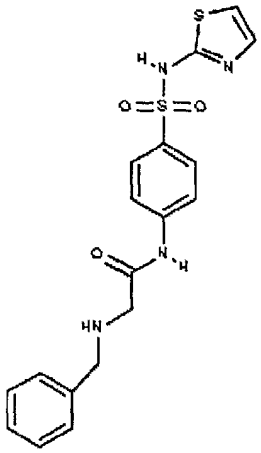
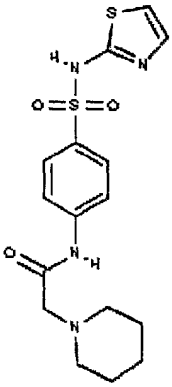
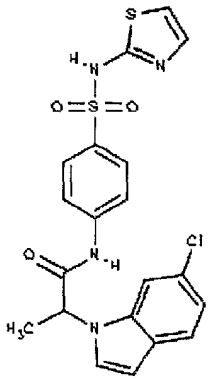
719	
720	
721	

Figure 1-113

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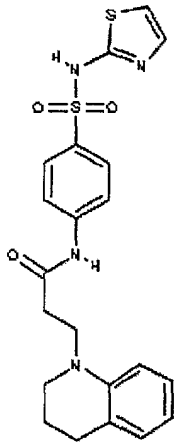
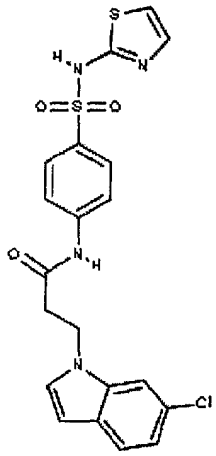
722	
723	

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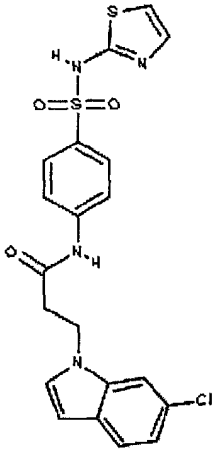
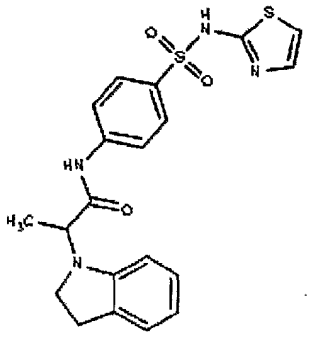
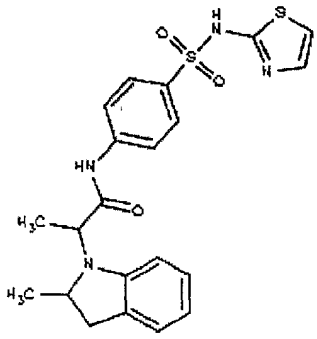
724	
725	
726	

Figure 1-114

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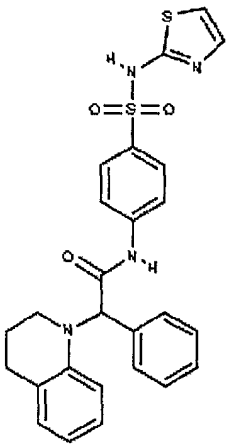
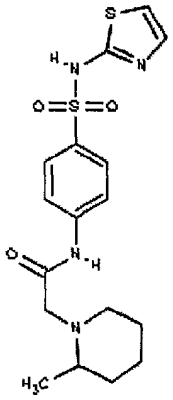
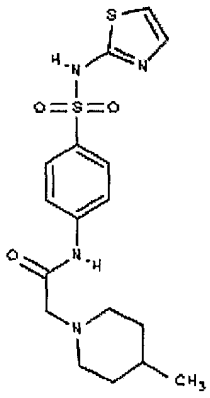
727	
728	
729	

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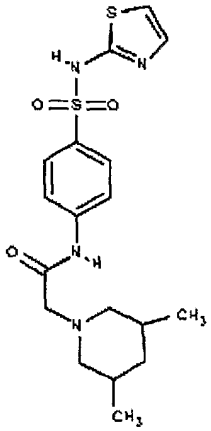
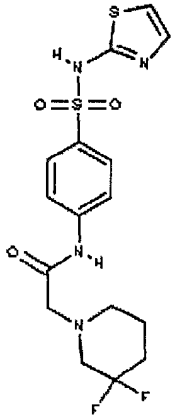
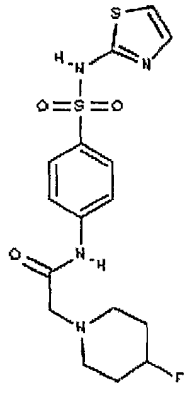
730	
731	
732	

Figure 1-115

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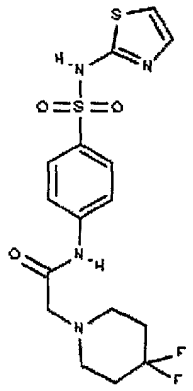
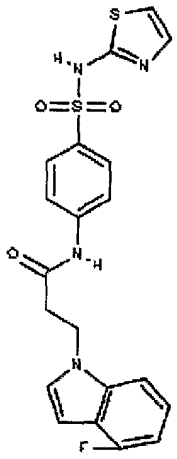
733	
734	

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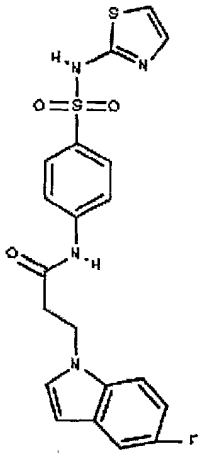
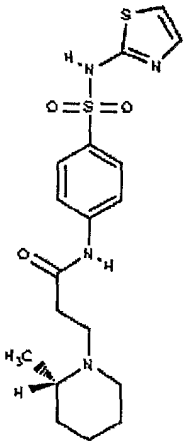
735	
736	

Figure 1-116

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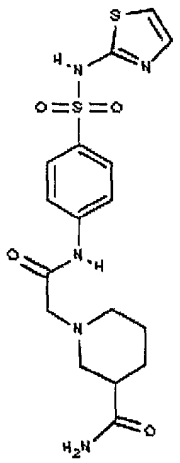
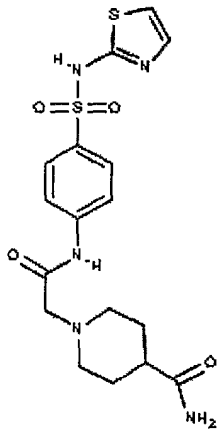
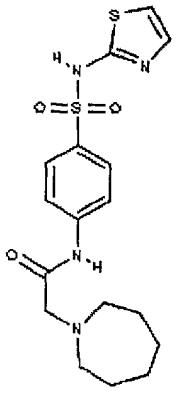
737	
738	
739	

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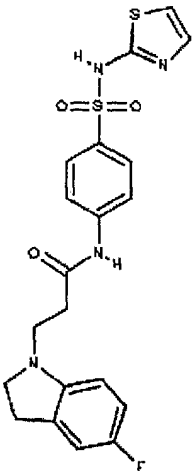
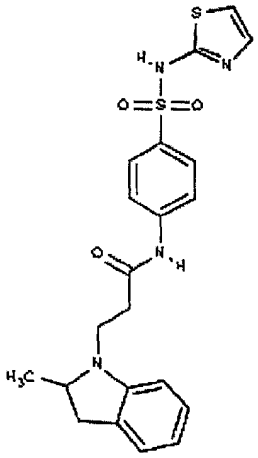
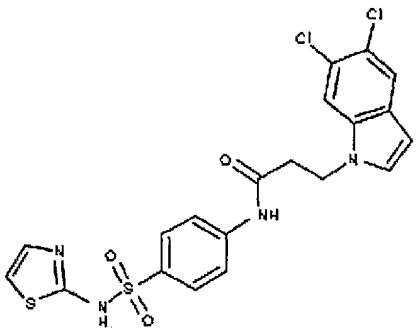
740	
741	
742	

Figure 1-117

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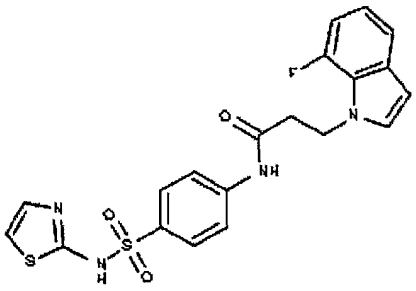
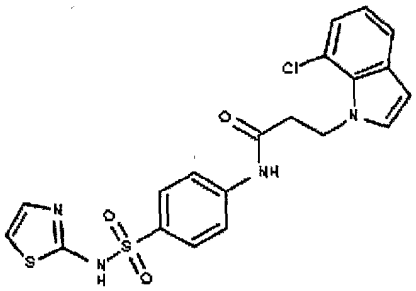
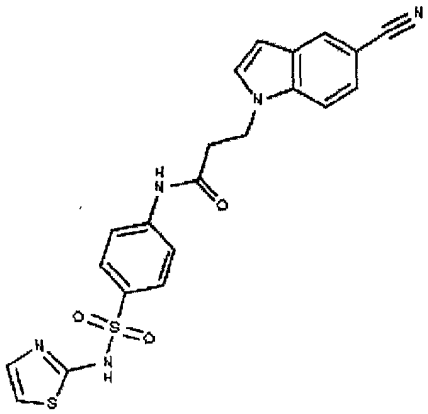
743	
744	
745	

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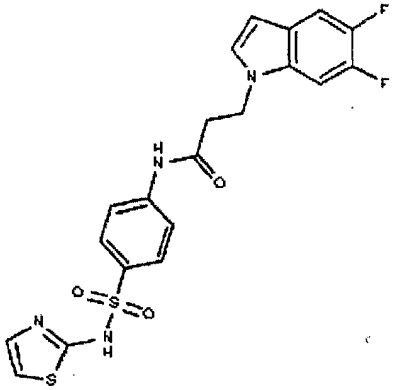
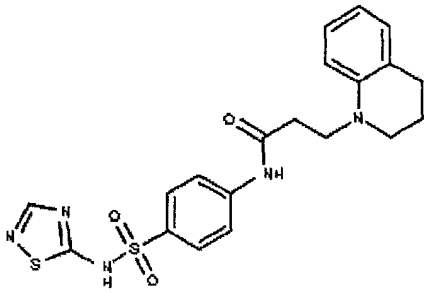
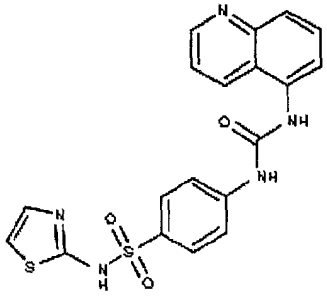
746	
747	
748	

Figure 1-118

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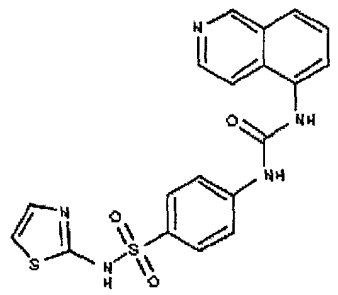
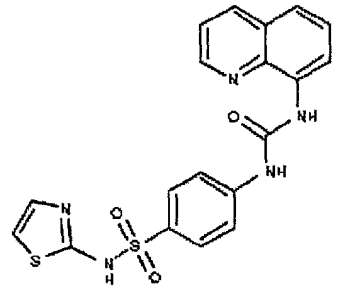
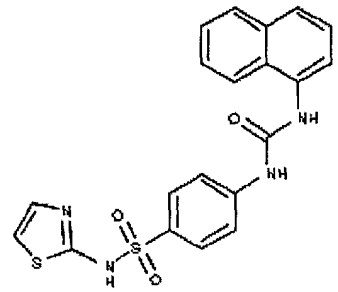
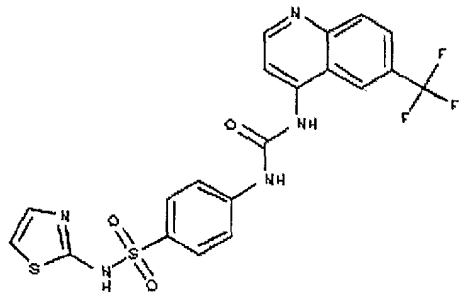
749	
750	
751	
752	

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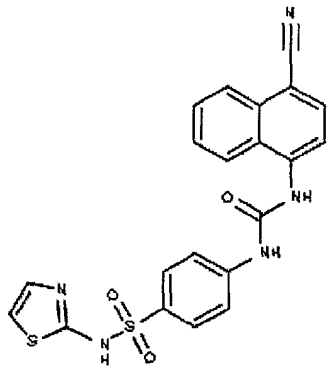
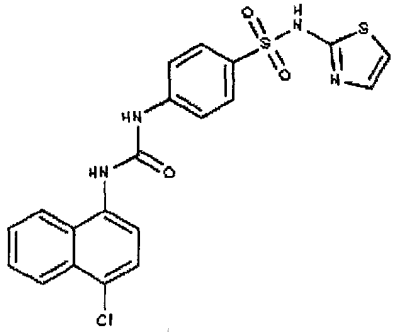
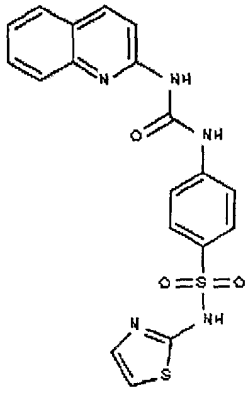
753	
754	
755	

Figure 1-119

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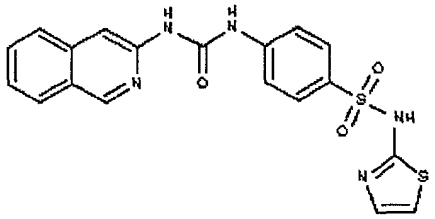
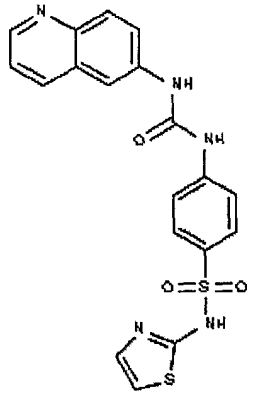
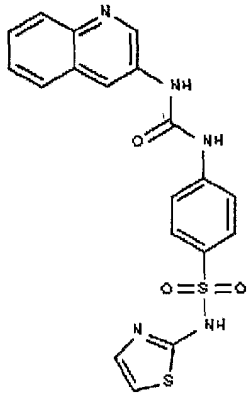
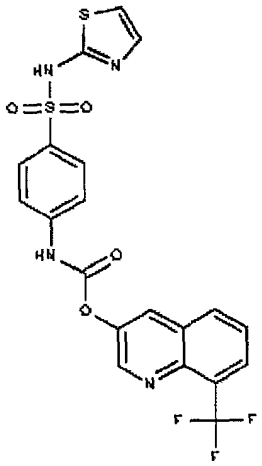
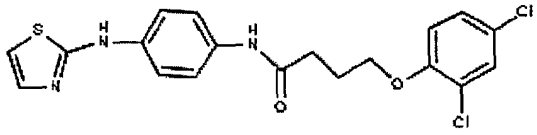
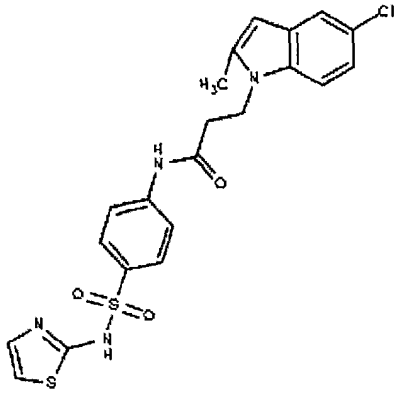
756	
757	
758	
759	
760	
761	

Figure 1-120

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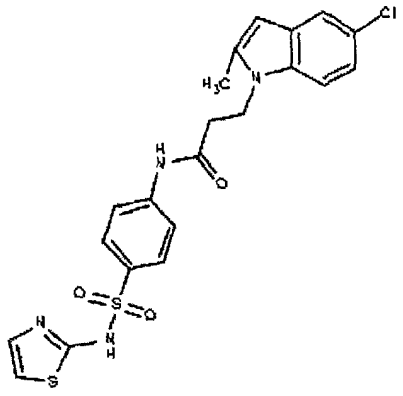
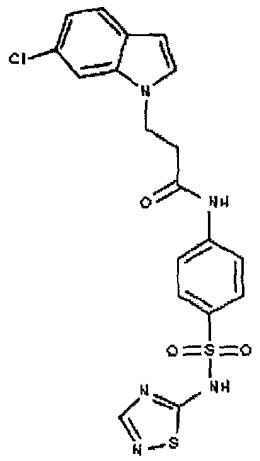
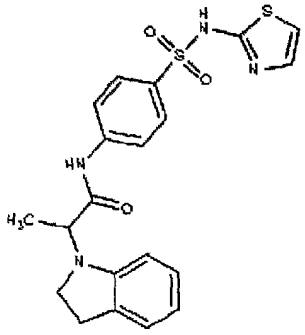
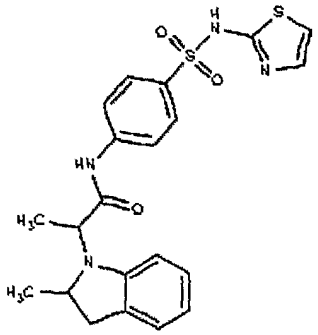
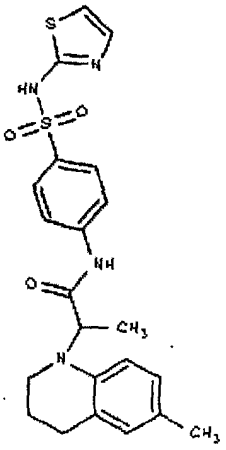
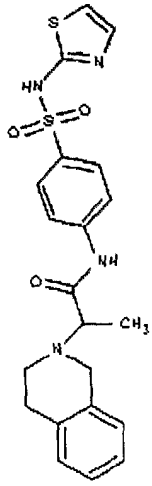
762	
763	
764	
765	
766	
767	

Figure 1-121

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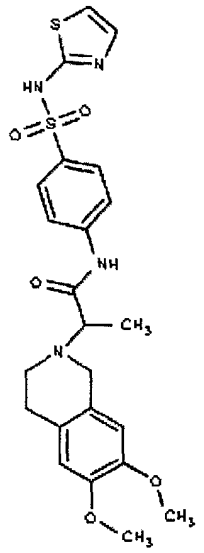
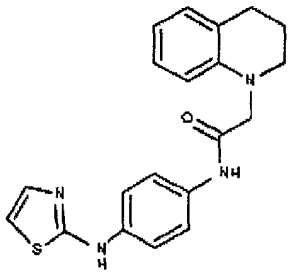
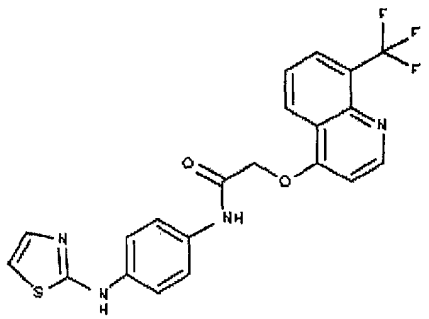
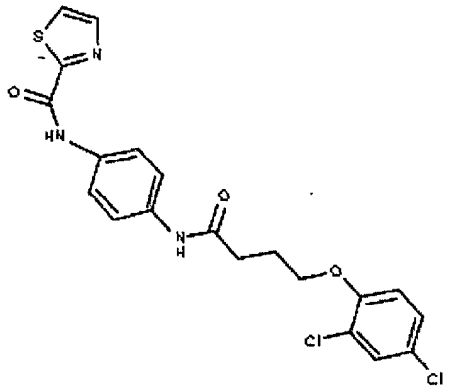
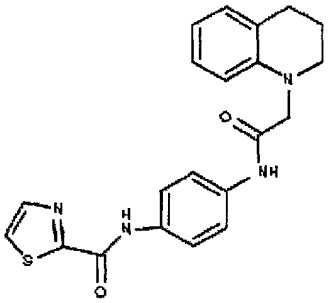
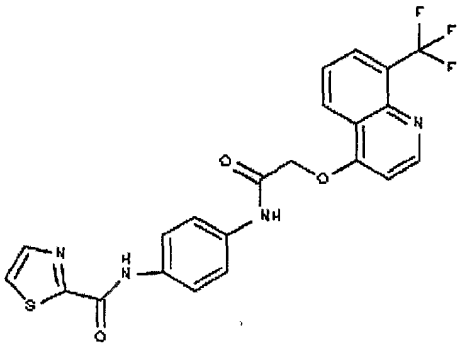
768	
769	
770	
771	
772	
773	

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