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ERTY, Bruce [US/US]; 82 Ironia Road, Mendham, NJ 07945 (US).

(74) Agents: HALEY, James, F. et al.; Ropes & Gray LLP, 1211 Avenue of the Americas, New York, NY 10036-8704 (US).

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(72) Inventors; and

(71) Applicants : LEDERMAN, Seth [US/US]; 166 E. 96th Street, Apt. 17A, New York, NY 10128 (US). DAUGH-

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(54) Title: COMPOUNDS FOR USE AS PAIN THERAPEUTICS

(57) Abstract: This disclosure provides compounds and compositions for use as analgesics and for the treatment of one or more conditions selected from: pain; psychic pain; psychological pain; psychiatric pain; depression; allodynia; fibromyalgia; fibromyalgia-ness; central sensitization; centralization; regional pain syndrome; temporomandibular joint syndrome (TMJ); lower back pain; interstitial cystitis; Gulf War syndrome; visceral pain; phantom limb pain; kidney stones; gout; neuropathic pain; post-herpetic neuralgia; diabetic neuropathy; sickle cell pain; priapism; nociceptive pain; post-operative pain; orthopedic injury pain; bunionectomy; dental extraction; pain after severed spinal cord injury; osteoarthritis; rheumatoid arthritis; Lyme disease; Parkinson's disease; opioid-induced constipation; an opioid withdrawal symptom; pain associated with post-traumatic stress disorder (PTSD); and combinations of any of the foregoing conditions. This disclosure also provides compounds that are ligands, and in some embodiments, modulators (e.g., agonists), for the imidazoline receptor type 1.



COMPOUNDS FOR USE AS PAIN THERAPEUTICS

Related Applications

This application claims priority to and benefit from U.S. Provisional Patent Application 62/095,679, filed December 22, 2014, and U.S. Provisional Patent Application 62/181,012, filed June 17, 2015. The contents and disclosures of each of
5 the foregoing applications are hereby incorporated by reference in their entirety.

Background of the Disclosure

For the treatment of various painful conditions, such as tension or migraine headaches, fibromyalgia, and allodynia, ameliorative compounds and analgesics are needed.

10 Tension-type headaches (TTH) are the most common type of headaches among adults, and as a result of their high prevalence, impose the greatest socioeconomic impact of any primary headache type. The pain of TTH may render a sufferer unable to attend activities, force them to stay home from work, or impair their ability to function at work. According to Mayo Clinic, tension headaches affect 90% of women and 70%
15 of men. The pathogenesis of tension-type headache is poorly understood.

Migraine affects people of all races and both sexes with women accounting for 79% (61% between 20 and 49 years of age) of physician visits for migraines and Caucasians for 91% of the physician visits. The pathogenesis of migraine headache is believed to involve a) the cranial blood vessels, b) the trigeminal innervation of these
20 vessels, and c) the reflex connection of the trigeminovascular system in the cranial parasympathetic outflow. In view of these various aspects of migraine, a wide variety of prospective targets for migraine treatment exists. TTH may be a mild form of migraine headache or may have a distinct etiology. Recurrent TTH and migraine headache syndromes may be co-morbid and have been termed “mixed” headache
25 syndrome.”

Nociceptive pain results from injury, compression, infection, inflammation, degeneration, metabolic or genetic pathology, or neoplasm affecting tissues including

skin, muscles, joints, bones, and internal organs. Injury can include exposure to extreme temperatures, trauma, and physical exposure to blunt or sharp objects or physical exposure to caustic, irritating, or allergenic substances. Nociceptive pain can be acute or chronic.

- 5 Neuropathic pain results from injury, compression, infection, inflammation, degeneration, metabolic or genetic pathology, or neoplasm affecting nerves in the peripheral or central nervous system. Injury can include exposure to extreme temperatures, trauma, and physical exposure to blunt or sharp objects or physical exposure to caustic, irritating, or allergenic substances. Neuropathic pain can be acute
10 or chronic:

Regional pain is pain associated with one or more areas of the body. Visceral pain is pain associated with one or more internal organs. Regional and visceral pain can be nociceptive or neuropathic or a combination of nociceptive and neuropathic. In “complex regional pain syndromes” (CRPS) nerves and blood vessels are involved.
15 CRPS are chronic conditions characterized by pain, burning, swelling, sweating and skin color changes. In the reflex sympathetic dystrophy type of CRPS nerve damage is either not present or represents a small component of the pathology. In the causalgia type of CRPS nerve injury is present.

Fibromyalgia is a chronic disorder characterized by widespread musculoskeletal pain
20 accompanied by fatigue, sleep, memory, and mood issues. Research indicates that fibromyalgia amplifies painful sensations by affecting the way the brain processes pain signals. Symptoms of fibromyalgia sometimes begin after a physical trauma, surgery, infection, menopause, or significant psychological stress. In other cases, symptoms gradually accumulate over time. In many cases, fibromyalgia develops in
25 people suffering for many years from chronic regional pain, including lower back pain or temporomandibular joint syndrome. The causes of fibromyalgia are unclear. The pathogenesis of fibromyalgia is believed to involve sensitization of the central nervous system (CNS) to perceiving painful stimuli, which is termed “central sensitization” or “centralization”. Centralization leads to the perception of widespread pain. Pain of

this type is termed, “central neuropathic pain” or “central pain”. Centralization also leads to other symptoms, including visceral pain such as irritable bowel, TTH, and migraine. Centralization increases the sensitivity of the brain to light, sound, taste and odor stimuli. Non-restorative sleep is a key feature of fibromyalgia and disturbed sleep can exacerbate other symptoms. Fibromyalgia is estimated to impact 5-15 million Americans age 18 or older. Between 80 and 90% of people diagnosed with fibromyalgia are women. Fibromyalgia is believed to be an extreme manifestation of symptoms, termed “fibromyalgia-ness” that can occur in lesser severity below the threshold that qualifies for the diagnosis of fibromyalgia by the American College of Rheumatology (ACR) 2010 criteria. Fibromyalgia and fibromyalgia-ness have overlap with other conditions including Gulf War Syndrome and Post-traumatic Stress Disorder (PTSD) and are sometimes co-morbid with these conditions.

Allodynia, or pain due to a stimulus that does not usually provoke pain, is a prominent symptom in patients with neuropathic pain. Allodynia is seen in various peripheral neuropathies and central pain disorders, and affects 15-50% of patients with neuropathic pain. Allodynia is classified according to the sensory modality (touch, pressure, pinprick, cold, and heat) that elicits the sensation. Allodynia can be co-morbid with fibromyalgia and can be a feature of fibromyalgia. Like fibromyalgia, the causes of allodynia are unclear. Centralization and allodynia can be acute as well as chronic. For example, migraine can be accompanied by acute symptoms of: nausea and vomiting, loss of appetite, abdominal pain, and sensitivity to light, odor, taste and sound.

Pain, including widespread pain, can occur after traumatic brain injury (TBI) or in post-traumatic stress disorder (PTSD). When pain, TBI, and PTSD are all present, it is termed the “polytrauma triad”.

Withdrawal from addictive substances, including alcohol, barbiturates, benzodiazepines, nicotines, ketamines and opiates is associated with widespread pain and other symptoms. Widespread pain can persist for long periods of time after drug withdrawal. Regional pain syndromes including headaches can occur after medication

discontinuation or even missed doses of a chronic regimen. For example, caffeine withdrawal headache is a headache syndrome associated with the discontinuation of caffeine.

5 Withdrawal of the use of various medications can result in pain symptoms upon withdrawal of the medication. For example, medication overuse headache is a headache syndrome associated with use and withdrawal of medications. Other medications that can result in pain upon withdrawal include non-steroidal anti-inflammatory drugs (NSAIDs) and tumor necrosis factor (TNF)-alpha blockers. A medication that treats widespread or regional pain syndromes, including tension-type
10 headache, migraine headache and fibromyalgia, but does not result in medication overuse syndromes would be very desirable.

Psychogenic pain is pain that results from psychological mechanisms including traumatic experiences, empathic reactions, or somatization. For example, loss of a loved friend or relative by death or other separation can result in widespread pain,
15 regional pain, and other symptoms including reactive depression.

Psychiatric pain is pain that results from conditions that are believed to have biological causes. For example, endogenous depression or the depressed phases of bipolar disorder can be associated with the onset or exacerbation of widespread pain or regional pain disorders.

20 The mechanisms of action for any pain, headache, fibromyalgia, or allodynia treatment are not yet fully understood, and numerous therapies have been tested. Some of these therapies have disadvantages. For example, specific drugs, such as ergotamine and dihydroergotamine, used in the treatment of migraine, interact with vascular receptors, a fact that has raised concerns about the cardiovascular safety of
25 these pharmaceutical agents. Other treatments for pain relief, such as ketamine, barbiturates, and opioids, can lead to addiction. Duloxetine is a serotonin and norepinephrine reuptake inhibitor (SNRI) antidepressant drug that is also useful in treating fibromyalgia and back pain, but has side effects that limit long term treatment

in some patients. Other treatments for pain are the gabapenoids (or alpha-2 delta ligands), including pregabalin, gabapentin and mirogabalin/DS-5565; antagonists of nerve growth factor receptor, including tanezumab; blockers of voltage-gated sodium channels, including Nav1.7, Nav1.8, and Nav1.9; alcohol; cannabinoids, including 5 tetrahydrocannabinol (THC) and cannabidiol; and gamma-hydroxy butyrate. Tramadol and tapentadol are pain treatments having both SNRI activity and mu-opioid activity. Racemic tramadol combines the SNRI activity of one isomer with the opiate receptor activity of the other isomer. Agonists of central alpha-2 adrenergic receptors, including clonidine and dexmedetomidine, cause sedation and have been used in 10 anesthesia and analgesia. Corticosteroids have been used to inhibit pain in inflammatory conditions. TNF-alpha blockers, particularly antibodies against TNF-alpha, decrease pain in several autoimmune diseases including rheumatoid arthritis, inflammatory bowel disease, and psoriasis. Each of the known treatments has side effects that limit use in some patients.

15 Another pain therapeutic is isometheptene. Racemic isometheptene has been used in the treatment of tension-type headache, vascular headache, and migraine headache, either alone or as one or more than one active ingredients in various combination drug products. One theory of headache pathogenesis is that cranial vasodilation results in pressure on the pain producing areas surrounding blood vessels. Under this theory, the 20 effect of racemic isometheptene on relieving headache is believed to be due to isometheptene-induced cranial vasoconstriction which reduces the pressure on the pain producing areas surrounding blood vessels. Racemic isometheptene has sympathomimetic effects, and based on pharmacological studies, some of these effects are blocked by α - and β -adrenergic receptor antagonists. This has led some to 25 conclude that racemic isometheptene interacts with α - and β -adrenergic receptors or that its effects are mediated by alpha and beta adrenergic receptors indirectly. Racemic isometheptene has also been shown to increase heart rate and diastolic blood pressure, which are properties associated with sympathomimetic agents.

Purified (R)-isometheptene has a significant binding affinity for the imidazoline-1 (I_1) receptor (See WO2014/113734, incorporated herein by reference), and binds to the I_1 receptor with higher affinity than (S)-isometheptene. (R)-isometheptene binds preferentially to the bovine I_1 receptor versus the α -adrenergic receptor, with a K_i of 5 18 nM for the I_1 receptor and a K_i of 2300 nM for the α -adrenergic receptor. For (S)-isometheptene, the K_i was 1100 nM for the I_1 receptor and 2700 nM for the α -adrenergic receptor. Studies have also suggested that (R)-isometheptene may have lower potential adverse effects to the cardiovascular system than (S)-isometheptene.

The imidazoline receptor system modulates sympathetic effects and three types of 10 receptors have been identified: I_1 , I_2 , and I_3 . The best characterized is the I_1 receptor, which has been connected with a cloned cDNA. I_2 and I_3 are still described only as activities of activated membranes and may or may not correspond to single proteins. Present understanding of the I_1 receptor is that of a cell-surface receptor mediating 15 cellular responses, participating in cardiovascular control by the CNS, and providing a potential therapeutic target for multiple cardiovascular and metabolic disorders. It was also recently found that knockout mice lacking the I_1 receptor had a lower pain threshold than that of wild type in both hot-plate and tail-flick tests, indicating that nociceptive perception was potentiated in the knockout mice (See Zhang, L., *et al.*, Generation and Primary Phenotypes of Imidazoline Receptor Antisera-Selected (IRAS) 20 Knockout Mice, CAN Neuroscience and Therapeutics 19 (2013) 978-981).

New therapeutics for pain treatment and relief would be useful.

Summary of the Disclosure

Among the embodiments of this disclosure are compounds and compositions that are useful in treating pain; psychic pain; psychological pain; psychiatric pain; depression; 25 allodynia; fibromyalgia; fibromyalgia-ness; central sensitization; centralization; regional pain syndrome; temporomandibular joint syndrome (TMJ); lower back pain; interstitial cystitis; Gulf War syndrome; visceral pain; phantom limb pain; kidney stones; gout; neuropathic pain; post-herpetic neuralgia; diabetic neuropathy; sickle cell

pain; priapism; nociceptive pain; post-operative pain; orthopedic injury pain; bunionectomy; dental extraction; pain after severed spinal cord injury; osteoarthritis; rheumatoid arthritis; Lyme disease; Parkinson's disease; pain associated with cancer; opioid-induced constipation; an opioid withdrawal symptom; or pain associated with
5 post-traumatic stress disorder (PTSD); or a combination of any of the foregoing conditions. In some embodiments, the compounds and compositions of this disclosure act as analgesics. In some embodiments, the compounds and compositions of this disclosure are used in conjunction simultaneously, separately, or sequentially with acetaminophen, a non-steroidal anti-inflammatory drug (NSAID), ibuprofen,
10 naprosyn, a cyclooxygenase-2 inhibitor, aspirin, caffeine, dichloralphenazone, a triptan, a chemotherapeutic drug, an antidepressant, a serotonin–norepinephrine reuptake inhibitor (SNRI), a gabapentinoid, an antiproliferative agent, an anti-inflammatory agent, a corticosteroid, an anti-asthmatic agent, an anti-allergic agent, an immunosuppressive agent, an immunomodulatory agent, a cardiovascular disease
15 treatment agent, an anti-diabetic agent, a blood disorder treatment agent, a nerve growth factor receptor antagonist, a sodium channel blocker, a CYP2D6 inhibitor, a TNF-alpha inhibitor, one or more opiates, or a combination of any of the foregoing therapeutics.

In some embodiments, the compounds of this disclosure are selected from a group of
20 compounds having the formula 1-54, or a pharmaceutically acceptable salt, free base form, enantiomer, diastereomer, tautomer, solvate, or prodrug of any of the foregoing compounds.

In some embodiments, the compounds of this disclosure selected from a group of
25 compounds having the formula 1-54, or a pharmaceutically acceptable salt, free base form, enantiomer, diastereomer, tautomer, solvate, or prodrug of any of the foregoing compounds, are useful as analgesics.

In some embodiments, the compositions of this disclosure relate to pharmaceutical compositions comprising one or more compounds selected from a group of

compounds having the formula 1-54, or a pharmaceutically acceptable salt, free base form, enantiomer, diastereomer, tautomer, solvate, or prodrug of any of the foregoing compounds. In some embodiments, the pharmaceutical compositions are useful as analgesics.

- 5 In some embodiments, the disclosure of this application relates to a method of treating or preventing one or more conditions selected from: pain; psychic pain; psychological pain; psychiatric pain; depression; allodynia; fibromyalgia; fibromyalgia-ness; central sensitization; centralization; regional pain syndrome; temporomandibular joint syndrome (TMJ); lower back pain; interstitial cystitis; Gulf War syndrome; visceral
10 pain; phantom limb pain; kidney stones; gout; neuropathic pain; post-herpetic neuralgia; diabetic neuropathy; sickle cell pain; priapism; nociceptive pain; post-operative pain; orthopedic injury pain; bunionectomy; dental extraction; pain after severed spinal cord injury; osteoarthritis; rheumatoid arthritis; Lyme disease; Parkinson's disease; pain associated with cancer; opioid-induced constipation; an
15 opioid withdrawal symptom; or pain associated with post-traumatic stress disorder (PTSD), in a patient in need thereof, comprising administering to said patient a therapeutically effective amount of one or more compounds selected from a group of compounds having the formula 1-54, or a pharmaceutically acceptable salt, free base
20 form, enantiomer, diastereomer, tautomer, solvate, or prodrug of any of the foregoing compounds. In some embodiments, the method further comprises administering simultaneously, separately, or sequentially an additional therapeutic selected from the group consisting of acetaminophen, a non-steroidal anti-inflammatory drug (NSAID), ibuprofen, naprosyn, a cyclooxygenase-2 inhibitor, aspirin, caffeine, dichloralphenazone, a triptan, a chemotherapeutic drug, an antidepressant, a
25 serotonin-norepinephrine reuptake inhibitor (SNRI), a gabapentinoid, an antiproliferative agent, an anti-inflammatory agent, a corticosteroid, an anti-asthmatic agent, an anti-allergic agent, an immunosuppressive agent, an immunomodulatory agent, a cardiovascular disease treatment agent, an anti-diabetic agent, a blood disorder treatment agent, a nerve growth factor receptor antagonist, a sodium channel

blocker, a CYP2D6 inhibitor, a TNF-alpha inhibitor, one or more opiates, or a combination of any of the foregoing therapeutics.

In some embodiments, the disclosure of this application relates to a method of treating or preventing one or more conditions selected from: pain; psychic pain; psychological
5 pain; psychiatric pain; depression; allodynia; fibromyalgia; fibromyalgia-ness; central sensitization; centralization; regional pain syndrome; temporomandibular joint syndrome (TMJ); lower back pain; interstitial cystitis; Gulf War syndrome; visceral pain; phantom limb pain; kidney stones; gout; neuropathic pain; post-herpetic neuralgia; diabetic neuropathy; sickle cell pain; priapism; nociceptive pain; post-
10 operative pain; orthopedic injury pain; bunionectomy; dental extraction; pain after severed spinal cord injury; osteoarthritis; rheumatoid arthritis; Lyme disease; Parkinson's disease; pain associated with cancer; opioid-induced constipation; an opioid withdrawal symptom; or pain associated with post-traumatic stress disorder (PTSD), in a patient in need thereof, comprising administering to said patient a
15 therapeutically effective amount of a pharmaceutical composition comprising one or more compounds selected from a group of compounds having the formula 1-54, or a pharmaceutically acceptable salt, free base form, enantiomer, diastereomer, tautomer, solvate, or prodrug of any of the foregoing compounds. In some embodiments, the method further comprises administering an additional therapeutic selected from the
20 group consisting of acetaminophen, a non-steroidal anti-inflammatory drug (NSAID), ibuprofen, naprosyn, a cyclooxygenase-2 inhibitor, aspirin, caffeine, dichloralphenazone, a triptan, a chemotherapeutic drug, an antidepressant, a serotonin-norepinephrine reuptake inhibitor (SNRI), a gabapentinoid, an antiproliferative agent, an anti-inflammatory agent, a corticosteroid, an anti-asthmatic
25 agent, an anti-allergic agent, an immunosuppressive agent, an immunomodulatory agent, a cardiovascular disease treatment agent, an anti-diabetic agent, a blood disorder treatment agent, a nerve growth factor receptor antagonist, a sodium channel blocker, a CYP2D6 inhibitor, a TNF-alpha inhibitor, one or more opiates, or a

combination of any of the foregoing therapeutics simultaneously, separately, or sequentially with the pharmaceutical compositions disclosed herein.

In some embodiments, one or more compounds selected from a group of compounds having the formula **1-54**, or a pharmaceutically acceptable salt, free base form, enantiomer, diastereomer, tautomer, solvate, or prodrug of any of the foregoing compounds, is used for the manufacture of a medicament for treating or preventing one or more conditions selected from: pain; psychic pain; psychological pain; psychiatric pain; depression; allodynia; fibromyalgia; fibromyalgia-ness; central sensitization; centralization; regional pain syndrome; temporomandibular joint syndrome (TMJ); lower back pain; interstitial cystitis; Gulf War syndrome; visceral pain; phantom limb pain; kidney stones; gout; neuropathic pain; post-herpetic neuralgia; diabetic neuropathy; sickle cell pain; priapism; nociceptive pain; post-operative pain; orthopedic injury pain; bunionectomy; dental extraction; pain after severed spinal cord injury; osteoarthritis; rheumatoid arthritis; Lyme disease; Parkinson's disease; pain associated with cancer; opioid-induced constipation; an opioid withdrawal symptom; or pain associated with post-traumatic stress disorder (PTSD). In further embodiments, the medicament is administered simultaneously, separately, or sequentially with one or more additional therapeutics selected from the group consisting of acetaminophen, a non-steroidal anti-inflammatory drug (NSAID), ibuprofen, naprosyn, a cyclooxygenase-2 inhibitor, aspirin, caffeine, dichloralphenazone, a triptan, a chemotherapeutic drug, an antidepressant, a serotonin–norepinephrine reuptake inhibitor (SNRI), a gabapentinoid, an antiproliferative agent, an anti-inflammatory agent, a corticosteroid, an anti-asthmatic agent, an anti-allergic agent, an immunosuppressive agent, an immunomodulatory agent, a cardiovascular disease treatment agent, an anti-diabetic agent, a blood disorder treatment agent, a nerve growth factor receptor antagonist, a sodium channel blocker, a CYP2D6 inhibitor, a TNF-alpha inhibitor, or one or more opiates.

In some embodiments, a pharmaceutical composition comprising one or more compounds selected from a group of compounds having the formula **1-54**, or a

- pharmaceutically acceptable salt, free base form, enantiomer, diastereomer, tautomer, solvate, or prodrug of any of the foregoing compounds, is used for the manufacture of a medicament for treating or preventing one or more conditions selected from: pain; psychic pain; psychological pain; psychiatric pain; depression; allodynia;
- 5 fibromyalgia; fibromyalgia-ness; central sensitization; centralization; regional pain syndrome; temporomandibular joint syndrome (TMJ); lower back pain; interstitial cystitis; Gulf War syndrome; visceral pain; phantom limb pain; kidney stones; gout; neuropathic pain; post-herpetic neuralgia; diabetic neuropathy; sickle cell pain; priapism; nociceptive pain; post-operative pain; orthopedic injury pain; bunionectomy;
- 10 dental extraction; pain after severed spinal cord injury; osteoarthritis; rheumatoid arthritis; Lyme disease; Parkinson's disease; pain associated with cancer; opioid-induced constipation; an opioid withdrawal symptom; or pain associated with post-traumatic stress disorder (PTSD). In further embodiments, the medicament is administered simultaneously, separately, or sequentially with one or more additional
- 15 therapeutics selected from the group consisting of acetaminophen, a non-steroidal anti-inflammatory drug (NSAID), ibuprofen, naprosyn, a cyclooxygenase-2 inhibitor, aspirin, caffeine, dichloralphenazone, a triptan, a chemotherapeutic drug, an antidepressant, a serotonin-norepinephrine reuptake inhibitor (SNRI), a gabapentinoid, an antiproliferative agent, an anti-inflammatory agent, a corticosteroid,
- 20 an anti-asthmatic agent, an anti-allergic agent, an immunosuppressive agent, an immunomodulatory agent, a cardiovascular disease treatment agent, an anti-diabetic agent, a blood disorder treatment agent, a nerve growth factor receptor antagonist, a sodium channel blocker, a CYP2D6 inhibitor, a TNF-alpha inhibitor, or one or more opiates.
- 25 In some embodiments, one or more compounds selected from a group of compounds having the formula 1-54, or a pharmaceutically acceptable salt, free base form, enantiomer, diastereomer, tautomer, solvate, or prodrug of any of the foregoing compounds, is used in treating or preventing one or more conditions selected from: pain; psychic pain; psychological pain; psychiatric pain; depression; allodynia;

fibromyalgia; fibromyalgia-ness; central sensitization; centralization; regional pain syndrome; temporomandibular joint syndrome (TMJ); lower back pain; interstitial cystitis; Gulf War syndrome; visceral pain; phantom limb pain; kidney stones; gout; neuropathic pain; post-herpetic neuralgia; diabetic neuropathy; sickle cell pain; 5 priapism; nociceptive pain; post-operative pain; orthopedic injury pain; bunionectomy; dental extraction; pain after severed spinal cord injury; osteoarthritis; rheumatoid arthritis; Lyme disease; Parkinson's disease; pain associated with cancer; opioid-induced constipation; an opioid withdrawal symptom; or pain associated with post-traumatic stress disorder (PTSD). In further embodiments, the compound or 10 compounds are used simultaneously, separately, or sequentially with one or more additional therapeutics selected from the group consisting of acetaminophen, a non-steroidal anti-inflammatory drug (NSAID), ibuprofen, naprosyn, a cyclooxygenase-2 inhibitor, aspirin, caffeine, dichloralphenazone, a triptan, a chemotherapeutic drug, an antidepressant, a serotonin-norepinephrine reuptake inhibitor (SNRI), a 15 gabapentinoid, an antiproliferative agent, an anti-inflammatory agent, a corticosteroid, an anti-asthmatic agent, an anti-allergic agent, an immunosuppressive agent, an immunomodulatory agent, a cardiovascular disease treatment agent, an anti-diabetic agent, a blood disorder treatment agent, a nerve growth factor receptor antagonist, a sodium channel blocker, a CYP2D6 inhibitor, a TNF-alpha inhibitor, or one or more 20 opiates.

In some embodiments, a pharmaceutical composition comprising one or more compounds selected from a group of compounds having the formula **1-54**, or a pharmaceutically acceptable salt, free base form, enantiomer, diastereomer, tautomer, solvate, or prodrug of any of the foregoing compounds, is used in treating or 25 preventing one or more conditions selected from: pain; psychic pain; psychological pain; psychiatric pain; depression; allodynia; fibromyalgia; fibromyalgia-ness; central sensitization; centralization; regional pain syndrome; temporomandibular joint syndrome (TMJ); lower back pain; interstitial cystitis; Gulf War syndrome; visceral pain; phantom limb pain; kidney stones; gout; neuropathic pain; post-herpetic

neuralgia; diabetic neuropathy; sickle cell pain; priapism; nociceptive pain; post-operative pain; orthopedic injury pain; bunionectomy; dental extraction; pain after severed spinal cord injury; osteoarthritis; rheumatoid arthritis; Lyme disease; Parkinson's disease; pain associated with cancer; opioid-induced constipation; an
5 opioid withdrawal symptom; or pain associated with post-traumatic stress disorder (PTSD). In further embodiments, the pharmaceutical composition is used simultaneously, separately, or sequentially with one or more additional therapeutics selected from the group consisting of acetaminophen, a non-steroidal anti-inflammatory drug (NSAID), ibuprofen, naprosyn, a cyclooxygenase-2 inhibitor,
10 aspirin, caffeine, dichloralphenazone, a triptan, a chemotherapeutic drug, an antidepressant, a serotonin-norepinephrine reuptake inhibitor (SNRI), a gabapentinoid, an antiproliferative agent, an anti-inflammatory agent, a corticosteroid, an anti-asthmatic agent, an anti-allergic agent, an immunosuppressive agent, an immunomodulatory agent, a cardiovascular disease treatment agent, an anti-diabetic
15 agent, a blood disorder treatment agent, a nerve growth factor receptor antagonist, a sodium channel blocker, a CYP2D6 inhibitor, a TNF-alpha inhibitor, or one or more opiates.

Brief Description of the Drawings

Figure 1 illustrates data related to analgesic activity using the Formalin Test, late
20 phase (licking score) in a mouse of compound **8** mucate salt, (R)-isometheptene mucate, and compound **26** mucate salt, (S)-isometheptene mucate.

Figure 2 illustrates data related to analgesic activity using the Tail-flick Test in a mouse of compound **8** mucate salt, (R)-isometheptene mucate, and compound **26** mucate salt, (S)-isometheptene mucate.

25 *Figures 3A-B* illustrate data from the TAAR1 cAMP assay for compound **8** mucate salt, (R)-isometheptene mucate (isomer 2), and compound **26** mucate salt, (S)-isometheptene mucate (isomer 1). For compound **8** mucate salt, (R)-isometheptene mucate, the EC₅₀ was 29.45 μM and for compound **26** mucate salt, (S)-isometheptene

mucate, the EC₅₀ was 21.12 μM. Compound **26** mucate salt, thus, more potently activated TAAR1 than compound **8** mucate salt did.

Figure 4 illustrates data from tactile sensory testing in STA rats using von Frey monofilaments for compound **8** mucate salt, (R)-isomethetene mucate, and compound **26** mucate salt, (S)-isomethetene mucate. STA rats treated with compound **8** showed a dramatic increase in threshold values versus STA rats treated with compound **26** or the control rats, demonstrating the analgesic effect of compound **8**.

Figures 5A-D illustrate data on the impact of compound **8** mucate salt, (R)-isomethetene mucate (isomer 2), and compound **26** mucate salt, (S)-isomethetene mucate (isomer 1), on arterial blood pressure (BP) and heart rate. A) Mean arterial blood pressure (mmHg), B) Systolic arterial blood pressure (mmHg), C) Diastolic arterial blood pressure (mmHg), and D) Heart rate (bpm).

Figures 6A-D illustrate data related to analgesic efficacy in a rat chronic constrictive nerve injury (CCI) model of neuropathic pain of (S)-isomethetene mucate (compound **26** mucate salt) and (R)-isomethetene mucate (compound **8** mucate salt). Gabapentin, (R)-isomethetene mucate (100 mg/kg), and (S)-isomethetene mucate (100 mg/kg) significantly increased paw withdrawal threshold (PWT) compared to the vehicle-treated rats. In addition (S)-isomethetene mucate (30 mg/kg) showed a non-significant trend to also increasing PWT. A) Baseline ipsilateral PWT prior to test. Data are presented as mean ± SEM. B) Effect of test compounds on ipsilateral PWT. Data are presented as mean ± SEM. *p<0.05 compared to vehicle. ~p<0.1 compared to vehicle. C) Baseline Contralateral PWT. Data are presented as mean ± SEM. D) Effect of test compounds on contralateral PWT. Data are presented as mean ± SEM.

Figures 7A-D illustrate data related to analgesic efficacy in a rat model of bortezomib (BTZ)-induced neuropathy of (S)-isomethetene mucate (compound **26** mucate salt) and (R)-isomethetene mucate (compound **8** mucate salt). Gabapentin, (R)-isomethetene mucate (100 mg/kg), and (S)-isomethetene mucate (30 and 100

mg/kg) significantly increased PWT as compared to the BTZ-treated control group suggesting potential analgesic efficacy of these compounds on BTZ-induced neuropathic pain. A) Body weight of all treatment groups throughout the study. Data are presented as mean \pm SEM. Arrow indicated time of BTZ injection. B) Baseline PWT prior to BTZ injection. Data are presented as mean \pm SEM. C) Baseline PWT nine days after BTZ injection. Data are presented as mean \pm SEM. * $p < 0.05$ compared to vehicle-vehicle. D) Effects of (R)- and (S)-isometheptene mucate on PWT 15 minutes post administration. Data are presented as mean \pm SEM. * $p < 0.05$ compared to BTZ-treated group.

10 **Figure 8** illustrates data related to analgesic activity using the Hot Plate Test in a mouse of compound **8** mucate salt, (R)-isometheptene mucate, and compound **26** mucate salt, (S)-isometheptene mucate.

Figures 9A-B illustrate expression of the imidazoline-1 receptor in CHO cells. A) Construct confirmation by restriction digestion and B) The RT-PCR result from the transient transfection of imidazoline-1 receptor/CHO cells, indicating imidazoline-1 receptor was expressed.

Figures 10A-C illustrate a functional assay for the imidazoline-1 receptor in PC-12 cells or a cell line stably expressing the imidazoline-1 receptor to evaluate the impact of imidazoline-1 receptor agonists and antagonists on forskolin-stimulated cAMP induction. A) Both benazoline and efaroxan inhibit forskolin-stimulated cAMP in PC-12 cells. B) The inhibitory effect of benazoline on forskolin induced cAMP production in PC-12 cells was antagonized by clonidine. C) Both efaroxan and benazoline showed an inhibitory effect on forskolin-induced cAMP in imidazoline-1 receptor/CHO cells, but not in the parent CHO cell line. This result suggests functional imidazoline-1 receptor was expressed in transiently transfected CHO cells.

Figures 11A-D illustrate preliminary human pharmacokinetic studies using racemic isometheptene and compound **8** mucate salt, (R)-isometheptene mucate. A) Cohort 1 with 35 mg compound **8** (n=9) or 70 mg racemic isometheptene (n=3). B) Cohort 1

with 70 mg racemic isometheptene (n=3). C) Cohort 2 with 70 mg compound **8** (n=9) or 70 mg racemic isometheptene (n=3). D) Cohort 2 with 70 mg racemic isometheptene (n=3).

Figures 12A-D illustrate preliminary human pharmacokinetic studies using racemic isometheptene and compound **8** mucate salt, (R)-isometheptene mucate. A) Cohort 3 treated with 140 mg compound **8** (n=9) or 70 mg racemic isometheptene (n=3). B) Cohort 3 treated with 140 mg compound **8** (n=9) or 70 mg racemic isometheptene (n=3). C) Cohort 3 with 70 mg racemic isometheptene (n=3). D) Cohort 3 with 70 mg racemic isometheptene (n=3).

Figure 13 illustrates effects of 1 mg/kg of R- or S-isometheptene mucate on trigeminal sensitivity in the inflammatory soup model. The data show that no significant changes in trigeminal sensitivity were seen when inflammatory soup (IS) rats were treated with 1 mg/kg R- or S-isometheptene mucate (compounds **8** and **26** mucate salt, n=8 IS rats/group).

Figure 14 illustrates effects of 30 mg/kg of R- or S-isometheptene mucate on trigeminal sensitivity in the inflammatory soup model. The data show that 30 mg/kg of R-isometheptene mucate (compound **8** mucate salt) decreased trigeminal sensitivity while 30 mg/kg of S-isometheptene mucate (compound **26** mucate salt) had no effect on sensory thresholds. Rats receiving saline treatment had no change in sensory thresholds over the course of the experimental timeline. (n=8 IS rats/group, *p<0.05, **p<0.01, ***p<0.001).

Figure 15 illustrates effects of 30 mg/kg of R- or S-isometheptene mucate on trigeminal sensitivity in the STA rat model. The data were from tactile sensory testing in STA rats using von Frey monofilaments for compound **8** mucate salt, (R)-isometheptene mucate, and compound **26** mucate salt, (S)-isometheptene mucate. STA rats treated with compound **8** mucate salt showed an increase in threshold values versus STA rats treated with compound **26** mucate salt or the control rats, demonstrating the analgesic effect of compound **8** mucate salt.

- Figure 16* illustrates trigeminal sensitivity in the inflammatory soup model. Periorbital von Frey thresholds were measured for rats receiving infusions of saline (n = 10) or IS (n = 10) 3 days/week.
- Figure 17* illustrates effects of 1 mg/kg of R- or S-isomethptene mucate on trigeminal sensitivity in the STA rat model. The data show that 1 mg/kg of R-isomethptene mucate (compound **8** mucate salt) and 1 mg/kg of S-isomethptene mucate (compound **26** mucate salt) had no effect on sensory thresholds. Rats receiving saline treatment had no change in sensory thresholds over the course of the experimental timeline. (n=8 IS rats/group).
- 5
- Figure 18* illustrates data on the impact of compound **8** mucate salt, (R)-isomethptene mucate (isomer 2), and compound **26** mucate salt, (S)-isomethptene mucate (isomer 1), on mean arterial blood pressure (mmHg).
- 10
- Figure 19* illustrates data on the impact of compound **8** mucate salt, (R)-isomethptene mucate (isomer 2), and compound **26** mucate salt, (S)-isomethptene mucate (isomer 1), on systolic arterial blood pressure (mmHg).
- 15
- Figure 20* illustrates data on the impact of compound **8** mucate salt, (R)-isomethptene mucate (isomer 2), and compound **26** mucate salt, (S)-isomethptene mucate (isomer 1), on diastolic arterial blood pressure (mmHg).
- Figure 21* illustrates data on the impact of compound **8** mucate salt, (R)-isomethptene mucate (isomer 2), and compound **26** mucate salt, (S)-isomethptene mucate (isomer 1), on heart rate (bpm).
- 20
- Figure 22* illustrates a model of I₁-imidazoline receptor signaling pathways.
- Figure 23* illustrates data of activation via phosphorylation of ERK in human I₁-imidazoline receptor transfected 293T cells after treatment with compound **8** mucate salt, (R)-isomethptene mucate, or compound **26** mucate salt, (S)-isomethptene mucate.
- 25

- Figure 24* illustrates periorbital allodynia after treatment with compound **8** mucate salt, (R)-isometheptene mucate, in a NO donor-evoked medication overuse headache rat model.
- Figure 25* illustrates hindpaw allodynia after treatment with compound **8** mucate salt, (R)-isometheptene mucate, in a NO donor-evoked medication overuse headache rat model.
- Figure 26* illustrates the effect of compound **8** mucate salt, (R)-isometheptene mucate, on ipsilateral paw withdrawal threshold (PWT) in a rat chronic constructive nerve injury model of neuropathic pain.
- Figure 27* illustrates the effect of compound **8** mucate salt, (R)-isometheptene mucate, on ipsilateral paw withdrawal threshold (PWT) 15 minutes post administration in a rat model of bortezomib-induced neuropathy.
- Figure 28* illustrates the effect of compound **8** mucate salt, (R)-isometheptene mucate, or compound **26** mucate salt, (S)-isometheptene mucate, on naloxone-precipitated withdrawal test in mice.
- Figure 29* illustrates the effect of a positive control, diclofenac, on sodium monoiodoacetate (MIA)-induced osteoarthritic pain.
- Figure 30* illustrates the effect of compound **8** mucate salt, (R)-isometheptene mucate, on sodium monoiodoacetate (MIA)-induced osteoarthritic pain.
- Figure 31* illustrates the effect of compound **8** mucate salt, (R)-isometheptene mucate, and diclofenac on sodium monoiodoacetate (MIA)-induced osteoarthritic pain.
- Figure 32* illustrates the effect of compound **8** mucate salt, (R)-isometheptene mucate, on fecal boli in a naloxone-precipitated withdrawal test in mice.
- Figure 33* illustrates the effect of compound **8** mucate salt, (R)-isometheptene mucate, on diarrhea in a naloxone-precipitated withdrawal test in mice.

Figure 34 illustrates the effect of compound **8** mucate salt, (R)-isomethene mucate, on salivation in a naloxone-precipitated withdrawal test in mice.

Figure 35 illustrates the effect of compound **8** mucate salt, (R)-isomethene mucate, on teeth chattering in a naloxone-precipitated withdrawal test in mice.

5 *Figure 36* illustrates the effect of compound **8** mucate salt, (R)-isomethene mucate, on wet dog shakes in a naloxone-precipitated withdrawal test in mice.

Figure 37 illustrates the effect of compound **8** mucate salt, (R)-isomethene mucate, on writhing in a naloxone-precipitated withdrawal test in mice.

10 *Figure 38* illustrates the effect of compound **8** mucate salt, (R)-isomethene mucate, on weight loss in a naloxone-precipitated withdrawal test in mice.

When the Figures refer to (R)-isomethene, they refer to (R)-isomethene mucate.

When the Figures refer to (S)-isomethene, they refer to (S)-isomethene mucate.

Detailed Description of the Disclosure

15 In order that this disclosure may be fully understood, the following detailed description is set forth.

Definitions

The definitions set forth in this application are intended to clarify terms used throughout this application.

The term "herein" means the entire application.

20 Unless defined otherwise, all technical and scientific terms used herein have the same meaning as those commonly understood by one of ordinary skill in the art to which these inventions belong. Although methods and materials similar or equivalent to those described herein can be used in the practice or testing of the inventions, suitable methods and materials are described below. The materials, methods and examples are

illustrative only, and are not intended to be limiting. All publications, patents and other documents mentioned herein are incorporated by reference in their entirety.

Each embodiment of this disclosure may be taken alone or in combination with one or more other embodiments of this disclosure.

- 5 Throughout this application, the word “a” will be understood to imply the inclusion of one or more of the integers modified by the article “a.”

Throughout this application, the word “comprise” or variations such as “comprises” or “comprising” will be understood to imply the inclusion of a stated integer or groups of integers but not the exclusion of any other integer or group of integers.

- 10 Throughout the application, where compositions are described as having, including, or comprising, specific components, it is contemplated that compositions also may consist essentially of, or consist of, the recited components. Similarly, where methods or processes are described as having, including, or comprising specific process steps, the processes also may consist essentially of, or consist of, the recited processing
- 15 steps. Further, it should be understood that the order of steps or order for performing certain actions is immaterial so long as the compositions and methods described herein remain operable. Moreover, two or more steps or actions can be conducted simultaneously.

All percentages and ratios used herein, unless otherwise indicated, are by weight.

- 20 The term “analgesic” refers to a painkiller or a drug that is able to provide relief from pain.

- The term “agonist” refers to a molecule that activates a receptor to provoke a biological response. Agonists may bind directly to a receptor to activate it or they may activate a receptor through another mechanism, such as through second messengers like cAMP
- 25 and pErk.

The term “antagonist” refers to a receptor ligand that blocks or dampens agonist-mediated responses rather than provoking a biological response upon binding to a receptor.

5 The terms “Imidazoline-1 Receptor-Independent Isometheptene Pain Modulatory pathway” or “IRIPM pathway” refer to a pain perception pathway mediated by isometheptene that is independent of the imidazoline-1 (I₁) receptor.

The term “or” as used herein should be understood to mean “and/or,” unless the context clearly indicates otherwise.

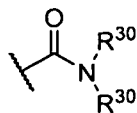
10 The term “acyl” is art-recognized and refers to a group represented by the general formula hydrocarbylC(O)-, preferably alkylC(O)-.

The term “alkoxy” refers to an alkyl group, preferably a lower alkyl group, having an oxygen attached thereto. Representative alkoxy groups include methoxy, ethoxy, propoxy, *tert*-butoxy and the like.

15 An “alkyl” group or “alkane” is a straight chained or branched non-aromatic hydrocarbon which is completely saturated. Typically, a straight chained or branched alkyl group has from 1 to about 20 carbon atoms, preferably from 1 to about 10 unless otherwise defined. Examples of straight chained and branched alkyl groups include methyl, ethyl, *n*-propyl, *iso*-propyl, *n*-butyl, *sec*-butyl, *tert*-butyl, pentyl, hexyl, pentyl and octyl.

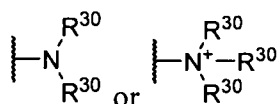
20 Moreover, the term “alkyl” is intended to include both “unsubstituted alkyls” and “substituted alkyls,” the latter of which refers to alkyl moieties having substituents replacing a hydrogen on one or more carbons of the hydrocarbon backbone.

The term “amide,” as used herein, refers to a group



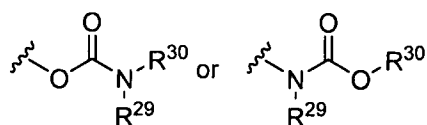
wherein each R³⁰ independently represent a hydrogen or hydrocarbyl group, or two R³⁰ are taken together with the N atom to which they are attached complete a heterocycle having from 4 to 12 atoms in the ring structure.

The terms “amine” and “amino” are art-recognized and refer to both unsubstituted and substituted amines and salts thereof, e.g., a moiety that can be represented by



wherein each R³⁰ independently represents a hydrogen or a hydrocarbyl group, or two R³⁰ are taken together with the N atom to which they are attached complete a heterocycle having from 4 to 12 atoms in the ring structure.

10 The term “carbamate” is art-recognized and refers to a group



wherein R²⁹ and R³⁰ independently represent hydrogen or a hydrocarbyl group, such as an alkyl group, or R²⁹ and R³⁰ taken together with the intervening atom(s) complete a heterocycle having from 4 to 12 atoms in the ring structure.

15 The term “carbonate” is art-recognized and refers to a group -OCO₂-R₁, wherein R₁ represents a hydrocarbyl group.

The term “carboxy,” as used herein, refers to a group represented by the formula -CO₂H.

The term “ester,” as used herein, refers to a group -C(O)OR³⁰ wherein R³⁰ represents a hydrocarbyl group.

The term “ether,” as used herein, refers to a hydrocarbyl group linked through an oxygen to another hydrocarbyl group. Accordingly, an ether substituent of a

hydrocarbyl group may be hydrocarbyl-O-. Ethers may be either symmetrical or unsymmetrical. Examples of ethers include, but are not limited to, heterocycle-O-heterocycle and aryl-O-heterocycle. Ethers include "alkoxyalkyl" groups, which may be represented by the general formula alkyl-O-alkyl.

- 5 The term "hydrocarbyl," as used herein, refers to a group that is bonded to the base scaffold through a carbon atom that does not have a =O or =S substituent, and typically has at least one carbon-hydrogen bond and a primarily carbon backbone, but may optionally include heteroatoms. Thus, groups like methyl, ethoxyethyl, 2-pyridyl, and trifluoromethyl are considered to be hydrocarbyl for the purposes of this
- 10 application, but substituents such as acetyl (which has a =O substituent on the linking carbon) and ethoxy (which is linked through oxygen, not carbon) are not. Hydrocarbyl groups include, but are not limited to aryl, heteroaryl, carbocycle, heterocyclyl, alkyl, alkenyl, alkynyl, and combinations thereof.

The term "hydroxyl," as used herein, refers to an -OH group.

- 15 The term "nitro" is art-recognized and refers to the group represented by $-\text{NO}_2$.
- "Optional" or "optionally" means that the subsequently described circumstance may or may not occur, so that the application includes instances where the circumstance occurs and instances where it does not. For example, the phrase "optionally substituted" means that a non-hydrogen substituent may or may not be present on a
- 20 given atom, and, thus, the application includes structures wherein a non-hydrogen substituent is present and structures wherein a non-hydrogen substituent is not present.

- The term "stability," "stable," "stable compound," or "stable structure" in the context of a chemical structure refers to the chemical state when a system is in its lowest energy state, or in chemical equilibrium with its environment. Thus, a stable
- 25 compound (or, e.g., a compound containing a number of atoms or substitutions that are stable) is not particularly reactive in the environment or during normal use, and retains its useful properties on the timescale of its expected usefulness. A stable compound is

sufficiently robust to survive isolation, and as appropriate, purification from a reaction mixture, and formulation into an efficacious therapeutic agent.

The terms “free compound” or “free base” are used herein to describe a compound in the unbound state. Where a compound of this disclosure is provided as a
5 pharmaceutically acceptable salt, the free base form of the compound is also contemplated and the disclosed salt form should not be considered as limiting. All such free base forms are intended to be included in the embodiments of this disclosure, even where a salt form of a compound of this disclosure is specifically indicated.

The term “derivative” refers to compounds that have a common core structure, and are
10 substituted with various groups as described herein.

The term “analogue” refers to a chemical compound that is structurally similar to another but differs slightly in composition (as in the replacement of one atom by an atom of a different element or in the presence of a particular functional group, or the replacement of one functional group by another functional group). Thus, an analogue
15 is a compound that is similar or comparable in function and appearance, but not in structure or origin to the reference compound.

The term “small molecule” is an art-recognized term. In some embodiments, this term refers to a molecule, which has a molecular weight of less than about 2000 amu, or less than about 1000 amu, and even less than about 500 amu.

20 The term "healthcare providers" refers to individuals or organizations that provide healthcare services to a person, community, etc. Examples of "healthcare providers" include doctors, hospitals, continuing care retirement communities, skilled nursing facilities, sub acute care facilities, clinics, multispecialty clinics, freestanding ambulatory centers, home health agencies, and HMO's.

25 The terms “IC₅₀,” or “half maximal inhibitory concentration” is intended to refer to the concentration of a substance (e.g., a compound or a drug) that is required for 50%

inhibition of a biological process, or component of a process, including a protein, subunit, organelle, ribonucleoprotein, etc.

The terms “EC₅₀” or “half maximal effective concentration” refers to the concentration of a compound, molecule, or drug, which induces a response halfway between the
5 baseline and maximum after a specified exposure time.

The terms “healthy” and “normal” are used interchangeably herein to refer to a subject or particular cell or tissue that is devoid (at least to the limit of detection) of a disease condition.

Compounds

10 Embodiments of this disclosure relate to compounds that, in some embodiments, are useful for treating or preventing one or more conditions selected from: pain; an inflammatory disease or disorder, an allergic disease or disorder, a metabolic disease, a cardiovascular disease or disorder, a neurogenic vascular disease or a painful
15 condition associated with any of the foregoing conditions; an episodic tension-type headache; a migraine headache; a headache; cramping; a cognitive disorder; a tension or migraine headache due to a vascular, neurovascular, or neurogenic disorder or dysfunction during a menstrual cycle episode; a tension or migraine headache due to a vascular, neurovascular, or neurogenic disorder or dysfunction during a migraine
20 episode; a headache from mild to moderate hypertension; mild to moderate essential hypertension; organ transplant rejection; hot and cold flashes; traumatic brain injury (TBI); neurotoxicity; psychic pain; psychological pain; psychiatric pain; depression; schizophrenia; anxiety; epilepsy; a stress disorder; excess sweating; a symptom related to drug withdrawal, including opioid-induced constipation or an opioid withdrawal
25 symptom; allodynia; fibromyalgia; fibromyalgia-ness; central sensitization; centralization; regional pain syndrome; temporomandibular joint syndrome (TMJ); lower back pain; interstitial cystitis; Gulf War syndrome; visceral pain; kidney stones; gout; neuropathic pain; post-herpetic neuralgia; diabetic neuropathy; sickle cell pain; priapism; nociceptive pain; post-operative pain; orthopedic injury pain; phantom limb

pain; bunionectomy; dental extraction; pain after severed spinal cord injury; osteoarthritis; rheumatoid arthritis; Lyme disease; Parkinson's disease; pain associated with cancer; opioid-induced constipation; an opioid withdrawal symptom; or pain associated with post-traumatic stress disorder (PTSD). The compounds of this disclosure are also useful as analgesics. In some embodiments, the compounds are ligands of the imidazoline-1 (I_1) receptor. In some embodiments, the compounds modulate I_1 receptor. In some embodiments, the compounds modulate the I_1 receptor to reduce pain. Without wishing to be bound by theory, in some embodiments, the compounds activate the I_1 receptor to reduce pain. In some embodiments, the compounds may reduce pain through a pathway that is independent of the I_1 receptor (the Imidazoline-1 Receptor-Independent Isomethoptene Pain Modulatory pathway, or IRIPM pathway).

The compounds in accordance with the various embodiments of this disclosure can be used alone or in combination simultaneously, separately, or sequentially with each other or with acetaminophen, a non-steroidal anti-inflammatory drug (NSAID), ibuprofen, naprosyn, a cyclooxygenase-2 inhibitor, aspirin, caffeine, dichloralphenazone, a triptan, a chemotherapeutic drug, an antidepressant, a serotonin-norepinephrine reuptake inhibitor (SNRI), a gabapentinoid, an antiproliferative agent, an anti-inflammatory agent, a corticosteroid, an anti-asthmatic agent, an anti-allergic agent, an immunosuppressive agent, an immunomodulatory agent, a cardiovascular disease treatment agent, an anti-diabetic agent, a blood disorder treatment agent, a nerve growth factor receptor antagonist, a sodium channel blocker, a CYP2D6 inhibitor, a TNF-alpha inhibitor, one or more opiates, or a combination of any of the foregoing therapeutics for the treatment of the conditions disclosed herein.

Analgesic and pain reduction activity of the compounds of this disclosure that is modulated through the I_1 receptor can be evaluated by determining trigeminal von Frey thresholds in spontaneous trigeminal allodynia (STA) rats, as described herein. Therapeutic activity of the compounds described herein can also be evaluated using

rats in an inflammatory soup model of chronic migraine and an opiate-like dependence model with the naloxone-precipitated withdrawal (Saelens) test in mice. The analgesic potential of the compounds described herein can also be evaluated using a monosodium iodacetate (MIA) induced model of osteoarthritic pain in adult male rats.

5 To assess the rescue efficacy of the compounds described herein for the reversal of cutaneous allodynia, sumatriptan-induced medication overuse headache (MOH) can be triggered by nitric oxide (NO) donors in rats. Other methods known or developed in the art may be similarly used.

Analgesic and pain reduction activity of the compounds described herein that are modulated through the IRIPM pathway can be evaluated in a rat chronic constrictive nerve injury (CCI) model of neuropathic pain or a rat model of bortezomib-induced neuropathy, also described herein. Additionally, the analgesic and pain reduction activity of the compounds described herein that is modulated through the IRIPM pathway can be identified using the mouse formalin, hot plate, and tail-flick tests.

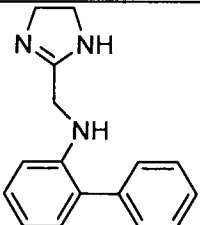
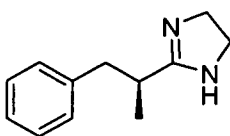
10 Binding of the compounds described herein to the I₁ receptor can be determined through radioligand binding competition assays. Evaluation of the impact of I₁ receptor agonists and antagonists on forskolin-stimulated cAMP induction can be conducted using a functional assay for the I₁ receptor with PC-12 cells or a transiently-expressing or stably-expressing I₁ receptor cell line. Other methods known or developed in the art may be similarly used.

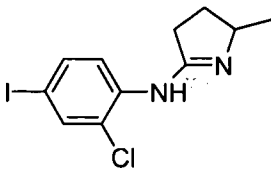
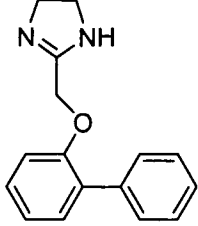
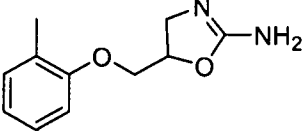
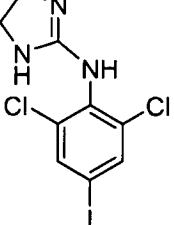
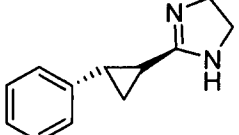
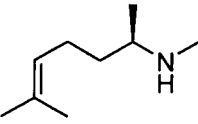
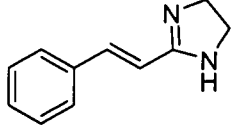
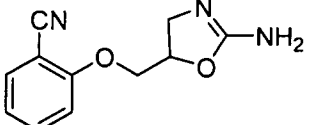
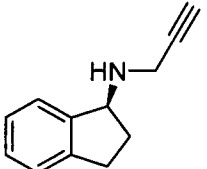
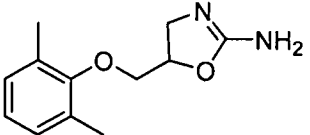
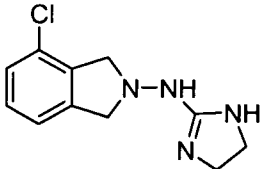
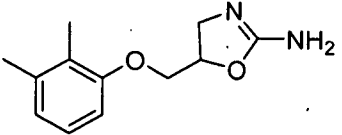
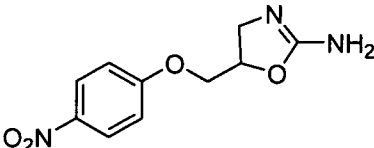
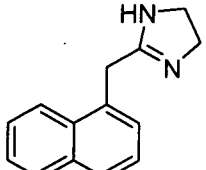
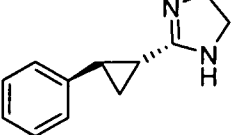
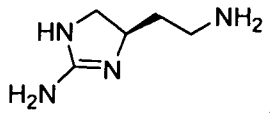
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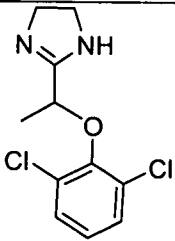
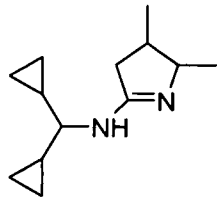
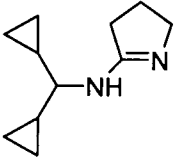
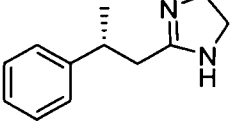
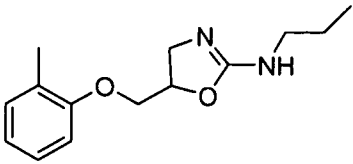
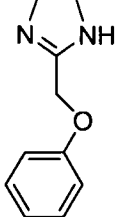
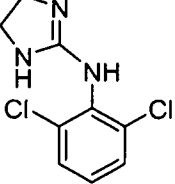
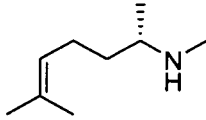
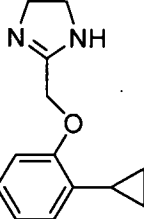
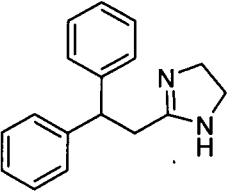
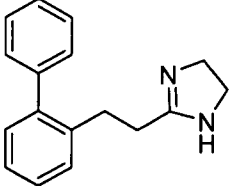
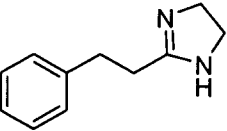
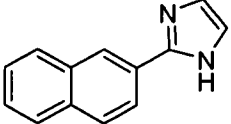
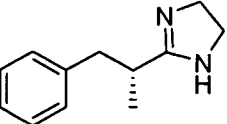
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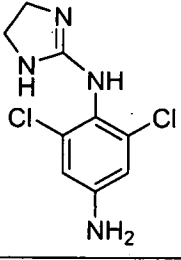
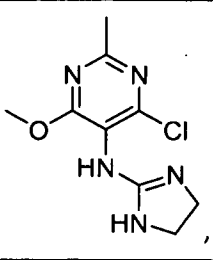
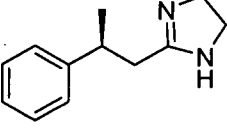
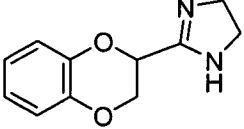
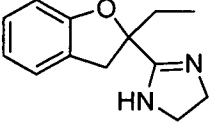
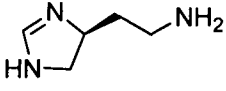
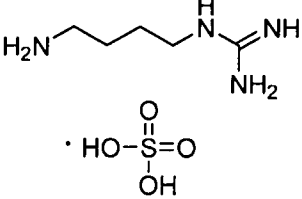
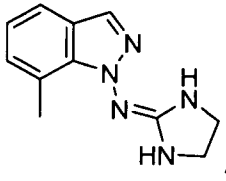
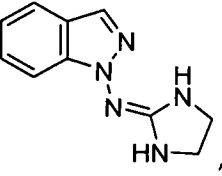
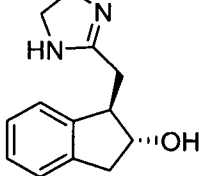
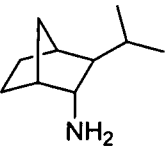
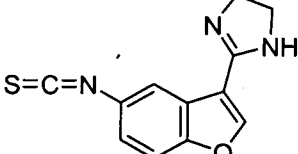
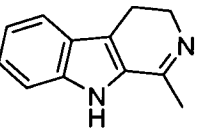
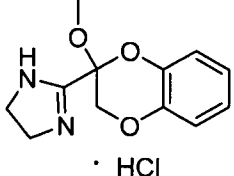
Stability of the compounds of this disclosure can be assessed, inter alia, using pharmacokinetic studies in animals such as dogs, rats, and humans.

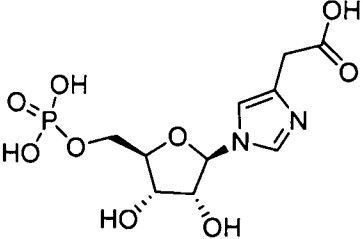
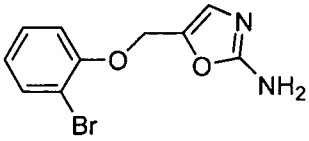
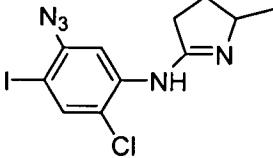
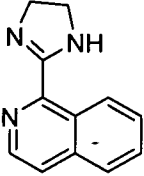
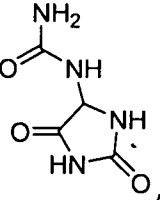
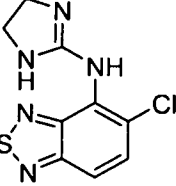
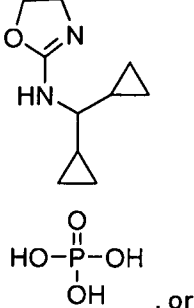
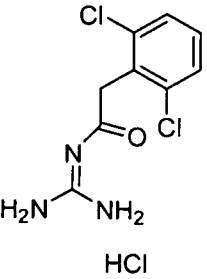
In some embodiments, the compounds disclosed herein have the formula:

Cpd ID	Structure	Cpd ID	Structure
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51		52	
53		54	

or a pharmaceutically acceptable salt, tautomer, enantiomer, diastereomer, solvate, prodrug, or a free base form of any of the foregoing compounds. For example, the compounds are selected from a group of compounds having the formula **1-54**, or a pharmaceutically acceptable salt, tautomer, solvate, enantiomer, diastereomer, prodrug, or a free base form of any of the foregoing compounds. In some embodiments, the compounds are selected from a group of compounds having the formula **8, 26, 48**, or **52**, or a pharmaceutically acceptable salt, tautomer, solvate, or prodrug of any of the foregoing compounds. In some embodiments, the compounds are selected from the group of compounds having the formula **8** or **26**, or a pharmaceutically acceptable salt, solvate, or prodrug of any of the foregoing compounds. In some embodiments, the compounds are selected from the group of

compounds having the formula **48** or **52**, or a pharmaceutically acceptable salt, tautomer, solvate, or prodrug of any of the foregoing compounds.

The compounds described herein can also be prepared as esters, for example pharmaceutically acceptable esters. For example, a carboxylic acid function group in
5 a compound can be converted to its corresponding ester, e.g., a methyl, ethyl, or other ester. Also, an alcohol group in a compound can be converted to its corresponding ester, e.g., an acetate, propionate, or other ester.

In some embodiments, the disclosure of this application includes prodrugs of the compounds selected from a group of compounds having the formula **1-54**, or a
10 pharmaceutically acceptable salt, tautomer, enantiomer, diastereomer, solvate, or free base form of any of the foregoing compounds. The term “prodrug” is intended to encompass compounds which, under physiologic conditions, are converted into the therapeutically active agents of the disclosure of this application (e.g., any one of a
15 compound selected from the group of compounds having the formula **1-54**, or a pharmaceutically acceptable salt, enantiomer, diastereomer, tautomer, solvate, or free base form of any of the foregoing compounds). A common method for making a prodrug is to include one or more selected moieties which are hydrolyzed under physiologic conditions to yield the desired molecule. In some embodiments, the prodrug is converted by an enzymatic activity of the host animal. For example, a
20 prodrug with a nitro group on an aromatic ring can be reduced by an endogenous reductase to generate the desired amino group of the corresponding active compound *in vivo*. In another example, functional groups such as a hydroxyl, carbonate, or carboxylic acid in the parent compound are presented as an ester, which can be cleaved by esterases. Additionally, amine groups in the parent compounds are
25 presented in, but not limited to, carbamate, *N*-alkylated or *N*-acylated forms (Simplício, *et al.*, “Prodrugs for Amines,” *Molecules*, (2008), 13:519-547). In some embodiments, some or all of the compounds of formula **1-54**, or a pharmaceutically acceptable salt, tautomer, enantiomer, diastereomer, solvate, or free base form of any

of the foregoing compounds described herein or used in the methods described herein can be replaced with the corresponding suitable prodrug.

Some embodiments of this disclosure include metabolites of the compounds selected from the group of compounds having the formula 1-7, 9-25, or 27-54, or a
5 pharmaceutically acceptable salt, free base form, enantiomer, diastereomer, tautomer, solvate, or prodrug of any of the foregoing compounds. The term "metabolite" is intended to encompass compounds that are produced by metabolism/biochemical modification of the parent compound under physiological conditions, e.g. through certain enzymatic pathways. For example, an oxidative metabolite is formed by
10 oxidation of the parent compound during metabolism, such as the oxidation of a pyridine ring to pyridine-*N*-oxide. In another example, an oxidative metabolite is formed by demethylation of a methoxy group to result in a hydroxyl group.

A variety of compounds of the embodiments of disclosure may exist in particular geometric or stereoisomeric forms. This disclosure includes all such compounds,
15 including tautomers, cis- and trans-isomers, R- and S-enantiomers, diastereomers, (D)-isomers, (L)-isomers, the racemic mixtures thereof, and other mixtures thereof, as being covered within the scope of this disclosure. All tautomeric forms are encompassed in this disclosure. Additional asymmetric carbon atoms may be present in a substituent, such as an alkyl group. All such isomers, as well as mixtures thereof,
20 are intended to be included in this disclosure, unless the stereochemistry or isomeric form is specifically indicated:

Compounds described herein containing one or multiple asymmetrically substituted atoms may be isolated in optically active or racemic forms. It is well known in the art how to prepare optically active forms, such as by resolution of racemic forms, by
25 synthesis from optically active starting materials, or by synthesis using optically active reagents.

In some embodiments, the therapeutic preparations of the disclosure may be enriched to provide predominantly one enantiomer of a compound described herein (e.g.,

5 compounds of any of formulae 1-54, or a pharmaceutically acceptable salt, free base form, enantiomer, diastereomer, tautomer, solvate, or prodrug of any of the foregoing compounds). An enantiomerically enriched mixture may comprise, for example, at least 60 mol percent of one enantiomer, or more preferably at least 75, 80, 85, 90, 95,
10 96, 97, 98, 99, 99.5 or even 100 mol percent. In some embodiments, the compound described herein enriched in one enantiomer is substantially free of the other enantiomer, wherein substantially free means that the substance in question makes up less than 10%, or less than 5%, or less than 4%, or less than 3%, or less than 2%, or less than 1% as compared to the amount of the other enantiomer, e.g., in the
15 composition or compound mixture. For example, if a composition or compound mixture contains 98 grams of a first enantiomer and 2 grams of a second enantiomer, it would be said to contain 98 mol percent of the first enantiomer and only 2% of the second enantiomer.

In some embodiments, the therapeutic preparation may be enriched to provide
15 predominantly one diastereomer of a compound disclosed herein (e.g., compounds of any of formulae 1-54, or a pharmaceutically acceptable salt, free base form, enantiomer, diastereomer, tautomer, solvate, or prodrug of any of the foregoing compounds). A diastereomerically enriched mixture may comprise, for example, at least 60 mol percent of one diastereomer, or more preferably at least 75, 90, 95, 96,
20 97, 98, 99, or even 100 mol percent.

The compounds described herein further include all pharmaceutically acceptable isotopically labeled compounds (e.g., compounds of any of formulae 1-54, or a pharmaceutically acceptable salt, free base form, enantiomer, diastereomer, tautomer, solvate, or prodrug of any of the foregoing compounds). An "isotopically" or "radio-
25 labeled" compound is a compound where one or more atoms are replaced or substituted by an atom having an atomic mass or mass number different from the atomic mass or mass number typically found in nature (i.e., naturally occurring). For example, in some embodiments, in the compounds described herein (e.g., compounds of any of formulae 1-54, or a pharmaceutically acceptable salt, free base form,

enantiomer, diastereomer, tautomer, solvate, or prodrug of any of the foregoing compounds), hydrogen atoms are replaced or substituted by one or more deuterium or tritium (e.g., hydrogen atoms on a C₁₋₆ alkyl or a C₁₋₆ alkoxy are replaced with deuterium, such as *d*₃-methoxy or 1,1,2,2-*d*₄-3-methylbutyl).

- 5 Certain isotopically labeled compounds (e.g., compounds of any of formulae 1-54, or a pharmaceutically acceptable salt, free base form, enantiomer, diastereomer, tautomer, solvate, or prodrug of any of the foregoing compounds), in this disclosure, for example, those incorporating a radioactive isotope, are useful in drug and/or substrate tissue distribution studies. The radioactive isotopes tritium, i.e. ³H, and
10 carbon 14, i.e., ¹⁴C, are particularly useful for this purpose in view of their ease of incorporation and ready means of detection.

Substitution with heavier isotopes such as deuterium, i.e., ²H, may afford certain therapeutic advantages resulting from greater metabolic stability, for example, increased *in vivo* half-life or reduced dosage requirements, and hence may be preferred
15 in some circumstances. In some embodiments, the isotopically labeled compound is a substituted mucate salt of compound 8, such as (R)-isomethoptene-N-CD₃ mucate, 6,7-D₆-(R)-isomethoptene mucate {IUPAC name: (2R,3S,4R,5S)-2,3,4,5-tetrahydroxyhexanedioic acid; bis(methyl[(2R)-6-(²H₃)methyl(7,7,7-²H₃)hept-5-en-2-yl]amine)}, or 6,7-D₆-(R)-isomethoptene-N-CD₃ mucate.

- 20 Substitution with positron emitting isotopes, such as ¹¹C, ¹⁸F, ¹⁵O, and ¹³N, can be useful in Positron Emission Topography (PET) studies for examining substrate receptor occupancy.

Isotopically labeled compounds (e.g., compounds of any of formulae 1-54, or a pharmaceutically acceptable salt, tautomer, enantiomer, diastereomer, solvate, or free
25 base form of any of the foregoing compounds), or their corresponding prodrugs described herein are prepared by conventional techniques known to those skilled in the art or by processes analogous to those described in the accompanying examples using an appropriate isotopically labeled reagent in place of the non-labeled reagent

previously employed. Suitable isotopes that may be incorporated in compounds described herein include but are not limited to ^2H (also written as D for deuterium), ^3H (also written as T for tritium), ^{11}C , ^{13}C , ^{14}C , ^{13}N , ^{15}N , ^{15}O , ^{17}O , ^{18}O , ^{18}F , ^{35}S , ^{36}Cl , ^{82}Br , ^{75}Br , ^{76}Br , ^{77}Br , ^{123}I , ^{124}I , ^{125}I , and ^{131}I .

5 This disclosure includes pharmaceutically acceptable salts of compounds described herein. The term "pharmaceutically acceptable salts" includes salts of the active compounds described herein which are prepared with relatively nontoxic acids or bases, depending on the particular substituents found on the compounds. When compounds described herein contain relatively acidic functionalities, base addition
10 salts can be obtained by contacting the neutral form of such compounds with a sufficient amount of the desired base, either neat or in a suitable inert solvent. Examples of pharmaceutically acceptable base addition salts include sodium, potassium, calcium, ammonium, organic amino, or magnesium salt, or a similar salt. When compounds described herein contain relatively basic functionalities, such as an
15 amine, acid addition salts can be obtained by contacting the neutral form of such compounds with a sufficient amount of the desired acid, either neat or in a suitable inert solvent. Examples of pharmaceutically acceptable acid addition salts include those derived from inorganic acids like hydrochloric, hydrobromic, nitric, carbonic, monohydrogencarbonic, phosphoric, monohydrogenphosphoric,
20 dihydrogenphosphoric, sulfuric, monohydrogensulfuric, hydriodic, or phosphorous acids, and the like, as well as the salts derived from relatively nontoxic organic acids like acetic, trifluoroacetic, propionic, isobutyric, malic, maleic, malonic, benzoic, succinic, suberic, fumaric, lactic, mandelic, phthalic, benzenesulfonic, *p*-tolylsulfonic, citric, tartaric, methanesulfonic, camphorsulfonic, and the like. In some embodiments,
25 the pharmaceutically acceptable salt is a hydrochloride salt. In some embodiments, the pharmaceutically acceptable salt is a sulfate acid salt. In some embodiments, the pharmaceutically acceptable salt is a phosphate salt. In some embodiments, the pharmaceutically acceptable salt is a mucate salt. In some embodiments, the pharmaceutically acceptable salt is an oxalate salt. In some embodiments, the
30 pharmaceutically acceptable salt is a tartrate salt. In some embodiments, the

pharmaceutically acceptable salt is a malate salt. In some embodiments, the pharmaceutically acceptable salt is a maleate salt. In some embodiments, contemplated salts of the compounds include, but are not limited to, alkyl, dialkyl, trialkyl or tetra-alkyl ammonium salts. In some embodiments, contemplated salts of compounds include, but are not limited to, L-arginine, benenthamine, benzathine, 5 betaine, calcium hydroxide, choline, deanol, diethanolamine, diethylamine, 2-(diethylamino)ethanol, ethanolamine, ethylenediamine, *N*-methylglucamine, hydrabamine, 1*H*-imidazole, lithium, L-lysine, magnesium, 4-(2-hydroxyethyl)morpholine, piperazine, potassium, 1-(2-hydroxyethyl)pyrrolidine, 10 sodium, triethanolamine, tromethamine, and zinc salts. In some embodiments, contemplated salts of compounds include, but are not limited to, Li, Na, Ca, K, Mg, Zn or other metal salts. Also included are the salts of amino acids such as arginate and the like, and salts of organic acids like glucuronic or galactunoric acids and the like (see, for example, Berge, *et al.*, "Pharmaceutical Salts," Journal of Pharmaceutical 15 Science, 1977, 66, 1-19). Certain specific compounds described herein may contain both basic and acidic functionalities, as such, these compounds can be converted into either base or acid addition salts. Where a compound of this disclosure is provided as a pharmaceutically acceptable salt, other pharmaceutically acceptable salts of the compound are also contemplated and the disclosed salt should not be considered as 20 limiting. All such pharmaceutically acceptable salts are intended to be included in the embodiments of this disclosure, even where a salt form of a compound of this disclosure is specifically indicated.

The neutral forms of the compounds are preferably regenerated by contacting the salt with a base or acid, as is appropriate, and isolating the parent compound in the 25 conventional manner. The parent form of the compound may differ from the various salt forms in certain physical properties, such as solubility in polar solvents, but otherwise the salts are equivalent to the parent form of the compound for the purposes of this disclosure.

The compounds described herein, including their pharmaceutically acceptable salts and prodrugs, can also exist as various solvates, such as with water (also known as hydrates), methanol, ethanol, dimethylformamide, diethyl ether, acetamide, and the like. Mixtures of such solvates can also be prepared. The source of such solvate can
5 be from the solvent of crystallization, inherent in the solvent of preparation or crystallization, or adventitious to such solvent.

The compounds described herein, including their pharmaceutically acceptable salts and prodrugs, can also exist as various polymorphs, pseudopolymorphs, or in amorphous state. As used herein, the term "polymorph" refers to different crystalline
10 forms of the same compound and other solid state molecular forms including pseudopolymorphs, such as hydrates, solvates, or salts of the same compound. Different crystalline polymorphs have different crystal structures due to a different packing of molecules in the lattice, as a result of changes in temperature, pressure, or variations in the crystallization process. Polymorphs differ from each other in their physical
15 properties, such as X-ray diffraction characteristics, stability, melting points, solubility, or rates of dissolution in certain solvents. Thus crystalline polymorphic forms are important aspects in the development of suitable dosage forms in pharmaceutical industry.

Uses of the Compounds and Compositions

20 In some embodiments, this disclosure relates to use of one or more compounds of formula 1-54, or a pharmaceutically acceptable salt, free base form, enantiomer, diastereomer, tautomer, solvate, or prodrug of any of the foregoing compounds, as analgesics. In some embodiments, the compounds of this disclosure modulate the I₁ receptor to reduce pain. Without wishing to be bound by theory, in some
25 embodiments, the compounds of this disclosure activate the I₁ receptor to reduce pain. In some embodiments, the compounds of this disclosure may reduce pain through a pathway that is independent of the I₁ receptor (the Imidazoline-1 Receptor-Independent Isometheptene Pain Modulatory pathway, or IRIPM pathway).

In some embodiments, this disclosure relates to any one of a compound of formula 1-54, or a mixture thereof, or a pharmaceutically acceptable salt, free base form, enantiomer, diastereomer, tautomer, solvate, or prodrug, or mixtures thereof, of any of the foregoing compounds, for use in treating or preventing pain; an inflammatory disease or disorder, an allergic disease or disorder, a metabolic disease, a cardiovascular disease or disorder, a neurogenic vascular disease or a painful condition associated with any of the foregoing conditions; an episodic tension-type headache; a migraine headache; a headache; cramping; a cognitive disorder; a tension or migraine headache due to a vascular, neurovascular, or neurogenic disorder or dysfunction during a menstrual cycle episode; a tension or migraine headache due to a vascular, neurovascular, or neurogenic disorder or dysfunction during a migraine episode; a headache from mild to moderate hypertension; mild to moderate essential hypertension; organ transplant rejection; hot and cold flashes; traumatic brain injury (TBI); neurotoxicity; psychic pain; psychological pain; psychiatric pain; depression; schizophrenia; anxiety; epilepsy; a stress disorder; excess sweating; a symptom related to drug withdrawal, including opioid-induced constipation or an opioid withdrawal symptom; allodynia; fibromyalgia; fibromyalgia-ness; central sensitization; centralization; regional pain syndrome; temporomandibular joint syndrome (TMJ); lower back pain; interstitial cystitis; Gulf War syndrome; visceral pain; kidney stones; gout; neuropathic pain; post-herpetic neuralgia; diabetic neuropathy; sickle cell pain; priapism; nociceptive pain; post-operative pain; orthopedic injury pain; phantom limb pain; bunionectomy; dental extraction; pain after severed spinal cord injury; osteoarthritis; rheumatoid arthritis; Lyme disease; Parkinson's disease; pain associated with cancer; opioid-induced constipation; an opioid withdrawal symptom; or pain associated with post-traumatic stress disorder (PTSD), or a combination of any of the foregoing conditions.

In some embodiments, this disclosure relates to the use of any one of a compound of formula 1-54, or a mixture thereof, or a pharmaceutically acceptable salt, free base form, enantiomer, diastereomer, tautomer, solvate, or prodrug, or mixtures thereof, of any of the foregoing compounds, in the manufacture of a medicament for the

treatment of pain; an inflammatory disease or disorder, an allergic disease or disorder, a metabolic disease, a cardiovascular disease or disorder, a neurogenic vascular disease or a painful condition associated with any of the foregoing conditions; an episodic tension-type headache; a migraine headache; a headache; cramping; a
5 cognitive disorder; a tension or migraine headache due to a vascular, neurovascular, or neurogenic disorder or dysfunction during a menstrual cycle episode; a tension or migraine headache due to a vascular, neurovascular, or neurogenic disorder or dysfunction during a migraine episode; a headache from mild to moderate hypertension; mild to moderate essential hypertension; organ transplant rejection; hot
10 and cold flashes; traumatic brain injury (TBI); neurotoxicity; psychic pain; psychological pain; psychiatric pain; depression; schizophrenia; anxiety; epilepsy; a stress disorder; excess sweating; a symptom related to drug withdrawal, including opioid-induced constipation or an opioid withdrawal symptom; allodynia; fibromyalgia; fibromyalgia-ness; central sensitization; centralization; regional pain
15 syndrome; temporomandibular joint syndrome (TMJ); lower back pain; interstitial cystitis; Gulf War syndrome; visceral pain; kidney stones; gout; neuropathic pain; post-herpetic neuralgia; diabetic neuropathy; sickle cell pain; priapism; nociceptive pain; post-operative pain; orthopedic injury pain; phantom limb pain; bunionectomy; dental extraction; pain after severed spinal cord injury; osteoarthritis; rheumatoid
20 arthritis; Lyme disease; Parkinson's disease; pain associated with cancer; opioid-induced constipation; an opioid withdrawal symptom; or pain associated with post-traumatic stress disorder (PTSD), or a combination of any of the foregoing conditions.

In some embodiments, this disclosure relates to a method of treating or preventing pain; an inflammatory disease or disorder, an allergic disease or disorder, a metabolic
25 disease, a cardiovascular disease or disorder, a neurogenic vascular disease or a painful condition associated with any of the foregoing conditions; an episodic tension-type headache; a migraine headache; a headache; cramping; a cognitive disorder; a tension or migraine headache due to a vascular, neurovascular, or neurogenic disorder or dysfunction during a menstrual cycle episode; a tension or migraine headache due
30 to a vascular, neurovascular, or neurogenic disorder or dysfunction during a migraine

episode; a headache from mild to moderate hypertension; mild to moderate essential hypertension; organ transplant rejection; hot and cold flashes; traumatic brain injury (TBI); neurotoxicity; psychic pain; psychological pain; psychiatric pain; depression; schizophrenia; anxiety; epilepsy; a stress disorder; excess sweating; a symptom related
5 to drug withdrawal, including opioid-induced constipation or an opioid withdrawal symptom; allodynia; fibromyalgia; fibromyalgia-ness; central sensitization; centralization; regional pain syndrome; temporomandibular joint syndrome (TMJ); lower back pain; interstitial cystitis; Gulf War syndrome; visceral pain; kidney stones; gout; neuropathic pain; post-herpetic neuralgia; diabetic neuropathy; sickle cell pain;
10 priapism; nociceptive pain; post-operative pain; orthopedic injury pain; phantom limb pain; bunionectomy; dental extraction; pain after severed spinal cord injury; osteoarthritis; rheumatoid arthritis; Lyme disease; Parkinson's disease; pain associated with cancer; opioid-induced constipation; an opioid withdrawal symptom; or pain associated with post-traumatic stress disorder (PTSD), or a combination of any of the
15 foregoing conditions, comprising administering to a patient in need thereof a therapeutically effective amount of any one of a compound of formula 1-54, or a mixture thereof, or a pharmaceutically acceptable salt, free base form, tautomer, enantiomer, diastereomer, solvate, or prodrug, or mixtures thereof, of any of the foregoing compounds.

20 In some embodiments, this disclosure relates to a pharmaceutical composition comprising as an active ingredient a therapeutically effective amount of one or more compounds selected from a group of compounds having the formula 1-54, or a pharmaceutically acceptable salt, free base form, enantiomer, diastereomer, tautomer, solvate, or prodrug of any of the foregoing compounds, in association with at least one
25 pharmaceutically acceptable excipient, carrier or diluent.

In some embodiments, this disclosure relates to use of a pharmaceutical composition comprising as an active ingredient a therapeutically effective amount of one or more compounds selected from the group of compounds having the formula 1-54, or a

pharmaceutically acceptable salt, free base form, enantiomer, diastereomer, tautomer, solvate, or prodrug of any of the foregoing compounds, as an analgesic.

In some embodiments, this disclosure relates to a method of treating or preventing pain; an inflammatory disease or disorder, an allergic disease or disorder, a metabolic disease, a cardiovascular disease or disorder, a neurogenic vascular disease or a
5 painful condition associated with any of the foregoing conditions; an episodic tension-type headache; a migraine headache; a headache; cramping; a cognitive disorder; a tension or migraine headache due to a vascular, neurovascular, or neurogenic disorder or dysfunction during a menstrual cycle episode; a tension or migraine headache due
10 to a vascular, neurovascular, or neurogenic disorder or dysfunction during a migraine episode; a headache from mild to moderate hypertension; mild to moderate essential hypertension; organ transplant rejection; hot and cold flashes; traumatic brain injury (TBI); neurotoxicity; psychic pain; psychological pain; psychiatric pain; depression; schizophrenia; anxiety; epilepsy; a stress disorder; excess sweating; a symptom related
15 to drug withdrawal, including opioid-induced constipation or an opioid withdrawal symptom; allodynia; fibromyalgia; fibromyalgia-ness; central sensitization; centralization; regional pain syndrome; temporomandibular joint syndrome (TMJ); lower back pain; interstitial cystitis; Gulf War syndrome; visceral pain; kidney stones; gout; neuropathic pain; post-herpetic neuralgia; diabetic neuropathy; sickle cell pain;
20 priapism; nociceptive pain; post-operative pain; orthopedic injury pain; phantom limb pain; bunionectomy; dental extraction; pain after severed spinal cord injury; osteoarthritis; rheumatoid arthritis; Lyme disease; Parkinson's disease; pain associated with cancer; opioid-induced constipation; an opioid withdrawal symptom; or pain associated with post-traumatic stress disorder (PTSD), or a combination of any of the
25 foregoing conditions, comprising administering to a patient in need thereof a therapeutically effective amount of a pharmaceutical composition comprising one or more of the compounds selected from the group of compounds having the formula 1-54, or a pharmaceutically acceptable salt, tautomer, enantiomer, diastereomer, solvate, or prodrug of any of the foregoing compounds.

In the treatment of pain; an inflammatory disease or disorder, an allergic disease or disorder, a metabolic disease, a cardiovascular disease or disorder, a neurogenic vascular disease or a painful condition associated with any of the foregoing conditions; an episodic tension-type headache; a migraine headache; a headache; cramping; a
5 cognitive disorder; a tension or migraine headache due to a vascular, neurovascular, or neurogenic disorder or dysfunction during a menstrual cycle episode; a tension or migraine headache due to a vascular, neurovascular, or neurogenic disorder or dysfunction during a migraine episode; a headache from mild to moderate hypertension; mild to moderate essential hypertension; organ transplant rejection; hot
10 and cold flashes; traumatic brain injury (TBI); neurotoxicity; psychic pain; psychological pain; psychiatric pain; depression; schizophrenia; anxiety; epilepsy; a stress disorder; excess sweating; a symptom related to drug withdrawal, including opioid-induced constipation or an opioid withdrawal symptom; allodynia; fibromyalgia; fibromyalgia-ness; central sensitization; centralization; regional pain
15 syndrome; temporomandibular joint syndrome (TMJ); lower back pain; interstitial cystitis; Gulf War syndrome; visceral pain; kidney stones; gout; neuropathic pain; post-herpetic neuralgia; diabetic neuropathy; sickle cell pain; priapism; nociceptive pain; post-operative pain; orthopedic injury pain; phantom limb pain; bunionectomy; dental extraction; pain after severed spinal cord injury; osteoarthritis; rheumatoid
20 arthritis; Lyme disease; Parkinson's disease; pain associated with cancer; opioid-induced constipation; an opioid withdrawal symptom; or pain associated with post-traumatic stress disorder (PTSD), or a combination of any of the foregoing conditions, different compounds and compositions of this disclosure may be (e.g., conjointly) administered simultaneously, separately, or sequentially with one or more other
25 compounds and compositions of this disclosure.

In some embodiments, one or more of the compounds or compositions described herein may be used alone or together or conjointly administered with another type of therapeutic agent. As used herein, the phrase "conjoint administration" refers to any
30 form of administration of two or more different therapeutic compounds or compositions such that the second compound or composition is administered while the

previously administered therapeutic compound or composition is still effective in the body. For example, the different therapeutic compounds or compositions can be administered either in the same formulation or in a separate formulation, either simultaneously, sequentially, or by separate dosing of the individual components of
5 the treatment. In some embodiments, the different therapeutic compounds or compositions can be administered within one hour, 12 hours, 24 hours, 36 hours, 48 hours, 72 hours, or a week of one another. Thus, an individual who receives such treatment can benefit from a combined effect of different therapeutic compounds or compositions.

10 In some embodiments, conjoint administration of compounds or compositions described herein with one or more additional therapeutic agent(s) provides improved efficacy relative to each individual administration of the compound and compositions of this disclosure (e.g., any one of a compound selected from the group of compounds having the formula 1-54, or a pharmaceutically acceptable salt, free base form,
15 enantiomer, diastereomer, tautomer, solvate, or prodrug of any of the foregoing compounds or a composition comprising one or more compounds selected from the group of compounds having the formula 1-54, or a pharmaceutically acceptable salt, free base form, enantiomer, diastereomer, tautomer, solvate, or prodrug of any of the foregoing compounds) or the one or more additional therapeutic agent(s). In certain
20 such embodiments, the conjoint administration provides an additive effect, wherein an additive effect refers to the sum of each of the effects of individual administration of the compound or composition of this disclosure and the one or more additional therapeutic agent(s).

In further embodiments, the compounds and compositions described herein are used
25 simultaneously, separately, or sequentially with one or more additional therapeutics selected from the group consisting of acetaminophen, a non-steroidal anti-inflammatory drug (NSAID), ibuprofen, naprosyn, a cyclooxygenase-2 inhibitor, aspirin, caffeine, dichloralphenazone, a triptan, a chemotherapeutic drug, an antidepressant, a serotonin-norepinephrine reuptake inhibitor (SNRI), a gabapentinoid,

an antiproliferative agent, an anti-inflammatory agent, a corticosteroid, an anti-asthmatic agent, an anti-allergic agent, an immunosuppressive agent, an immunomodulatory agent, a cardiovascular disease treatment agent, an anti-diabetic agent, a blood disorder treatment agent, a nerve growth factor receptor antagonist, a sodium channel blocker, a CYP2D6 inhibitor, or a TNF-alpha inhibitor. In some
5 embodiments, the compound is used simultaneously, separately, or sequentially with one or more opiates.

The compounds and compositions disclosed herein, and mixtures thereof, may also be used in the manufacture of medicaments for the treatment of any diseases or
10 conditions disclosed herein.

Methods of Treatment and Use

The compounds and compositions of this disclosure, or mixtures thereof, are useful as analgesics and to treat pain; an inflammatory disease or disorder, an allergic disease or disorder, a metabolic disease, a cardiovascular disease or disorder, a neurogenic
15 vascular disease or a painful condition associated with any of the foregoing conditions; an episodic tension-type headache; a migraine headache; a headache; cramping; a cognitive disorder; a tension or migraine headache due to a vascular, neurovascular, or neurogenic disorder or dysfunction during a menstrual cycle episode; a tension or migraine headache due to a vascular, neurovascular, or neurogenic disorder or
20 dysfunction during a migraine episode; a headache from mild to moderate hypertension; mild to moderate essential hypertension; organ transplant rejection; hot and cold flashes; traumatic brain injury (TBI); neurotoxicity; psychic pain; psychological pain; psychiatric pain; depression; schizophrenia; anxiety; epilepsy; a stress disorder; excess sweating; a symptom related to drug withdrawal, including
25 opioid-induced constipation or an opioid withdrawal symptom; allodynia; fibromyalgia; fibromyalgia-ness; central sensitization; centralization; regional pain syndrome; temporomandibular joint syndrome (TMJ); lower back pain; interstitial cystitis; Gulf War syndrome; visceral pain; kidney stones; gout; neuropathic pain; post-herpetic neuralgia; diabetic neuropathy; sickle cell pain; priapism; nociceptive

pain; post-operative pain; orthopedic injury pain; phantom limb pain; bunionectomy; dental extraction; pain after severed spinal cord injury; osteoarthritis; rheumatoid arthritis; Lyme disease; Parkinson's disease; pain associated with cancer; opioid-induced constipation; an opioid withdrawal symptom; or pain associated with post-traumatic stress disorder (PTSD), or a combination of any of the foregoing conditions.

In some embodiments, the compounds of this disclosure are ligands of the imidazoline-1 (I_1) receptor. In some embodiments, the compounds and compositions of this disclosure modulate the I_1 receptor. In some embodiments, the compounds and compositions of this disclosure modulate the I_1 receptor to reduce pain. Without wishing to be bound by theory, in some embodiments, the compounds and compositions of this disclosure activate the I_1 receptor to reduce pain. In some embodiments, the compounds and compositions of the disclosure may reduce pain through a pathway that is independent of the I_1 receptor (the Imidazoline-1 Receptor-Independent Isometheptene Pain Modulatory pathway, or IRIPM pathway).

15 *Analgesic*

The compounds and compositions of this disclosure act as potent and selective pain inhibitors or painkillers. An analgesic is a member of the group of drugs used to achieve analgesia or relief from pain

Pain

20 The compounds and compositions of this disclosure are useful in the treatment or prevention of pain. Pain is an unpleasant feeling triggered by the nervous system. It is often classified by the region of the body involved, the system whose dysfunction may be causing the pain, the duration and pattern of occurrence, the intensity and time since onset, and the etiology. Many types of pain exist, including, but not limited to, 25 nociceptive pain, neuropathic pain, psychogenic pain, visceral pain, and chronic pain.

Inflammatory diseases or disorders and allergic diseases or disorders

The compounds and compositions of this disclosure are useful in the treatment or prevention of diseases of inflammation and allergy as manifested in cells required to mount an inflammatory response, such as neutrophils, macrophages, mast cells, T-cells, B-cells, plasma cells, dendritic cells, basophils, and eosinophils. The pain and tension associated with inflammatory diseases or conditions which are treatable by the compounds and compositions of this disclosure include, but are not limited to, autoimmune diseases and common arthritis types, including rheumatoid arthritis, osteoarthritis, ankylosing spondylitis, psoriatic arthritis; psoriasis, systemic lupus erythematosus, glomerulonephritis, scleroderma, general renal failure, inflammatory bowel disease, ulcerative colitis, Crohn's disease, pancreatitis, multiple sclerosis; inflammation due to hyper-responsiveness to cytokine production, chronic obstructive pulmonary, airway or lung disease (COPD, COAD, or COLD), acute respiratory distress syndrome (ARDS) and occupation-related diseases such as aluminosis, anthracosis, asbestosis, chalicosis, ptilosis, siderosis, silicosis, tabacosis and byssinosis. Additionally, the compounds and compositions of this disclosure are useful in the treatment or prevention of parasite-related diseases involving hypereosinophilia.

The compounds and compositions of this disclosure are useful for the treatment or prevention of diseases and conditions related to immediate-type hypersensitivity, also referred to as allergic responses, conditions and diseases. These diseases and conditions include, but are not limited to, asthma (extrinsic or intrinsic), asthma related sequelae including small and large airway hyperactivity, bronanaphylaxis, aspirin induced asthma, allergic airway inflammation, urticaria, Steven-Johnson syndrome, atopic dermatitis, bolus pemphigoid and the like.

Metabolic diseases

The compounds and compositions of this disclosure are useful in the treatment or prevention of discomfort and pain due to inflammation associated with metabolic diseases, such as diabetes and obesity.

5 *Cardiovascular diseases or disorders*

Cardiovascular diseases, acute heart failure, enlargement of the heart, and atherosclerosis are also diseases that are suitable for ameliorating the treatment or prevention using the compounds and compositions of this disclosure. Nonlimiting examples of cardiovascular diseases also include pulmonary hypertension, deep
10 venous thrombosis, stroke, myocardial infarction, myocardial contractility diseases or disorders, ischemia, thromboembolism, pulmonary embolism, acute arterial ischemia, peripheral thrombotic occlusions, coronary artery disease and acute coronary syndrome (ACS). In some embodiments, the cardiovascular disease treated or prevented by compounds and compositions, or mixtures thereof, of this disclosure is
15 atherosclerosis. In some embodiments, the neurovascular effect on cardiovascular disease treated or prevented by compounds and compositions of this disclosure, or mixtures thereof, is a myocardial contractility disease or disorder or an acute coronary syndrome.

Neurogenic vascular diseases or painful conditions associated therewith

20 In some embodiments, compounds and compositions of this disclosure are useful in the treatment or prevention of pain caused by neurogenic vascular diseases. Symptoms are caused by the compression of the spinal cord or nerve roots in the lower region of the spine or by narrowing of the arteries in the legs, and include leg pain, leg weakness, tingling, fatigue, a sensation of heaviness, and weakness.

25 *Headaches and episodic tension-type headaches*

In some embodiments, compounds and compositions of this disclosure are useful in the treatment or prevention of pain caused by headaches and episodic tension-type

headaches. A headache is pain in any region of the head, and may occur on one or both sides of the head, be isolated to a certain location, radiate across the head from one point, or have a vise-like quality. Headaches can cause sharp pain, a throbbing sensation, or a dull ache. Primary headaches can be caused by problems with or
5 overactivity of pain-sensitive structures in the head, and secondary headaches can be caused by diseases, such as brain cancer, glaucoma, and trigeminal neuralgia, which activate the pain-sensitive nerves in the head.

A tension-type headache is classified into subtypes based on how often it occurs: infrequent episodic tension-type headache (ETTH) (<1 day/month on average),
10 frequent ETTH (1-14 days/month on average), or chronic TTH, or CTTH, (~ 15 days/month on average). An ETTH (infrequent or frequent) may be described as a mild to moderate constant band-like pain, tightness, or pressure around the forehead or back of the head and neck. ETTH may last from 30 minutes to several days. ETTH usually begins gradually, and often occurs in the middle of the day. The severity of a
15 tension headache generally increases significantly with its frequency. Because the symptoms of ETTH overlap with other primary headache types, diagnosis is generally made, not only by inclusion, but also of exclusion of certain symptoms such as nausea, exacerbation by physical exercise and occurrence of both photophobia and phonophobia.

20 *Migraine*

In some embodiments, compounds and compositions of this disclosure are useful in the treatment or prevention of migraines; tension or migraine headaches due to a vascular, neurovascular, or neurogenic disorder or dysfunction during a menstrual cycle episode; or tension or migraine headaches due to a vascular, neurovascular, or
25 neurogenic disorder or dysfunction during a migraine episode. Migraine is described as a paroxysmal disorder or a recurrent, incapacitating, neurovascular disorder characterized by unilateral and throbbing headaches associated characterized by attacks of headache, nausea, vomiting, photophobia, and phonophobia.

Migraine affects people of all races and both sexes with women accounting for 79% (61% between 20 and 49 years of age) of physician visits for migraines and Caucasians for 91% of the physician visits. Migraine without aura often has a strict menstrual relationship. The pathogenesis of migraine headache involves a) the cranial
5 blood vessels, b) the trigeminal innervation of these vessels, and c) the reflex connection of the trigeminovascular system in the cranial parasympathetic outflow.

Migraine pathophysiology is believed by genetic predisposition to involve leakage of ion channels in the brain stem such that the decreased blood flow in the brain leads to neuropeptide release from trigeminal nerves inducing dilatation of cranial
10 extracerebral blood vessel. This condition stimulates the trigeminovascular system producing headache associated phonophobia and photophobia as well as nausea and vomiting.

Phantom limb pain

In some embodiments, the compounds and compositions of this disclosure are useful
15 in the treatment or prevention of alleviate phantom pain. Phantom pain is pain coming from a body part that's no longer there. This pain originates in the spinal cord and brain and may be described as shooting, stabbing, boring, squeezing, throbbing or burning.

Cramps or cramping

20 In some embodiments, the compounds and compositions of this disclosure are useful in the treatment or prevention of cramps or cramping. Cramps are unpleasant, sometimes painful sensations caused by involuntary muscle contraction or muscle over-shortening. Cramps can be symptoms of muscle spasm and can be separated into smooth muscle cramps and skeletal muscle cramps. Cramps related to internal (or
25 visceral) organs are related to spasm of smooth muscle or skeletal muscle or distension of organs by functional or pathological disorders, and can be associated with visceral pain. Smooth muscle cramps are commonly associated with menstruation or visceral disorders including gastrointestinal and urinary disorders. In the female, smooth

muscle cramps that are associated with menstruation are called menstrual cramps and may also occur before and during a female menstrual cycle. Severe or persistent smooth muscle cramps may also be symptomatic of endometriosis or other health problems. Moreover, smooth muscle cramps can be associated with gastrointestinal disorders, including infectious or autoimmune gastroenteritis and functional disorders such as irritable bowel syndrome (IBS). Thus, smooth muscle cramps are associated with visceral pain in many conditions, including interstitial cystitis.

Skeletal muscle cramps are associated with muscle fatigue, low sodium, low potassium and certain drugs, including statins. Skeletal muscle cramps also include nocturnal leg cramps which are involuntary muscle contractions that occur during the night or (less commonly) while resting. Nocturnal leg cramps are common in the elderly, teenagers or in women during the late stages of pregnancy, and can vary in intensity from mild to extremely painful.

Menopause

In some embodiments, the compounds and compositions of this disclosure are useful in the treatment or prevention of pain and discomfort associated with menopause. Menopause is an event that typically occurs in women that can be defined as the permanent cessation of the primary functions of the ovaries and is functionally evident when there is a termination of periodic shedding of the uterine lining (known as menses).

Hot and cold flashes

The compounds and compositions of this disclosure are useful in the treatment or prevention of hot and cold flashes, unpleasant sensations associated with vascular events. Hot flashes (also known as night sweats if they happen at night) are a symptom which may have several other causes, but which is often caused by the changing hormone levels that are characteristic of menopause.

Cognitive disorders

The compounds and compositions of this disclosure are useful to treat or prevent cognitive disorders. Cognitive disorders are a category of mental health disorders that primarily affect learning, memory, perception, and problem solving, and include
5 amnesia, dementia, and delirium. Causes vary between the different types of disorders but most include damage to the memory portions of the brain. Mild cognitive impairment (MCI, also known as incipient dementia, or isolated memory impairment) is a brain function syndrome involving the onset and evolution of cognitive
10 impairments beyond those expected based on the age and education of the individual, but which are not significant enough to interfere with their daily activities. MCI can be a transitional stage between normal aging and dementia. Alzheimer's disease (AD) is the most common form of dementia. AD is commonly diagnosed in people over 65 years of age, although the less-prevalent early-onset Alzheimer's can occur much
15 earlier. In the early stages, the most common symptom is difficulty in remembering recent events. As the disease advances, symptoms can include confusion, irritability and aggression, mood swings, trouble with language, and long-term memory loss. In later stages, AD patients often withdraw from family and society. Gradually, bodily functions are lost, ultimately leading to death. The compounds and compositions of this disclosure are also useful in the treatment of "agitation," or anxiety and tension, in
20 dementias.

Traumatic brain injury (TBI)

The compounds and compositions of this disclosure are useful in the treatment or prevention of pain associated with traumatic brain injury (TBI). TBI is also known as intracranial injury, occurs when an external force traumatically injures the brain. TBI
25 can be classified based on severity, mechanism (closed or penetrating head injury), or other features (e.g., occurring in a specific location or over a widespread area). Head injury usually refers to TBI, but is a broader category because it can involve damage to structures other than the brain, such as the scalp and skull.

Neurotoxicity

The compounds and compositions of this disclosure are useful to treat or prevent symptoms related to neurotoxicity. Neurotoxicity occurs when the exposure to natural or artificial toxic substances, which are called neurotoxins, alters the normal activity
5 of the nervous system in such a way as to cause damage to nervous tissue.

Neurotoxicity can result from exposure to substances used in chemotherapy, radiation treatment, drug therapies, certain drug abuse, and organ transplants, as well as exposure to heavy metals, certain foods and food additives, pesticides, industrial and/or cleaning solvents, cosmetics, and some naturally occurring substances.
10 Symptoms may appear immediately after exposure or be delayed. They may include limb weakness or numbness, loss of memory, vision, and/or intellect, uncontrollable obsessive and/or compulsive behaviors, delusions, headache, cognitive and behavioral problems, and sexual dysfunction.

Depression

15 The compounds and compositions of this disclosure are useful in the treatment and prevention of depression. Depression, clinical depression, major depression, unipolar depression, unipolar disorder, or recurrent depression in the case of repeated episodes is a psychiatric diagnosis for a mood disorder characterized by episodes of all encompassing low mood accompanied by low self-esteem and loss of interest or
20 pleasure in normally enjoyable activities (anhedonia) and disturbed sleep (typically early morning awakening). The term "depression" is ambiguous and can be used to describe manic-depressive disorder, but is also used to describe other mood disorders or to lower mood states lacking clinical significance. For example, endogenous depression or the depressed phases of bipolar disorder can be associated with
25 widespread pain or regional pain disorders.

Pain experienced during depression can include, but is not limited to, psychogenic pain, psychiatric pain, psychic pain, and psychological pain. Psychogenic pain is pain that results from psychological mechanisms including traumatic experiences, empathic

reactions or somatization. For example, loss of a loved friend or relative by death or other separation can result in widespread pain, regional pain, and other symptoms including reactive depression. Psychiatric pain is pain that results from conditions that are believed to have biological causes. Psychic pain and psychological pain are
5 caused by a non-physical origin and can lead to emotional suffering and mental agony.

Schizophrenia

Schizophrenia is a psychiatric diagnosis for a thought disorder characterized by a breakdown of thought processes and by a deficit of typical emotional responses. Common symptoms include auditory hallucinations, paranoid or bizarre delusions, or
10 disorganized speech and thinking. The compounds and compositions of this disclosure are useful in the treatment and prevention of the symptoms of schizophrenia.

Anxiety

Anxiety disorder is a blanket term covering several different forms of a type of common psychiatric disorder characterized by excessive rumination, worrying,
15 uneasiness, apprehension, and fear about future uncertainties either based on real or imagined events, which may affect both physical and psychological health. The compounds and compositions of this disclosure are useful in the treatment and prevention of the symptoms of anxiety. In some embodiments, the anxiety is associated with white coat syndrome. Patients with white coat syndrome feel anxiety
20 in a medical environment, which can lead to elevated blood pressure. In some embodiments, the compounds or compositions of this disclosure are useful in the treatment of anxiety and tension associated with dementias such as Alzheimer's disease.

Epilepsy

25 The compounds and compositions of this disclosure are useful in the treatment and prevention of epilepsy. Epilepsy is a common and diverse set of chronic neurological disorders characterized by seizures. In many cases a cause cannot be identified;

however, factors that are associated include brain trauma, strokes, brain cancer, and drug and alcohol misuse among others.

Stress disorders

Stress disorders are an increasingly recognized group of conditions relating to the
5 body's reaction to stressful circumstances and in some cases to decompensated
reactions. The compounds and compositions of this disclosure are useful in the
treatment and prevention of stress disorders.

Excess sweating

The compounds and compositions of this disclosure are useful in the treatment and
10 prevention of excess sweating. Hyperhidrosis, or excess sweating, can either be
generalized or localized to specific parts of the body. Hands, feet, armpits, and the
groin area are among the most active regions of perspiration due to the relatively high
concentration of sweat glands. When excessive sweating is localized it is referred to
as primary or focal hyperhidrosis. Generalized or secondary hyperhidrosis usually
15 involves the body as a whole and is the result of an underlying condition.
Hyperhidrosis can also be classified depending by onset, either congenital or acquired.
Primary or focal hyperhidrosis must be distinguished from secondary hyperhidrosis,
which can start at any point in life. The later form may be due to a disorder of the
thyroid or pituitary glands, diabetes mellitus, tumors, gout, menopause, certain drugs,
20 or mercury poisoning. Hyperhidrosis may also be divided into palmoplantar
(symptomatic sweating of primarily the hands or feet), gustatory and generalized
hyperhidrosis.

Symptoms related to drug withdrawal

Withdrawal is the group of symptoms that occur upon the abrupt discontinuation or
25 decrease in intake of medications or recreational drugs. In order to experience the
symptoms of withdrawal, one must have first developed a physical or mental
dependence (often referred to as chemical dependency). Symptoms of drug

withdrawal vary depending on the drug, but can include: anxiety, sweating, vomiting, diarrhea, irritability, fatigue, shaking, sweating, nausea, insomnia, headache, and difficulty concentrating. The compounds and compositions of this disclosure are useful in the treatment and prevention of symptoms of drug withdrawal.

5 *Side effects associated with opioid administration or treatment*

Opioid analgesics are a class of analgesic agents with morphine-like actions. Synthetic and semi-synthetic opioid analgesics are derivatives of five chemical classes of compound: phenanthrenes; phenylheptylamines; phenylpiperidines; morphinans; and benzomorphans. These compounds have pharmacologically diverse activities.

10 Some are strong agonists at the opioid receptors (e.g. morphine); others are moderate to mild agonists (e.g. codeine); still others exhibit mixed agonist-antagonist activity (e.g. nalbuphine); and yet others are partial agonists (e.g. nalorphine). While opioids are inexpensive and effective, serious and potentially life-threatening side effects occur with their use, most notably respiratory depression and muscle rigidity. In
15 addition, the doses of opioids which can be administered are limited by nausea, emesis, constipation, pruritis and urinary retention, often resulting in patients electing to receive suboptimal pain control rather than suffer these distressing side-effects. Moreover, patients often develop dependence on opioids and suffer opioid withdrawal symptoms upon discontinuation of treatment. The compounds and compositions of
20 this disclosure are useful in the treatment and prevention of side effects associated with opioid administration or treatment.

Headaches from mild to moderate hypertension and mild to moderate essential hypertension

25 The compounds and compositions of this disclosure are useful in the treatment and prevention of hypertension and the symptoms of hypertension. High blood pressure is a common condition in which the force of the blood against the artery walls is high enough that it may eventually cause health problems, such as heart disease. Hypertension puts strain on the heart, possibly leading to hypertensive heart disease

and coronary artery disease, and it is a major risk factor for stroke, aneurysms of the arteries, peripheral arterial disease, and chronic kidney disease. Symptoms of hypertension include dull headaches and dizzy spells.

Organ transplant rejection

- 5 The compounds and compositions of this disclosure are useful in treatment to help prevent the immune system from rejecting a new organ after an organ transplant.

Allodynia

The compounds and compositions of this disclosure are useful in the treatment or prevention of allodynia. Allodynia, or pain due to a stimulus that does not usually
10 provoke pain, is a prominent symptom in patients with neuropathic pain. Allodynia is seen in various peripheral neuropathies and central pain disorders, and affects 15—50% of patients with neuropathic pain. Allodynia is classified according to the sensory modality (touch, pressure, pinprick, cold, and heat) that is used to elicit the sensation.

15 *Fibromyalgia*

Fibromyalgia is a disorder characterized by widespread musculoskeletal pain accompanied by fatigue, sleep, memory and mood issues. Research indicates that fibromyalgia amplifies painful sensations by affecting the way the brain processes pain signals. Symptoms of fibromyalgia sometimes begin after a physical trauma,
20 surgery, infection, or significant psychological stress. In other cases, symptoms gradually accumulate over time with no single triggering event. Symptoms include: widespread pain on both sides of the body and above and below the waist, fatigue, cognitive difficulties, depression, headaches, and pain or cramping in the lower abdomen. The compounds and compositions of this disclosure are useful in the
25 treatment or prevention of fibromyalgia.

Fibromyalgia-ness

Fibromyalgia-ness is the tendency to respond to illness and psychosocial stress with fatigue and widespread pain. The compounds and compositions of this disclosure are useful in the treatment or prevention of fibromyalgia-ness.

5 *Central sensitization*

The compounds and compositions of this disclosure are useful in the treatment or prevention of central sensitization. Central or chronic sensitization is a condition of the nervous system that is associated with the development and maintenance of chronic pain. When central sensitization occurs, the nervous system goes through a process called “wind-up” and gets regulated in a persistent state of high reactivity. This persistent, or regulated, state of reactivity subsequently comes to maintain pain even after the initial injury might be healed.

Central sensitization has two main characteristics. Both involve a heightened sensitivity to pain and the sensation of touch. They are called ‘allodynia’ and ‘hyperalgesia.’ Allodynia occurs when a person experiences pain with things that are normally not painful. Hyperalgesia occurs when an actual painful stimulus is perceived as more painful than it should. With allodynia and hyperalgesia, the sensation of pain travels through the nervous system, which is in a persistent state of high reactivity, and the pain is registered in the brain as a heightened level of pain.

20 *Centralization*

The compounds and compositions of this disclosure are useful in the treatment or prevention of centralization. The pathogenesis of fibromyalgia is believed to involve sensitization of the central nervous system (CNS) to perceiving painful stimuli, which is termed “central sensitization” or “centralization”. Centralization leads to the perception of widespread pain. Pain of this type is termed, “central neuropathic pain” or “central pain”. Centralization also leads and to other symptoms, including visceral pain such as irritable bowel, tension-type headache, and migraine.

Regional pain syndrome

The compounds and compositions of this disclosure are useful in the treatment or prevention of regional pain syndrome. Regional pain syndrome or complex regional pain syndrome (CRPS) is a chronic pain condition most often affecting one of the limbs (arms, legs, hands, or feet), usually after an injury or trauma to that limb. CRPS is believed to be caused by damage to, or malfunction of, the peripheral and central nervous systems. CRPS is characterized by prolonged or excessive pain and mild or dramatic changes in skin color, temperature, and/or swelling in the affected area.

Temporomandibular joint syndrome (TMJ)

The compounds and compositions of this disclosure are useful in the treatment or prevention of temporomandibular joint syndrome (TMJ). TMJ disorders can cause pain in the jaw joint and in the muscles that control jaw movement. Signs and symptoms of TMJ disorders may include: pain or tenderness of the jaw, aching pain in and around the ear, difficulty chewing or discomfort while chewing, aching facial pain, locking of the jaw joint, and a clicking sound or grating sensation when opening the mouth or chewing.

Lower back pain

Lower back pain may be dull or sharp pain in the lower back. The pain may be in one small area or over a broad area and may include muscle spasms. Lower back pain may be caused by overuse, strain, or injury; aging; a herniated disc; arthritis; compression fractures; illness; a congenital spine problem; or other causes. The compounds and compositions of this disclosure are useful in the treatment or prevention of lower back pain.

Interstitial cystitis

Interstitial cystitis is a chronic condition in which one experiences bladder pressure, bladder pain, and sometimes pelvic pain, ranging from mild discomfort to severe pain.

Interstitial cystitis signs and symptoms include: pain in the pelvis or between the vagina and anus in women or between the scrotum and anus in men (perineum); chronic pelvic pain; a persistent, urgent need to urinate; frequent urination, often of small amounts, throughout the day and night; pain or discomfort while the bladder fills and relief after urinating; or pain during sexual intercourse. The compounds and compositions of this disclosure are useful in the treatment or prevention of interstitial cystitis.

Gulf War syndrome

A prominent condition affecting Gulf War Veterans is a cluster of medically unexplained chronic symptoms that can include fatigue, headaches, joint pain, indigestion, insomnia, dizziness, respiratory disorders, and memory problems. The compounds and compositions of this disclosure are useful in the treatment or prevention of Gulf War syndrome.

Visceral pain

The compounds and compositions of this disclosure are useful in the treatment or prevention of visceral pain. Visceral pain is caused by the activation of pain receptors in the chest, abdomen, or pelvic areas. Visceral pain is caused by problems with internal organs, such as the stomach, kidney, gallbladder, urinary bladder, and intestines. These problems include distension, perforation, inflammation, and impaction or constipation, which can cause associated symptoms, such as nausea, fever, malaise, and pain. Visceral pain is also caused by problems with abdominal muscles and the abdominal wall, such as spasm. Visceral pain is vague and not well localized and is usually described as pressure-like, deep squeezing, dull, or diffuse.

Kidney stones

Kidney stones form in the kidney and as they travel through the tubes of the urinary tract their movement may cause: sudden, severe pain that gets worse in waves; intense pain in the back, side, abdomen, groin, or genitals; nausea and vomiting; blood in the

urine (hematuria); and frequent and painful urination. The compounds and compositions of this disclosure are useful in the treatment of kidney stones.

Gout

The compounds and compositions of this disclosure are useful in the treatment of
5 gout. Gout occurs when urate crystals accumulate in joints, causing inflammation and
intense pain. The signs and symptoms of gout almost always occur suddenly and
include: intense joint pain, inflammation and redness, and decreased joint mobility.

Neuropathic pain

Neuropathic pain is a complex, chronic pain state that usually is accompanied by
10 tissue injury. With neuropathic pain, the nerve fibers themselves might be damaged,
dysfunctional, or injured, and these damaged nerve fibers send incorrect signals to
other pain centers. The impact of a nerve fiber injury includes a change in nerve
function both at the site of injury and areas around the injury. The compounds and
compositions of this disclosure are useful to treat or prevent neuropathic pain.

15 *Post-herpetic neuralgia*

The compounds and compositions of this disclosure are useful in the treatment or
prevention of post-herpetic neuralgia. Post-herpetic neuralgia is a complication of
shingles, which is caused by the chickenpox (herpes zoster) virus. Post-herpetic
neuralgia affects the nerve fibers and skin, and the burning pain associated with post-
20 herpetic neuralgia can be severe enough to interfere with sleep and appetite. The signs
and symptoms of post-herpetic neuralgia are generally limited to the area of the skin
where the shingles outbreak first occurred, and may include: pain, sensitivity to light
touch, itching and numbness, and weakness or paralysis.

25

Diabetic neuropathy

Diabetic neuropathy is a type of nerve damage that can occur with diabetes. Diabetic neuropathy most often damages nerves in the legs and feet. Symptoms of diabetic neuropathy can range from pain and numbness in the extremities, extreme sensitivity to touch, muscle weakness and difficulty walking, and serious foot problems to problems with the digestive system, urinary tract, blood vessels, and heart. The compounds and compositions of this disclosure are useful in the treatment or prevention of diabetic neuropathy.

Sickle cell pain

The compounds and compositions of this disclosure are useful in the treatment or prevention of sickle cell pain. Sickle cell disease causes red blood cells to form into a crescent shape, like a sickle. The sickle-shaped red blood cells break apart easily, causing anemia, and the damaged sickle red blood cells clump together and stick to the walls of blood vessels, blocking blood flow. This can cause severe pain and permanent damage to the brain, heart, lungs, kidneys, liver, bones, and spleen.

Priapism

Priapism is a prolonged erection of the penis. The unwanted, persistent erection is not caused by sexual stimulation or arousal, and priapism is usually painful. The compounds and compositions of this disclosure are useful in the treatment or prevention of priapism.

Nociceptive pain

Nociceptive pain is caused when special nerve endings—called nociceptors—are irritated. Nociceptors are the nerves which sense and respond to parts of the body which suffer from damage. They signal tissue irritation, impending injury, or actual injury. When activated, they transmit pain signals (via the peripheral nerves as well as the spinal cord) to the brain. The pain is typically well localized, constant, and often

with an aching or throbbing quality. The compounds and compositions of this disclosure are useful in the treatment or prevention of nociceptive pain.

Post-operative pain

5 Post-operative pain is pain that occurs after an operation. The compounds and compositions of this disclosure are useful in the treatment or prevention of post-operative pain.

Orthopedic injury pain

10 Orthopedic injuries are conditions involving the musculoskeletal system, and can include musculoskeletal trauma, sports injuries, degenerative diseases, or infections. Pain caused by orthopedic injury may be treated or prevented by the compounds and compositions of this disclosure.

Bunionectomy

15 A bunion is an enlargement of the joint at the base of the big toe and is comprised of bone and soft tissue. The pain of a bunion can make walking and other activities extremely difficult, leading to the need for bunionectomy, a surgical procedure to excise a bunion. The compounds and compositions of this disclosure are useful in the treatment before, during, or after bunionectomy.

Dental extraction

20 A dental extraction means having a tooth removed, usually because of disease, trauma, or crowding. The compounds and compositions of this disclosure are useful in the treatment before, during, or after dental extraction.

Pain after severed spinal cord injury

The compounds and compositions of this disclosure are useful in the treatment to alleviate pain associated with spinal cord injury.

Osteoarthritis

Osteoarthritis is the most common form of arthritis, affecting millions of people worldwide. It occurs when the protective cartilage on the ends of the bones wears down over time. Symptoms include: pain, tenderness, stiffness, loss of flexibility, 5 grating sensation, and bone spurs. The compounds and compositions of this disclosure are useful in the treatment of osteoarthritis.

Rheumatoid arthritis

The compounds and compositions of this disclosure are useful in the treatment of rheumatoid arthritis. Rheumatoid arthritis is a chronic inflammatory disorder that 10 typically affects the small joints in the hands and feet. Rheumatoid arthritis affects the lining of the joints, causing painful swelling that can eventually result in bone erosion and joint deformity. An autoimmune disorder, rheumatoid arthritis occurs when the immune system mistakenly attacks the body's own tissues. In addition to causing joint problems, rheumatoid arthritis sometimes can affect other organs of the body — such 15 as the skin, eyes, lungs, and blood vessels. Signs and symptoms of rheumatoid arthritis may include: tender, warm, swollen joints; morning stiffness; rheumatoid nodules; and fatigue, fever, and weight loss.

Lyme disease

Lyme disease is the most common tick-borne illness in North America and Europe. 20 Lyme disease is caused by the bacterium *Borrelia burgdorferi*, and deer ticks, which feed on the blood of animals and humans, can harbor the bacteria and spread it when feeding. Signs and symptoms of Lyme disease include: joint pain and neurological problems. The compounds and compositions of this disclosure are useful in the treatment of Lyme disease.

25

Parkinson's disease

The compounds and compositions of this disclosure are useful in the treatment of Parkinson's disease. Parkinson's disease is a neurodegenerative disorder of the central nervous system caused by the death of dopaminergic neurons in the substantia nigra.
5 Symptoms of Parkinson's disease may include tremor, bradykinesia, rigid muscles, impaired posture and balance, speech changes, and loss of automatic movements.

Pain associated with cancer

The compounds and compositions of this disclosure are useful in the treatment or prevention of pain associated with cancer. Cancer pain can result from the cancer
10 itself as the cancer grows into or destroys nearby tissues. As a tumor grows, it may put pressure on nerves, bones or organs, causing pain. Cancer pain may also not just be from the physical effect of the cancer on a region of the body, but also due to chemicals that the cancer may release in the region of the tumor.

Cancer treatments, such as chemotherapy, radiation and surgery, are another potential
15 source of cancer pain. Surgery can be painful, radiation may leave behind a burning sensation or painful scars, and chemotherapy can cause many potentially painful side effects, including mouth sores, diarrhea and nerve damage.

Pain associated with post-traumatic stress disorder (PTSD)

The compounds and compositions of this disclosure are useful in the treatment or
20 prevention of pain associated with post-traumatic stress disorder (PTSD). PTSD is a mental health condition that's triggered by a terrifying event — either experiencing it or witnessing it. Symptoms may include chronic pain, flashbacks, nightmares, and severe anxiety, as well as uncontrollable thoughts about the event.

The terms "treatment," "treating," and the like are used herein to generally mean
25 obtaining a desired pharmacologic and/or physiologic effect. "Treating" a condition or disease refers to curing as well as ameliorating at least one symptom of the

condition or disease, and includes administration of a composition which reduces the frequency of, or delays the onset of, symptoms of a medical condition in a subject in need relative to a subject which does not receive the composition. "Treatment" may also be use of any of the compounds and compositions of this disclosure as an
5 analgesic. In some embodiments, "treatment" may be use of any of the compounds and compositions of this disclosure to modulate an imidazoline-1 (I_1) receptor in a patient in need thereof. In some embodiments, "treatment" may be use of any of the compounds and compositions of this disclosure to modulate the I_1 receptor to reduce pain in a patient in need thereof. Without wishing to be bound by theory, in some
10 embodiments, "treatment" may be use of any of the compounds and compositions of this disclosure to activate the I_1 receptor to reduce pain in a patient in need thereof. In some embodiments, "treatment" may be use of any of the compounds and compositions of this disclosure to reduce pain through a pathway independent of the I_1 receptor (the Imidazoline-1 Receptor-Independent Isometheptene Pain Modulatory
15 pathway, or IRIPM pathway) in a patient in need thereof.

Merely to illustrate, "treatment" of a migraine headache may include, but is not limited to, an improvement in any of the following symptoms or conditions associated with migraine headache (or combination thereof): pain on one side or both sides of the head, sensitivity to light and sounds, nausea and vomiting, blurred vision, allodynia,
20 and lightheadness. "Treatment" of pain may include, but is not limited to, a reduction in the pain experienced by the patient. "Treatment" of fibromyalgia may include, but is not limited to, an improvement in any of the following symptoms or conditions associated with fibromyalgia (or combination thereof): widespread pain, fatigue, and cognitive difficulties (e.g., impaired ability to focus). "Treatment" of an inflammatory
25 disease or disorder may include, but is not limited to, an improvement in any of the following symptoms or conditions associated with an inflammatory disease or disorder (or combination thereof): pain, tension, redness, soreness, and irritation. "Treatment" of an allergic disease or disorder may include, but is not limited to, an improvement in any of the following symptoms or conditions associated with an allergic disease or

disorder (or combination thereof): asthma (extrinsic or intrinsic), asthma related sequelae including small and large airway hyperactivity, bronanaphylaxis, aspirin induced asthma, allergic airway inflammation, urticaria, and atopic dermatitis.

“Treatment” of a metabolic disease or disorder may include, but is not limited to, an
5 improvement in any of the following symptoms or conditions associated with a metabolic disease or disorder (or combination thereof): discomfort, pain, and inflammation. “Treatment” of a cardiovascular disease or disorder may include, but is not limited to, an improvement in any of the following symptoms or conditions associated with a cardiovascular disease or disorder (or combination thereof): chest
10 pain; shortness of breath; pain, numbness, weakness, or coldness in the arms or legs; and pain in the neck, jaw, throat, upper abdomen, or back. “Treatment” of a neurogenic vascular disease or a painful condition associated therewith may include, but is not limited to, an improvement in any of the following symptoms or conditions associated with a neurogenic vascular disease or a painful condition associated
15 therewith (or combination thereof): leg pain, leg weakness, tingling, fatigue, a sensation of heaviness, and weakness. “Treatment” of a headache or an episodic tension-type headache may include, but is not limited to, an improvement in any of the following symptoms or conditions associated with a headache or an episodic tension-type headache (or combination thereof): sharp pain, throbbing sensation, dull ache,
20 and nausea. “Treatment” of phantom limb pain may include, but is not limited to, an improvement in any of the following symptoms or conditions associated with phantom limb pain (or combination thereof): shooting, stabbing, or squeezing pain coming from the body part that is no longer there. “Treatment” of cramping may include, but is not limited to, an improvement in any of the following symptoms or conditions
25 associated with cramping (or combination thereof): skeletal muscle cramps, smooth muscle cramps, and muscle spasms. “Treatment” of a headache from mild to moderate hypertension and mild to moderate essential hypertension may include, but is not limited to, an improvement in any of the following symptoms or conditions associated with a headache from mild to moderate hypertension and mild to moderate
30 essential hypertension (or combination thereof): high blood pressure, dull headaches,

and dizzy spells. "Treatment" of a cognitive disorder may include, but is not limited to, an improvement in any of the following symptoms or conditions associated with a cognitive disorder (or combination thereof): amnesia, dementia, delirium, confusion, irritability and aggression, mood swings, trouble with language, anxiety and tension, and long-term memory loss. "Treatment" of organ transplant rejection may include, but is not limited to, an improvement in the body's acceptance of the organ.

"Treatment" of hot and cold flashes may include, but is not limited to, an improvement in any of the following symptoms or conditions associated with hot and cold flashes (or combination thereof): warmth, flushing, and perspiration.

"Treatment" of traumatic brain injury (TBI) may include, but is not limited to, an improvement in any of the following symptoms or conditions associated with TBI (or combination thereof): headache, vomiting or nausea, and convulsions or seizures.

"Treatment" of neurotoxicity may include, but is not limited to, an improvement in any of the following symptoms or conditions associated with neurotoxicity (or combination thereof): limb weakness or numbness; loss of memory, vision, and/or intellect; uncontrollable obsessive and/or compulsive behaviors; delusions; headache; cognitive and behavioral problems; and sexual dysfunction. "Treatment" of depression may include, but is not limited to, an improvement in any of the following symptoms or conditions associated with depression (or combination thereof): unexplained aches and pains, concentration problems, loss of energy, and anger or irritability. "Treatment" of psychic or psychological pain may include, but is not limited to, an improvement in any of the following symptoms or conditions associated with psychic or psychological pain (or combination thereof): emotional suffering and mental agony. "Treatment" of psychiatric pain may include, but is not limited to, an improvement in any of the following symptoms or conditions associated with psychiatric pain (or combination thereof): widespread pain and regional pain.

"Treatment" of schizophrenia may include, but is not limited to, an improvement in any of the following symptoms or conditions associated with schizophrenia (or combination thereof): hallucinations, delusions, depression, and social withdrawal.

"Treatment" of anxiety may include, but is not limited to, an improvement in any of

the following symptoms or conditions associated with anxiety (or combination thereof): heart palpitations or chest pain, trouble breathing, hot flashes or chills, and surge of overwhelming panic. "Treatment" of epilepsy may include, but is not limited to, an improvement in any of the following symptoms or conditions associated with
5 epilepsy (or combination thereof): seizures, violent shaking, tingling, and loss of alertness. "Treatment" of a stress disorder may include, but is not limited to, an improvement in any of the following symptoms or conditions associated with a stress disorder (or combination thereof): depression, anxiety, headaches, pain, and nausea. "Treatment" of excess sweating may include, but is not limited to, an improvement in
10 any of the following symptoms or conditions associated with excess sweating (or combination thereof): sweating and wetness. "Treatment" of a symptom related to drug withdrawal may include, but is not limited to, an improvement in any of the following symptoms or conditions associated with a symptom related to drug withdrawal (or combination thereof): anxiety, sweating, vomiting, diarrhea, irritability,
15 fatigue, shaking, sweating, nausea, insomnia, headache, and difficulty concentrating. "Treatment" of allodynia may include, but is not limited to, an improvement in any of the following symptoms or conditions associated with a symptom related to allodynia (or combination thereof): pain due to a stimulus that does not usually provoke pain. "Treatment" of fibromyalgia-ness may include, but is not limited to, an improvement
20 in any of the following symptoms or conditions associated with a symptom related to fibromyalgia-ness (or combination thereof): fatigue and widespread pain. "Treatment" of central sensitization may include, but is not limited to, an improvement in any of the following symptoms or conditions associated with a symptom related to central sensitization (or combination thereof): allodynia and
25 hyperalgesia. "Treatment" of centralization may include, but is not limited to, an improvement in any of the following symptoms or conditions associated with a symptom related to centralization (or combination thereof): irritable bowel, tension-type headache, and migraine. "Treatment" of regional pain syndrome may include, but is not limited to, an improvement in any of the following symptoms or conditions
30 associated with a symptom related to regional pain syndrome (or combination

thereof): swelling and pain in the arms, legs, hands, or feet. "Treatment" of temporomandibular joint syndrome (TMJ) may include, but is not limited to, an improvement in any of the following symptoms or conditions associated with a symptom related to TMJ (or combination thereof): pain or tenderness of the jaw, aching pain in and around the ear, difficulty chewing or discomfort while chewing, aching facial pain, locking of the jaw joint, and a clicking sound or grating sensation when opening the mouth or chewing. "Treatment" of lower back pain may include, but is not limited to, an improvement in any of the following symptoms or conditions associated with a symptom related to lower back pain (or combination thereof): pain in the lower back and muscles spasms in the lower back. "Treatment" of interstitial cystitis may include, but is not limited to, an improvement in any of the following symptoms or conditions associated with a symptom related to interstitial cystitis (or combination thereof): chronic pelvic pain; a persistent, urgent need to urinate; frequent urination, often of small amounts, throughout the day and night; pain or discomfort while the bladder fills and relief after urinating; and pain during sexual intercourse. "Treatment" of Gulf War syndrome may include, but is not limited to, an improvement in any of the following symptoms or conditions associated with a symptom related to Gulf War syndrome (or combination thereof): fatigue, headaches, and joint pain. "Treatment" of visceral pain may include, but is not limited to, an improvement in any of the following symptoms or conditions associated with a symptom related to visceral pain (or combination thereof): pressure-like, deep squeezing, dull, or diffuse pain in the chest, abdomen, or pelvic areas. "Treatment" of kidney stones may include, but is not limited to, an improvement in any of the following symptoms or conditions associated with a symptom related to kidney stones (or combination thereof): intense pain in the back, side, abdomen, groin, or genitals, and nausea and vomiting. "Treatment" of gout may include, but is not limited to, an improvement in any of the following symptoms or conditions associated with a symptom related to gout (or combination thereof): intense joint pain, inflammation, and redness, and decreased joint mobility. "Treatment" of neuropathic pain may include, but is not limited to, an improvement in any of the following symptoms or

conditions associated with a symptom related to neuropathic pain (or combination thereof): shooting and burning pain, tingling, and numbness. "Treatment" of post-herpetic neuralgia may include, but is not limited to, an improvement in any of the following symptoms or conditions associated with a symptom related to post-herpetic neuralgia (or combination thereof): pain, sensitivity to light touch, itching and numbness, and weakness or paralysis. "Treatment" of diabetic neuropathy may include, but is not limited to, an improvement in any of the following symptoms or conditions associated with a symptom related to diabetic neuropathy (or combination thereof): pain and numbness in the extremities, extreme sensitivity to touch, muscle weakness, and difficulty walking. "Treatment" of sickle cell pain may include, but is not limited to, an improvement in any of the following symptoms or conditions associated with a symptom related to sickle cell pain (or combination thereof): pain in the chest, abdomen, joints, and bones. "Treatment" of priapism may include, but is not limited to, an improvement in any of the following symptoms or conditions associated with a symptom related to priapism (or combination thereof): unwanted, persistent and painful erection. "Treatment" of nociceptive pain may include, but is not limited to, an improvement in any of the following symptoms or conditions associated with a symptom related to nociceptive pain (or combination thereof): aching or throbbing pain. "Treatment" of post-operative pain may include, but is not limited to, an improvement in any of the following symptoms or conditions associated with a symptom related to post-operative pain (or combination thereof): pain, swelling, and irritation after an operation. "Treatment" of orthopedic injury pain may include, but is not limited to, an improvement in any of the following symptoms or conditions associated with a symptom related to orthopedic injury pain (or combination thereof): pain, swelling, and irritation after an orthopedic injury. "Treatment" of bunionectomy may include, but is not limited to, an improvement in any of the following symptoms or conditions associated with a symptom related to bunionectomy (or combination thereof): pain, swelling, and irritation after a bunionectomy. "Treatment" of dental extraction may include, but is not limited to, an improvement in any of the following symptoms or conditions associated with a

symptom related to dental extraction (or combination thereof): pain, swelling, and irritation after a dental extraction. "Treatment" of pain after severed spinal cord injury may include, but is not limited to, an improvement in any of the following symptoms or conditions associated with a symptom related to pain after severed spinal cord injury (or combination thereof): pain and irritation after severed spinal cord injury.

5 "Treatment" of osteoarthritis may include, but is not limited to, an improvement in any of the following symptoms or conditions associated with a symptom related to osteoarthritis (or combination thereof): pain, tenderness, stiffness, loss of flexibility, grating sensation, and bone spurs. "Treatment" of rheumatoid arthritis may, but is not limited to, include an improvement in any of the following symptoms or conditions associated with a symptom related to rheumatoid arthritis (or combination thereof):

10 tender, warm, swollen joints; morning stiffness; rheumatoid nodules; and fatigue, fever and weight loss. "Treatment" of Lyme disease may include, but is not limited to, an improvement in any of the following symptoms or conditions associated with a symptom related to Lyme disease (or combination thereof): joint pain and neurological problems. "Treatment" of Parkinson's disease may include, but is not limited to, an improvement in any of the following symptoms or conditions associated with a symptom related to Parkinson's disease (or combination thereof): tremor and muscle rigidity.

15 "Treatment" of pain associated with cancer may include, but is not limited to, an improvement in any of the following symptoms or conditions associated with a symptom related to pain associated with cancer (or combination thereof): chronic pain, pain from nerve damage, and burning sensation. "Treatment" of pain associated with post-traumatic stress disorder (PTSD) may include, but is not limited to, an improvement in any of the following symptoms or conditions associated with a symptom related to pain associated with post-traumatic stress disorder (PTSD) (or

20 combination thereof): chronic pain and headaches.

25

Improvements in any of these symptoms can be readily assessed according to standard methods and techniques known in the art. Symptoms are not limited to those listed above and other symptoms may also be monitored in order to determine the

effectiveness of treatment. The population of subjects treated by the method of this disclosure includes subjects suffering from the undesirable condition or disease, as well as subjects at risk for development of the condition or disease. Without wishing to be bound by theory, administering any of the compounds and compositions described herein may have any one or more of the following effects: analgesia; alleviation of widespread pain; decrease in pain from headaches, tension-type headaches, and migraines; reduction in depression, seizures, convulsions, and fatigue; decrease in inflammation, pain, tension, redness, soreness, and irritation; relief from asthma, atopic dermatitis, chest pain, shortness of breath, and numbness; lowered blood pressure; decreased cramping; reduction of leg pain, leg weakness, tingling, fatigue, and weakness; improvement in amnesia, dementia, delirium, confusion, irritability and aggression, mood swings, trouble with language, and long-term memory loss; reductions in hot and cold flashes and excessive sweating; reduced muscle rigidity associated with Parkinson's disease; and relief of pain associated with cancer, PTSD, rheumatoid arthritis, allodynia, kidney stones, gout, fibromyalgia, and fibromyalgia-ness. It should be noted that any of the compounds and compositions described herein are useful in any of the methods described herein. Effects are not limited to those listed above and other effects may also be noted during treatment.

The term "preventing" is art-recognized and includes stopping a disease, disorder, or condition from occurring in a subject, which may be predisposed to the disease, disorder and/or condition but has not yet been diagnosed as having it. Preventing a condition related to a disease includes stopping the condition from occurring after the disease has been diagnosed but before the condition has been diagnosed.

A "patient," "subject," or "host" to be treated by the disclosed methods may mean either a human or non-human animal, such as a mammal, a fish, a bird, a reptile, or an amphibian. Thus, the subject of the herein disclosed methods can be a human, non-human primate, horse, pig, rabbit, dog, sheep, goat, cow, cat, guinea pig, or rodent. The term does not denote a particular age or sex. Thus, adult and newborn subjects, as well as fetuses, whether male or female, are intended to be covered. In some

embodiments, the subject is a mammal. In some embodiments, the subject is a human. A patient refers to a subject afflicted with a disease or disorder.

The term "therapeutic" treatment is art-recognized and includes administration to the host of one or more of the subject compositions. If treatment is administered after
5 manifestation of the unwanted condition, the treatment is therapeutic (i.e., it is intended to diminish, ameliorate, or stabilize the existing unwanted condition or side effects thereof).

The terms "therapeutic agent," "drug," "medicament" and "bioactive substance" are art-recognized terms and include molecules and other agents that are biologically,
10 physiologically, or pharmacologically active substances that act locally or systemically in a patient or subject to treat a disease or condition. The terms include without limitation pharmaceutically acceptable salts thereof and prodrugs. Such agents may be acidic, basic, or salts; they may be neutral molecules, polar molecules, or molecular complexes capable of hydrogen bonding; they may be prodrugs in the
15 form of ethers, esters, amides and the like that are biologically activated when administered into a patient or subject.

The term "therapeutically effective dose" refers to a dose that produces the desired effect for which it is administered. The exact dose will depend on the purpose of the treatment, and will be ascertainable by one skilled in the art using known techniques
20 (see, e.g., Lloyd (1999) The Art, Science and Technology of Pharmaceutical Compounding).

For any of the methods described herein, the embodiments of this disclosure contemplate the use of any of the compounds and/or compositions, or mixtures of them, described throughout the application. In addition, in various embodiments of
25 any of the methods described herein, combinations of any step or steps of one method with any step or steps from another method may be employed.

Combination Therapies

Any of the compounds and compositions of this disclosure are useful in combination with other therapeutics. In some embodiments, for example, any of the compounds and compositions of this disclosure, or mixtures of them, are useful as analgesics. In
5 some embodiments, for example, any of the compounds and compositions of this disclosure, or mixtures of them, are useful in combination with other therapeutics to treat pain; an inflammatory disease or disorder, an allergic disease or disorder, a metabolic disease, a cardiovascular disease or disorder, a neurogenic vascular disease or a painful condition associated with any of the foregoing conditions; an episodic
10 tension-type headache; a migraine headache; a headache; cramping; a cognitive disorder; a tension or migraine headache due to a vascular, neurovascular, or neurogenic disorder or dysfunction during a menstrual cycle episode; a tension or migraine headache due to a vascular, neurovascular, or neurogenic disorder or dysfunction during a migraine episode; a headache from mild to moderate
15 hypertension; mild to moderate essential hypertension; organ transplant rejection; hot and cold flashes; traumatic brain injury (TBI); neurotoxicity; psychic pain; psychological pain; psychiatric pain; depression; schizophrenia; anxiety; epilepsy; a stress disorder; excess sweating; a symptom related to drug withdrawal; allodynia; fibromyalgia; fibromyalgia-ness; central sensitization; centralization; regional pain
20 syndrome; temporomandibular joint syndrome (TMJ); lower back pain; interstitial cystitis; Gulf War syndrome; visceral pain; kidney stones; gout; neuropathic pain; post-herpetic neuralgia; diabetic neuropathy; sickle cell pain; priapism; nociceptive pain; post-operative pain; orthopedic injury pain; phantom limb pain; bunionectomy; dental extraction; pain after severed spinal cord injury; osteoarthritis; rheumatoid
25 arthritis; Lyme disease; Parkinson's disease; pain associated with cancer; opioid-induced constipation; an opioid withdrawal symptom; or pain associated with post-traumatic stress disorder (PTSD), or a combination of any of the foregoing conditions.

In some embodiments, the phrase "combination therapy" embraces the administration of the any of the compounds and compositions described herein, or mixtures of them,

and an additional therapeutic agent, or mixtures of them, as part of a specific treatment regimen intended to provide a beneficial effect from the co-action of these therapeutic agents. Administration of these therapeutic agents in combination typically is carried out over a defined time period (usually minutes, hours, days or weeks depending upon the combination selected). “Combination therapy” is intended to embrace administration of these therapeutic agents in a sequential manner, that is, wherein each therapeutic agent is administered at a different time, as well as administration of these therapeutic agents, or at least two of the therapeutic agents, in a substantially simultaneous manner. Substantially simultaneous administration can be accomplished, for example, by administering to the subject a single capsule having a fixed ratio of each therapeutic agent or in multiple, single capsules for each of the therapeutic agents. Sequential or substantially simultaneous administration of each therapeutic agent can be effected by any appropriate route including, but not limited to, oral routes, intravenous routes, intramuscular routes, and direct absorption through mucous membrane tissues. The therapeutic agents can be administered by the same route or by different routes. For example, a first therapeutic agent of the combination selected may be administered by intravenous injection while the other therapeutic agents of the combination may be administered orally. Alternatively, for example, all therapeutic agents may be administered orally or all therapeutic agents may be administered by intravenous injection. The sequence in which the therapeutic agents are administered is not narrowly critical. “Combination therapy” also can embrace the administration of the therapeutic agents as described herein in further combination with other biologically active ingredients (such as, but not limited to, a second and different therapeutic agent) and non-drug therapies (such as, but not limited to, surgery or radiation). Where the combination therapy further comprises radiation treatment, the radiation treatment may be conducted at any suitable time so long as a beneficial effect from the co-action of the combination of the therapeutic agents and radiation treatment is achieved. For example, in appropriate cases, the beneficial effect is still achieved when the radiation treatment is temporally removed from the administration of the therapeutic agents, perhaps by days or even weeks.

In another example of combination therapy, one or more compounds and compositions of this disclosure can be used as part of a therapeutic regimen combined with one or more additional treatment modalities. By way of example, such other treatment modalities include, but are not limited to, dietary therapy, occupational therapy, 5 physical therapy, ventilator supportive therapy, massage, acupuncture, acupressure, mobility aids, assistance animals, speech therapy, language therapy, educational therapy, psychological therapy, occupational therapy, and the like.

In some embodiments, the mammalian disease treated by the combination therapy can include any of the conditions described herein. Besides being useful for human 10 treatment, the combination therapy is also useful for veterinary treatment of companion animals, exotic and farm animals, including rodents, horses, dogs, and cats.

In some embodiments, the therapeutic agents administered in combination therapy simultaneously, separately, or sequentially with any of the compounds and 15 compositions of this disclosure, or mixtures thereof, can comprise: acetaminophen, a non-steroidal anti-inflammatory drug (NSAID), ibuprofen, naprosyn, a cyclooxygenase-2 inhibitor, aspirin, caffeine, dichloralphenazone, a triptan, an antidepressant, a serotonin–norepinephrine reuptake inhibitor (SNRI), and a gabapentinoid or mixtures thereof.

20 In some embodiments, the therapeutic agents administered simultaneously, separately, or sequentially in combination therapy with any of the compounds and compositions of this disclosure or mixtures thereof, can comprise: a chemotherapeutic drug, an antiproliferative agent, an anti-inflammatory agent, a corticosteroid, an anti-asthmatic agent, an anti-allergic agent, an immunosuppressive agent, an immunomodulatory 25 agent, a cardiovascular disease treatment agent, an anti-diabetic agent, a blood disorder treatment agent, a nerve growth factor receptor antagonist, a sodium channel blocker, a CYP2D6 inhibitor, and a TNF-alpha inhibitor or mixtures thereof.

In some embodiments, the therapeutic agents administered simultaneously, separately, or sequentially in combination therapy with any of the compounds and compositions of this disclosure or mixtures thereof can comprise one or more opiates.

Chemotherapeutic agents include, but are not limited to, mechlorethamine, chlorambucil, cyclophosphamide, ifosfamide, melphalan, streptozocin, carmustine (BCNU), lomustine, busulfan, dacarbazine (DTIC), temozolomide, thiotepa, 5
altretamine (hexamethylmelamine), cisplatin, carboplatin, oxalplatin, 5-fluorouracil (5-FU), 6-mercaptopurine (6-MP), capecitabine, cladribine, clofarabine, cytarabine, floxuridine, fludarabine, gemcitabine, hydroxyurea, methotrexate, pemetrexed, 10
pentostatin, thioguanine, daunorubicin, doxorubicin, epirubicin, idarubicin, actinomycin-D, bleomycin, mitomycin-C, mitoxantrone, topotecan, irinotecan (CPT-11), etoposide (VP-16), teniposide, paclitaxel, docetaxel, ixabepilone, vinblastine, vincristine, vinorelbine, estramustine, prednisone, methylprednisolone, dexamethasone, L-asparaginase, and bortezomib.

15 Antiproliferative agents include, but are not limited to, mycophenolate mofetil, azathioprine, sirolimus, cyclophosphamide, leflunomide, tanshinone, spiromustine, aclarubicin, dactinomycin, goserelin, loxiglumide, mepitiostane, amphetamine, amsacrine, caracemide, carmethizole hydrochloride, procarbazine, proglumide, teniposide, thaliblastine, rapamycin, rhizoxin, rodorubicin, sibanomycin, bestrabucil, 20
budotitane, cyclopentyl cytosine, cytarabine phosphate stearate, cytarabine conjugates, cytarabine ocfosfate, dezaguanine, dideoxycytidine, dideoxyguanosine, didox, doxifluridine, fazarabine, finasteride, floxuridine, fludarabine phosphate, toremifene, and uricytin.

Anti-inflammatory agents include, but are not limited to, non-steroidal anti- 25
inflammatory drugs (NSAIDs) such as ibuprofen and naprosyn (naproxen); TNF- α blockers or inhibitors such as infliximab, adalimumab, and etanercept; IL-RA; azathioprine; cyclophosphamide; sulfasalazine; cyclooxygenase-2 inhibitors such as aspirin; caffeine; acetaminophen; ketoprofen; dichloralphenzone, triptans such as

sumatriptan succinate; dexibuprofen; fenoprofen; dexketoprofen; flurbiprofen;
oxaprozin; loxoprofen; indomethacin; tolmetin; sulindac; droxicam; lornoxicam;
isoxicam; mefenamic acid; cortisol; corticosteroids such as cortisone, hydrocortisone,
prednisone, prednisolone, fludrocortisone, methylprednisone, dexamethasone,
5 betamethasone, and triamcinolone; and meclofenamic acid.

Gabapentinoids include, but are not limited to, gabapentin, pregabalin, gabapentin
enacarbil, atagabalin, 4-methylpregabalin, and PD-217,014.

Antidepressants include, but are not limited to, selective serotonin reuptake inhibitors
(SSRIs) such as fluoxetine, paroxetine, sertraline, citalopram, and escitalopram;
10 serotonin and norepinephrine reuptake inhibitors (SNRIs) such as duloxetine,
venlafaxine, desvenlafaxine, tramadol, tapentadol, and levomilnacipran;
norepinephrine and dopamine reuptake inhibitors (NDRIs) such as Bupropion;
trazodone; mirtazapine; vortioxetine; vilazodone; tricyclic antidepressants such as
imipramine, nortriptyline, amitriptyline, doxepin, trimipramine, desipramine, and
15 protriptyline; and monoamine oxidase inhibitors (MAOIs) such as tranylcypromine,
phenelzine, and isocarboxazid.

Sodium channel blockers include, but are not limited to, lidoderm, lidocaine,
lacosamide, and ralfinamide.

Nerve growth factor receptor antagonists include, but are not limited to, K252a,
20 tanezumab, REGN₄₇₅, ARRY-470, AR-786, and AR-256.

CYP2D6 inhibitors include, but are not limited to, fluoxetine, paroxetine, bupropion,
quinidine, cinacalcet, ritonavir, sertraline, duloxetine, and terbinafine. Not to be
bound by theory, but in some embodiments a compound of this disclosure is
metabolized by CYP2D6. In such embodiments, a CYP2D6 inhibitor may slow
25 metabolism of a compound of this disclosure.

Anti-asthmatic agents include, but are not limited to, beclometasone dipropionate,
budesonide, chromones, corticosteroids, fenoterol, fluticasone, formoterol,

hexoprenaline, isoprenaline, leukotrienes, mometasone, omalizumab, pirquinozol, pitrakinra, prednisone, reproterol, salbutamol, salmeterol, terbutaline, and tranilast.

Anti-allergic agents include, but are not limited to, astemizole, beclomethasone, brompheniramine, carbinoxamine, cetirizine, chlorpheniramine, clemastine,
 5 corticotrophin, desloratadine, dimethindene, diphenhydramine, doxylamine, ebastine, embramine, epinephrine, fexofenadine, flunisolide, hydrocortisone, hydroxyzine, ketamine, ketotifen, levocetirizine, loratadine, methdilazine, mizolastine, phenylephrine, pseudoephedrine, rupatadine, terfenadine, triamcinolone, trimeprazine, and xylometazoline.

10 Immunosuppressive agents include, but are not limited to, cyclosporine, tacrolimus, riloncept, tocilizumab, anakinra, ustekinumab, canakinumab, basiliximab, siltuximab, daclizumab, omalizumab, methotrexate, alefacept, sirolimus, efalizumab, dimethyl fumarate, mycophenolic acid, fingolimod, natalizumab, belimumab, everolimus, teriflunomide, leflunomide, abatacept, vedolizumab, belatacept, muromonab-cd3,
 15 eculizumab, infliximab, adalimumab, etanercept, certolizumab, and golimumab.

Immunomodulatory agents include, but are not limited to, thalidomide, pomalidomide, lenalidomide, apremilast, azathioprine, 6-mercaptopurine (6-MP), cyclosporine, tacrolimus, and methotrexate.

Cardiovascular disease treatment agents include, but are not limited to, ACE
 20 inhibitors, beta-blockers, diuretics, nitrates, calcium channel blockers, statins, benazepril, ramipril, captopril, losartan, valsartan, enoxaparin, heparin, warfarin, aspirin, clopidogrel, prasugel, metoprolol, labetalol, propranolol, amlodipine, diltiazem, nifedipine, statins (e.g., atorvastatin, pravastatin sodium, simvastatin, digoxin nesiritide, and hydralyzine), bile acid resins (e.g. cholestyramine), cholesterol
 25 absorption inhibitors (e.g. ezetimibe), fibric acid derivatives (e.g., fenofibrate), and nicotinic acid (e.g., niacin).

Anti-diabetic agents include, but are not limited to, insulin, exenatide, liraglutide, pramlintide, glitazones, sulfonylureas (e.g., chlorpropamide, glimepride, glipizide,

glyburide, tolazamide, and acetahexamide), metformin, alpha-glucosidase inhibitors, thiazolidinediones (e.g., rosiglitazone, pioglitazone, and troglitazone), saxagliptin, sitagliptin, linagliptin, alogliptin, albiglutide, dulaglutide, repaglinide, nateglinide, metformin, empagliflozin, canagliflozin, and dapagliflozin.

- 5 Blood disorder treatment agents include, but are not limited to, iron pills, Epogen, Procrit, prednisone, blood transfusion, chemotherapeutic agents, and heparin.

Opiates include, but are not limited to, codeine, thebaine, hydrocodone, hydromorphone, morphine, oxycodone, oxymorphone, and tramadol.

- 10 Such combination products employ any of the compounds and compositions of this disclosure or mixtures thereof within the dosage range described herein and the other pharmaceutically active compound or compounds within approved dosage ranges and/or the dosage described in the publication reference.

- 15 In some embodiments, any of the compounds and compositions described herein or mixtures thereof can allow the combination therapeutic agents and/or compounds and compositions described herein or mixtures thereof to be administered at a low dose, that is, at a dose lower than has been conventionally used in clinical situations.

Alternatively, the methods and combinations of this disclosure maximize the therapeutic effect at higher doses.

- 20 In some embodiments, when administered as a combination, the therapeutic agents can be formulated as separate compositions which are given at the same time or different times, or the therapeutic agents can be given as a single composition.

- 25 In some embodiments, the compounds and compositions of this disclosure, or mixtures thereof, are therapeutic in combination with existing therapies directed to hypertension and tissue swelling. In this context, a combination is defined as a fixed proportion of the compound or composition of this disclosure and another non-imidazoline-type compound or compounds to be administered to the patient simultaneously, as in a kit, or at separate and distinct, or predetermined time periods or

time intervals. The inhibitor compound or compounds need not be restricted to small molecular compounds such as those of this disclosure. The non-imidazoline inhibitor compound may be a biologic such as an antibody, receptor, binding protein, lipid, sugar or the like.

5 **Pharmaceutical Compositions and Modes of Administration**

The compounds and compositions of this disclosure are useful to treat an individual in need thereof. In some embodiments, the individual is a mammal such as a human, or a non-human mammal. When administered to an animal, such as a human, the compounds or mixtures thereof are preferably administered as a pharmaceutical
10 composition comprising, for example, one or more compounds and a pharmaceutically acceptable carrier.

The phrase "pharmaceutically acceptable carrier" as used herein means a pharmaceutically acceptable material, composition or vehicle, such as a liquid or solid filler, diluent, excipient, solvent or encapsulating material. Each carrier must be
15 "acceptable" in the sense of being compatible with the other ingredients of the formulation and not injurious to the patient. Some examples of materials which can serve as pharmaceutically acceptable carriers include: (1) sugars, such as lactose, glucose and sucrose; (2) starches, such as corn starch and potato starch; (3) cellulose, and its derivatives, such as sodium carboxymethyl cellulose, ethyl cellulose and
20 cellulose acetate; (4) powdered tragacanth; (5) malt; (6) gelatin; (7) talc; (8) excipients, such as cocoa butter and suppository waxes; (9) oils, such as peanut oil, cottonseed oil, safflower oil, sesame oil, olive oil, corn oil and soybean oil; (10) glycols, such as propylene glycol; (11) polyols, such as glycerin, sorbitol, mannitol and polyethylene glycol; (12) esters, such as ethyl oleate and ethyl laurate; (13) agar;
25 (14) buffering agents, such as magnesium hydroxide and aluminum hydroxide; (15) alginic acid; (16) water (including pyrogen-free water); (17) isotonic saline; (18) Ringer's solution; (19) ethyl alcohol; (20) phosphate buffer solutions; (21)

cyclodextrins and cyclodextrin derivatives; and (22) other non-toxic compatible substances employed in pharmaceutical compositions.

Pharmaceutical compositions of this disclosure can contain physiologically acceptable agents that act, for example, to stabilize, increase solubility or to increase the
5 absorption of a compound such as a compound of this disclosure. Such physiologically acceptable agents include, for example, carbohydrates, such as glucose, sucrose or dextrans, antioxidants, such as ascorbic acid or glutathione, chelating agents, low molecular weight proteins or other stabilizers or excipients. The choice of a pharmaceutically acceptable carrier, including a physiologically acceptable
10 agent, depends, for example, on the route of administration of the composition. The pharmaceutical compositions of this disclosure can be a self-emulsifying drug delivery system or a self-microemulsifying drug delivery system.

The phrase "pharmaceutically acceptable" is employed herein to refer to those compounds, materials, compositions, and/or dosage forms which are, within the scope
15 of sound medical judgment, suitable for use in contact with the tissues of human beings and animals without excessive toxicity, irritation, allergic response, or other problem or complication, commensurate with a reasonable benefit/risk ratio.

The pharmaceutical compositions and compounds described herein can be administered to a subject by any of a number of routes of administration including, for
20 example, orally (for example, aqueous or non-aqueous solutions or suspensions, tablets, capsules (including sprinkle capsules and gelatin capsules), boluses, powders, granules, pastes for application to the tongue); absorption through the oral mucosa (e.g., sublingually); buccally; anally, rectally or vaginally (for example, as a pessary, cream or foam); parenterally (including intramuscularly, intravenously,
25 subcutaneously or intrathecally as, for example, a sterile solution or suspension); nasally; intraperitoneally; subcutaneously; transdermally (for example as a patch applied to the skin); intrathoracically, epidurally, intracerebroventricularly; and topically (for example, as a cream, ointment or spray applied to the skin, or as an eye

drop). The compounds and compositions, or mixtures thereof, may also be formulated for inhalation (insufflation) and for injection into the joints. In some embodiments, the compounds and compositions, or mixtures thereof, may be simply dissolved or suspended in sterile water. Details of appropriate routes of administration and
5 compositions suitable for same can be found in, for example, U.S. Pat. Nos. 6,110,973, 5,763,493, 5,731,000, 5,541,231, 5,427,798, 5,358,970 and 4,172,896, as well as in patents cited therein, all of which are incorporated herein by reference.

To prepare solid dosage forms for oral administration (capsules (including sprinkle capsules and gelatin capsules), tablets, pills, dragees, powders, granules, and the like),
10 the compounds described herein are mixed with one or more pharmaceutically acceptable carriers, such as sodium citrate or dicalcium phosphate, and/or any of the following: (1) fillers or extenders, such as starches, lactose, sucrose, glucose, mannitol, and/or silicic acid; (2) binders, such as, for example, carboxymethylcellulose, alginates, gelatin, polyvinyl pyrrolidone, sucrose, and/or
15 acacia; (3) humectants, such as glycerol; (4) disintegrating agents, such as agar-agar, calcium carbonate, potato or tapioca starch, alginic acid, certain silicates, and sodium carbonate; (5) solution retarding agents, such as paraffin; (6) absorption accelerators, such as quaternary ammonium compounds; (7) wetting agents, such as, for example, cetyl alcohol and glycerol monostearate; (8) absorbents, such as kaolin and bentonite
20 clay; (9) lubricants, such as talc, calcium stearate, magnesium stearate, solid polyethylene glycols, sodium lauryl sulfate, and mixtures thereof; (10) complexing agents, such as, modified and unmodified cyclodextrins; and (11) coloring agents. In the case of capsules (including sprinkle capsules and gelatin capsules), tablets and pills, the pharmaceutical compositions may also comprise buffering agents. Solid
25 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 sugars, as well as high molecular weight polyethylene glycols and the like.

A tablet may be made by compression or molding, optionally with one or more accessory ingredients. Compressed tablets may be prepared using binder (for

example, gelatin or hydroxypropylmethyl cellulose), lubricant, inert diluent, preservative, disintegrant (for example, sodium starch glycolate or cross-linked sodium carboxymethyl cellulose), surface-active, or dispersing agent. Molded tablets may be made by molding in a suitable machine a mixture of the powdered compound moistened with an inert liquid diluent.

The tablets, and other solid dosage forms of the pharmaceutical compositions of this disclosure, such as capsules (including sprinkle capsules and gelatin capsules), pills, and granules, may optionally be scored or prepared with coatings and shells, such as enteric coatings and other coatings well known in the pharmaceutical-formulating art. They may also be formulated so as to provide slow or controlled release of the compound of this disclosure therein using, for example, hydroxypropylmethyl cellulose in varying proportions to provide the desired release profile, other polymer matrices, liposomes, and/or microspheres. They may be sterilized by, for example, filtration through a bacteria-retaining filter, or by incorporating sterilizing agents in the form of sterile solid compositions that can be dissolved in sterile water, or some other sterile injectable medium immediately before use. The compositions of this disclosure may also optionally contain opacifying agents and may be of a composition that they release the active ingredient(s) only, or preferentially, in a certain portion of the gastrointestinal tract, optionally, in a delayed manner. Examples of embedding compositions that can be used include polymeric substances and waxes. The compounds and compositions of this disclosure, or mixtures thereof, can also be in micro-encapsulated form, if appropriate, with one or more of the above-described excipients.

Liquid dosage forms useful for oral administration include pharmaceutically acceptable emulsions, lyophiles for reconstitution, microemulsions, solutions, suspensions, syrups, and elixirs. In addition to the compound of this disclosure, the liquid dosage forms may contain inert diluents commonly used in the art, such as, for example, water or other solvents, cyclodextrins and derivatives thereof, solubilizing agents and emulsifiers, such as ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl

acetate, benzyl alcohol, benzyl benzoate, propylene glycol, 1,3-butylene glycol, oils (in particular, cottonseed, groundnut, corn, germ, olive, castor and sesame oils), glycerol, tetrahydrofuryl alcohol, polyethylene glycols, and fatty acid esters of sorbitan, and mixtures thereof. Besides inert diluents, the oral compositions of this disclosure can also include adjuvants such as sweetening, flavoring, and perfuming agents. Formulations of the pharmaceutical compositions of this disclosure for administration to the mouth may be presented as a mouthwash, or an oral spray, or an oral ointment.

For example, excipients for oral and sublingual formulations of R-isometheptene mucate, R-isometheptene malate, R-isometheptene maleate, R-isometheptene tartrate and other salts of R-isometheptene (salts of compound **8**) include alpha-cyclodextrin and hydroxypropyl-beta cyclodextrin. Excipients for intravenous, intramuscular and subcutaneous formulations include hydroxypropyl-beta cyclodextrin. In some embodiments, the R-isometheptene salt is dissolved with at least 1 molar equivalent of cyclodextrin in water or a suitable mixed aqueous solvent prior to removal of solvent to ensure complete complexation. Without wishing to be bound by theory, the cyclodextrin may increase solubility and stability of the R-isometheptene through complexation of the R-isometheptene cation inside the tube-shaped cyclodextrin molecule.

Formulations of the compounds, pharmaceutical compositions, and mixtures thereof as described herein for rectal, vaginal, or urethral administration may be presented as a suppository, which may be prepared by mixing one or more compounds with one or more suitable nonirritating excipients or carriers comprising, for example, cocoa butter, polyethylene glycol, a suppository wax or a salicylate, and which is solid at room temperature, but liquid at body temperature and, therefore, will melt in the rectum or vaginal cavity and release the active compound.

Dosage forms for topical or transdermal administration include powders, sprays, ointments, pastes, creams, lotions, gels, solutions, patches, and inhalants. The

compound of this disclosure or mixtures thereof may be mixed under sterile conditions with a pharmaceutically acceptable carrier, and with any preservatives, buffers, or propellants that may be required. The ointments, pastes, creams, and gels may contain, in addition to one or more compounds and compositions of this disclosure, 5 excipients, such as animal and vegetable fats, oils, waxes, paraffins, starch, tragacanth, cellulose derivatives, polyethylene glycols, silicones, bentonites, perfuming agents, coloring agents, silicic acid, talc, and zinc oxide, or mixtures thereof.

Powders and sprays can contain, in addition to one or more compounds and compositions of this disclosure, excipients such as lactose, talc, silicic acid, aluminum 10 hydroxide, calcium silicates, and polyamide powder, or mixtures of these substances. Sprays can additionally contain customary propellants, such as chlorofluorohydrocarbons and volatile unsubstituted hydrocarbons, such as butane and propane.

Transdermal patches have the added advantage of providing controlled delivery of one 15 or more compounds or compositions of this disclosure to the body. Such dosage forms can be made by dissolving or dispersing the compound of this disclosure in the proper medium. Absorption enhancers can also be used to increase the flux of the compound across the skin. The rate of such flux can be controlled by either providing a rate controlling membrane or dispersing the compound in a polymer matrix or gel.

20 Ophthalmic compositions, eye ointments, powders, solutions and the like, are also contemplated as being within the scope of this disclosure. Exemplary ophthalmic compositions are described in U.S. Publication Nos. 2005/0080056, 2005/0059744, 2005/0031697 and 2005/004074 and U.S. Patent No. 6,583,124, the contents of which are incorporated herein by reference. If desired, liquid ophthalmic compositions have 25 properties similar to that of lacrimal fluids, aqueous humor or vitreous humor or are compatible with such fluids. One route of administration is local administration (e.g., topical administration, such as eye drops, or administration via an implant).

The phrases "parenteral administration" and "administered parenterally" as used herein means modes of administration other than enteral and topical administration, usually by injection, and includes, without limitation, intravenous, intramuscular, intraarterial, intrathecal, intracapsular, intraorbital, intracardiac, intradermal, intraperitoneal, transtracheal, subcutaneous, subcuticular, intraarticular, subcapsular, subarachnoid, intraspinal and intrasternal injection, and infusion.

Pharmaceutical compositions of this disclosure suitable for parenteral administration comprise one or more compounds or compositions as described herein in combination with one or more pharmaceutically acceptable sterile isotonic aqueous or nonaqueous solutions, dispersions, suspensions or emulsions, or sterile powders which may be reconstituted into sterile injectable solutions or dispersions just prior to use, which may contain antioxidants, buffers, bacteriostats, solutes which render the composition isotonic with the blood of the intended recipient, or suspending or thickening agents. Proper fluidity can be maintained, for example, by the use of coating materials, such as lecithin, by the maintenance of the required particle size in the case of dispersions, and by the use of surfactants.

In some cases, in order to prolong the effect of one or more compounds or compositions of this disclosure, it is desirable to slow the absorption of the compounds from subcutaneous or intramuscular injection. This may be accomplished by the use of a liquid suspension of crystalline or amorphous material having poor water solubility. The rate of absorption of the compounds then depends upon their rate of dissolution, which, in turn, may depend upon crystal size and crystalline form. Alternatively, delayed absorption of parenterally administered compounds or compositions of this disclosure is accomplished by dissolving or suspending the drug in an oil vehicle.

Injectable depot forms are made by forming microencapsulated matrices of the subject compounds of this disclosure in biodegradable polymers such as polylactide-polyglycolide. Depending on the ratio of compound or composition 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 compositions are also prepared by entrapping the compounds or compositions in liposomes or microemulsions that are compatible with
5 body tissue. Liposomes comprise phospholipids or other lipids, are nontoxic, physiologically acceptable and metabolizable carriers that are relatively simple to make and administer.

Methods of introduction may also be provided by rechargeable or biodegradable devices. Various slow release polymeric devices have been developed and tested *in*
10 *vivo* in recent years for the controlled delivery of drugs, including proteinacious biopharmaceuticals. A variety of biocompatible polymers (including hydrogels), including both biodegradable and non-degradable polymers, can be used to form an implant for the sustained release of one or more compounds of this disclosure at a particular target site. Compounds and compositions of this disclosure can be
15 formulated for delivery via a catheter, stent, wire, or other intraluminal device. Delivery via such devices may be especially useful for delivery to the bladder, urethra, ureter, rectum, or intestine.

Actual dosage levels of the compounds of this disclosure may be varied so as to obtain an amount of the compound that is effective to achieve the desired therapeutic
20 response for a particular patient, composition, and mode of administration, without being toxic to the patient. The selected dosage level will depend upon a variety of factors including the activity of the particular compound or combination of compounds employed, or the ester, salt, or amide thereof, the route of administration, the severity of the disease, the time of administration, the rate of excretion of the
25 particular compound(s) being employed, the duration of the treatment, other drugs, compounds and/or materials used in combination with the particular compound(s) employed, the age, sex, weight, condition, general health, and prior medical history of the patient being treated, and like factors well known in the medical arts. The quantity of the compounds or compositions or mixture thereof to be administered varies for the

patient being treated and varies from about 100 ng/kg of body weight to 100 mg/kg of body weight per day. The amount of active ingredient that can be used alone or combined with a carrier material to produce a single dosage form will generally be that amount of the compound which produces a therapeutic effect. Generally, out of
5 one hundred percent, this amount will range from about 1 percent to about ninety-nine percent of active ingredient, preferably from about 5 percent to about 70 percent, most preferably from about 10 percent to about 30 percent. Dosages can be readily ascertained by those skilled in the art from this disclosure and the knowledge in the art. Thus, the skilled artisan can readily determine the amount of compound and
10 optional additives, vehicles, and/or carrier in the compositions described herein and to be administered in methods or uses described herein. In general, a suitable daily dose of one or more compounds or compositions or mixtures thereof of this disclosure will be that amount of the compound that is the lowest dose effective to produce a therapeutic effect.

15 If desired, the effective daily dose of the compounds or compositions or mixtures thereof of this disclosure may be administered as one, two, three, four, five, six, or more sub-doses administered separately at appropriate intervals throughout the day, optionally, in unit dosage forms. In some embodiments of this disclosure, the compounds or compositions or mixtures thereof of this disclosure, or mixtures thereof,
20 may be administered two or three times daily. In some embodiments, the compound of this disclosure will be administered once daily.

A physician or veterinarian having ordinary skill in the art can readily determine and prescribe the therapeutically effective amount of the pharmaceutical composition of this disclosure required to treat a given disease or condition. For example, the
25 physician or veterinarian could start doses of the pharmaceutical compositions or compounds of this disclosure at levels lower than that required in order to achieve the desired therapeutic effect and gradually increase the dosage until the desired effect is achieved. By “therapeutically effective amount” or “pharmaceutically effective amount” is meant the concentration of one or more compounds of this disclosure that

is sufficient to elicit the desired therapeutic effect. It is generally understood that the effective amount of the compound of this disclosure will vary according to the weight, sex, age, and medical history of the subject. Other factors which influence the effective amount may include, but are not limited to, the severity of the patient's
5 condition, the disorder being treated, the stability of the compound, and, if desired, another type of therapeutic agent being administered with the compound of this disclosure. A larger total dose can be delivered by multiple administrations of the compounds or compositions or mixtures thereof described within. Methods to determine efficacy and dosage are known to those skilled in the art (Isselbacher, *et al.*
10 (1996) Harrison's Principles of Internal Medicine 13 ed., 1814-1882, herein incorporated by reference).

In some embodiments, this disclosure comprises a method for conducting a pharmaceutical business, by determining an appropriate formulation and dosage of the compounds or compositions of this disclosure, or mixtures thereof, for treating or
15 preventing any of the diseases or conditions as described herein, conducting therapeutic profiling of the compounds or compositions disclosed herein for efficacy and toxicity in animals, and providing a distribution network for selling an identified compound or composition as having an acceptable therapeutic profile. In some embodiments, the method further includes providing a sales group for marketing the
20 compositions disclosed herein to healthcare providers.

In some embodiments, this disclosure relates to a method for conducting a pharmaceutical business by determining an appropriate composition and dosage of the compounds of this disclosure, or mixtures thereof, for treating or preventing any of the diseases or conditions described herein, and licensing, to a third party, the rights for
25 further development and sale of the compositions.

Animal/Cell Models

Pain, headaches, and migraines have been modeled in animals such as mice and rats. For example, Oshinsky *et al.* (Oshinsky, M.L., *et al.*, Spontaneous Trigeminal

Allodynia in Rats: A Model of Primary Headache, *Headache*, 2012, 52: 1336-1349, herein incorporated by reference) describes spontaneous trigeminal allodynia (STA) rats with the inherited trait of spontaneously changing trigeminal von Frey thresholds. These rats are a model of spontaneous headache and can be used as a model of
5 primary headache. Through a series of tactile sensory tests, the periorbital, hind-paw, and jaw-pressure thresholds for STA rats are determined by applying von Frey monofilaments. These determinations are made both before and after receiving treatments with compounds or compositions of this disclosure, or mixtures thereof. Analgesic and pain reduction activities of the compounds or compositions described
10 herein, or mixtures thereof that are modulated through the I₁ receptor can be evaluated by determining trigeminal von Frey thresholds in STA rats.

Rats can also be used in an inflammatory soup model of migraine. Inflammatory soup, composed of a mixture of prostaglandin E₂, serotonin, bradykinin, and histamine, has frequently been used in the migraine literature to study activation of
15 nociceptors and to induce migraine. Activity of the compounds or compositions described herein, or mixtures thereof, can be evaluated using the inflammatory soup model.

Common mouse models for pain include the Formalin Test (Wheeler-Aceto, *et al.*, *Psychopharmacology*, 104, 35-44, 1991, herein incorporated by reference), the Hot
20 Plate Test (Eddy and Leimbach, *J. Pharmacol. Exp. Ther.*, 107, 385-393, 1953, herein incorporated by reference), and the Tail-flick Test (D'Amour and Smith, *J. Pharmacol. Exp. Ther.*, 1, 74-79, 1941, herein incorporated by reference). These methods detect analgesic and pain reduction activity of compounds or compositions of interest, or mixtures thereof. In the Formalin Test, mice are given an intraplantar injection of 5%
25 formalin into one posterior hindpaw to induce paw licking. Test compounds or compositions, or mixtures thereof, are given to the mice before treatment with formalin and the mice are evaluated and compared to a control group. In the Hot Plate Test, mice are placed onto a hot metal plate maintained at 54 °C and the latency to the first foot-lick is measured. As with the Formalin test, compounds or compositions of

interest, or mixtures thereof, are given to the mice before the test and the mice are evaluated and compared to a control group. In the Tail-flick Test, a mouse's tail is heated by means of a thermal light source, and the latency before the animal withdraws its tail is measured. Test compounds or compositions, or mixtures thereof, are administered before the test, and compared with a vehicle control group. The analgesic and pain reduction activity of the compounds or compositions described herein that is modulated through the IRIPM pathway can be identified using the mouse formalin, hot plate, and tail-flick tests.

Mice can also be used in the evaluation of the precipitated withdrawal (Saelens) test. In this study, the analgesic potential of test compounds or compositions, or mixtures thereof, is evaluated using an opiate-like dependence model with the Naloxone-precipitated Withdrawal (Saelens) Test in mice. Typically, when opiate-pretreated mice are administered the opiate antagonist naloxone, they demonstrate jumping behavior as a pain response to opiate withdrawal symptoms. The analgesic activity of compounds or compositions of this disclosure, or mixtures thereof, is assessed in this study by measuring whether test compound or composition administration can reduce this naloxone-induced jumping activity.

Common rat models for pain include a chronic constrictive nerve injury (CCI) model of neuropathic pain and bortezomib-induced neuropathy. In the CCI model, a sciatic nerve is ligated and on test days, rats are administered a test compound or composition. The animals are then evaluated by applying von Frey filaments to the hind paws and analyzing the post-treatment withdrawal threshold. In the rat model of bortezomib-induced neuropathy, rats are treated with bortezomib and then administered a test compound or composition. The animals are then evaluated by applying von Frey filaments to the hind paws and analyzing the post-treatment withdrawal threshold. The analgesic and pain reduction activity of the compounds or compositions described herein, or mixtures thereof, that is modulated through the IRIPM pathway can be evaluated in a rat CCI model of neuropathic pain or a rat model of bortezomib-induced neuropathy.

Rats can also be used to evaluate test compounds or compositions or mixtures thereof in models of osteoarthritis. The analgesic potential of the compounds or compositions of this disclosure, or mixtures thereof, is assessed using a monosodium iodacetate (MIA) induced model of osteoarthritic pain in adult male rats.

- 5 To assess the efficacy of test compounds or compositions or mixtures thereof in alleviating naloxone-precipitated withdrawal in chronic morphine-treated rats, male rats are implanted with morphine pellets (2 x 75 mg, s.c.). Seven days later, baseline body weight and hot plate latency are assessed. The animals then receive systemic administration of the vehicle or varying doses of the compounds or compositions of
10 this disclosure, or mixtures thereof, followed by naloxone (3 mg/kg i.p.) or saline. Then the jumping frequency, the existence of diarrhea, and wet dog shaking symptoms are recorded during the first 30 minutes post-naloxone administration.

- To assess the rescue efficacy of the test compounds or compositions or mixtures thereof for the reversal of cutaneous allodynia, sumatriptan-induced medication
15 overuse headache (MOH) is triggered by nitric oxide (NO) donors in rats and then the rescue efficacy of the compounds or compositions of this disclosure, or mixtures thereof, is assessed.

- Rats and mice can also be utilized to examine arterial blood pressure (BP) and heart rate effects of test compounds or compositions, or mixtures thereof, *in vivo*. Rats are
20 anesthetized with Inactin® (sodium thiobutobarbital 100 to 150 mg/kg i.p.) and prepared for the recording of the following parameters: 1) Mean, systolic and diastolic arterial blood pressure (mmHg), via a pressure transducer introduced into the left carotid artery and 2) Heart rate (beats/min), derived from pulse blood pressure. The parameters measured are allowed to stabilize for a period of at least 20 minutes before
25 one or more compounds or compositions of this disclosure are administered. Measurements of blood pressure and heart rate are then made after dosage and compared to pre-dose.

Stability of the compounds or compositions described herein can be assessed using pharmacokinetic studies in animals such as dogs, rats, and humans. Animals are treated with varying doses of the compounds or compositions described herein, or mixtures thereof, and after specified time periods, plasma samples are drawn and then
5 analyzed for the presence of the compound. Not wishing to be bound by theory, in some embodiments, such pharmacokinetic studies can be used to identify slow, normal, and fast metabolizers of the compounds of this disclosure.

The above models are exemplary of suitable animal model systems for assessing the activity and effectiveness of the compounds and pharmaceutical compositions and/or
10 formulations disclosed, or mixtures thereof. Activity of the subject compounds and pharmaceutical compositions and/or formulations disclosed herein, or mixtures thereof, are assessed in any one or more of these models, and the results compared to that observed in wild type control animals and animals not treated with the compounds and pharmaceutical compositions of this disclosure. In some embodiments, the
15 subject compounds and pharmaceutical compositions, or mixtures thereof, are evaluated using cells prepared from any of the foregoing mutant mice or other animals, as well as wild type cells.

In some embodiments, *in vitro* systems may be used to evaluate the ability of any of the compounds or pharmaceutical compositions of this disclosure, or mixtures thereof,
20 to mediate biological activity. For example, membrane homogenates of adrenal medulla glands are incubated with [³H]clonidine in the absence or presence of the compounds or compositions of this disclosure, or mixtures thereof, to determine compound binding to the imidazoline-1 (I₁) receptor. Following the incubation, the samples are analyzed to determine the percent inhibition of the control radioligand
25 ([³H]clonidine) specific binding. This protocol is adapted from Molderings, G.J., Moura, D., Fink, K., Bonisch, H. and Gothert, M. (1993), Binding of [³H]clonidine to I₁-imidazoline sites in bovine adrenal medullary membranes, Naun.-Sch. Arch. Pharm., 348: 70, herein incorporated by reference.

In some embodiments, *in vitro* systems are used for assays of compound affinity with the Imidazoline-1 (I₁) receptor. Membrane homogenates of PC-12 cells are incubated with [¹²⁵I]iodoclonidine in the absence or presence of a compound or composition of this disclosure, or mixtures thereof. Following incubation, the samples are analyzed to
5 determine the percent inhibition of [¹²⁵I]iodoclonidine specific binding. This protocol is adapted from Steffen, G., Dendorfer, A., and Dominiak, P., Imidazoline binding sites on PC-12 cells and bovine chromaffin cells. *Ann. N.Y. Acad. Sci.* **763**: 157-162 (1995), herein incorporated by reference, with modifications, and Piletz, J.E., Zhu, H.E., and Chikkala, D.N., Comparison of Ligand Binding Affinities at Human h-
10 Imidazoline Binding Sites and the High Affinity State of Alpha-2 Adrenergic Subtypes. *JPET.* **279**: 694-7002 (1996), herein incorporated by reference.

In additional *in vitro* experiments, the affinity of compounds for the central imidazoline receptor in the rat cerebral cortex is evaluated in a radioligand binding assay. Membrane homogenates of the cerebral cortex are incubated with [³H]idazoxan
15 in the absence or presence of a compound or composition of this disclosure, or a mixture thereof. Following incubation, the samples are analyzed to determine the percent inhibition of the control radioligand ([³H]idazoxan) specific binding. This protocol is adapted from Brown, C.M., MacKinnon, A.C., McGrath, J.C., Spedding, M. and Kilpatrick, A.T. (1990), α_2 -adrenoceptor subtypes and imidazoline-like
20 binding sites in the rat brain, *Brit. J. Pharmacol.*, **99**:803, herein incorporated by reference.

In some embodiments, a stable CHO cell line expressing the human imidazoline-1 (I₁) receptor is established using CHO cells transfected with a lentiviruses plasmid system containing a human I₁ receptor construct. In some embodiments, the CHO cells stably
25 expressing the human I₁ receptor are used to screen the I₁ receptor binding affinity for any of the compounds and compositions of this disclosure, or mixtures thereof.

In some embodiments, evaluation of the impact of I₁ receptor agonists and antagonists on forskolin-stimulated cAMP induction is conducted with PC-12 cells or a stably-

expressing I₁ receptor cell line. Cells are incubated with benazoline and efaroxan, inhibitors of forskolin-stimulated cAMP production, in the presence or absence of compounds and compositions of this disclosure, or mixtures thereof. The inhibitory effects of benazoline and efaroxan on forskolin induced cAMP are antagonized by
5 agonists of the I₁ receptor.

In some embodiments, a 293T cell line transiently expressing the human imidazoline-1 (I₁) receptor is established using 293T cells transfected with a plasmid system containing a human I₁ receptor construct. In some embodiments, the 293T cells stably expressing the human I₁ receptor are used to identify the I₁ receptor modulators of the
10 compounds of this disclosure, or mixtures thereof.

In some embodiments, the potential side effects of the compounds or compositions of this disclosure, or mixtures thereof, are analyzed using a cAMP Hunter cell line expressing human trace amine associated receptor (TAAR1). TAAR1 is a receptor expressed in the central nervous system (CNS) and belongs to the G-protein coupled
15 receptor (GPCR) receptor family. TAAR1 is activated by biogenic amines such as tyramine, a molecule found in trace levels in the CNS (Borowsky, *et al*, PNAS 98: 8966-8971 (2001), incorporated herein by reference)). For agonist determination, cells are incubated with samples selected from compounds or compositions described herein, or mixtures thereof, to induce response. After appropriate incubation, assay
20 signal is generated through incubation with cAMP XS+ ED/CL lysis cocktail followed by incubation with cAMP XS+ EA reagent. Microplates are read following signal generation with a PerkinEimer Envision™ instrument for chemiluminescent signal detection. Activity is analyzed using the CBIS data analysis suite (ChemInnovation, CA). For G_s agonist mode assays, percentage activity is calculated using the
25 following formula: % Activity=100% x (mean RLU of test sample – mean RLU of vehicle control) / (mean RLU of MAX control – mean RLU of vehicle control). Lower TAAR1 activation indicates lower side effects.

In some embodiments, *in vitro* systems can be used to study the interactions of compounds or compositions described herein, or mixtures thereof, with other molecules, such as proteins, nucleic acids, carbohydrates, ions, lipids, or amino acids. Such interactions can happen within or superficially to the cell and alter the molecule's function. For example, the compounds or compositions described herein may improve catalytic activity of a protein by blocking suppressing molecules or improving access to a catalytic domain or the compounds described herein may inhibit an active site on a protein, such as a catalytic domain or a binding site.

The effects of any of the pharmaceutical compositions and compounds disclosed herein, or mixtures thereof, may be tested in any of the cells or animal models disclosed herein. The pharmaceutical compositions and compounds described herein, or mixtures thereof, have numerous uses, including *in vitro* and *in vivo* uses. *In vivo* uses include not only therapeutic uses but also diagnostic and research uses in, for example, any of the foregoing animal models. By way of example, pharmaceutical compositions and compounds described herein, or mixtures thereof, may be used as research reagents and delivered to animals to understand bioactivity, enzymatic activity, gene expression, interactions with other molecules, and impacts on animal physiology in healthy or diseased animals or cells.

Kits

In some embodiments, this disclosure also provides a pharmaceutical package or kit comprising one or more containers filled with at least one compound or composition of this disclosure, or mixtures thereof. Optionally associated with such a container(s) can be a notice in the form prescribed by a governmental agency regulating the manufacture, use or sale of pharmaceuticals or biological products, which notice reflects (a) approval by the agency of manufacture, use or sale for human administration, (b) directions for use, or both. In some embodiments, the kit comprises at least two containers, at least one of which contains at least one compound or composition of this disclosure. In some embodiments, the kit contains at least two

containers, and each of at least two containers contains at least one compound or composition of this disclosure.

In some embodiments, the kit includes additional materials to facilitate delivery of the subject compounds and compositions. For example, the kit may include one or more
5 of a catheter, tubing, infusion bag, syringe, and the like. In some embodiments, the compounds and compositions, or mixtures thereof, are packaged in a lyophilized form, and the kit includes at least two containers: a container comprising the lyophilized compounds or compositions and a container comprising a suitable amount of water, buffer, or other liquid suitable for reconstituting the lyophilized material.

10 The foregoing applies to any of the compounds, compositions, methods, and uses described herein. This disclosure specifically contemplates any combination of the features of such compounds, compositions, methods, and uses (alone or in combination) with the features described for the various kits described in this section.

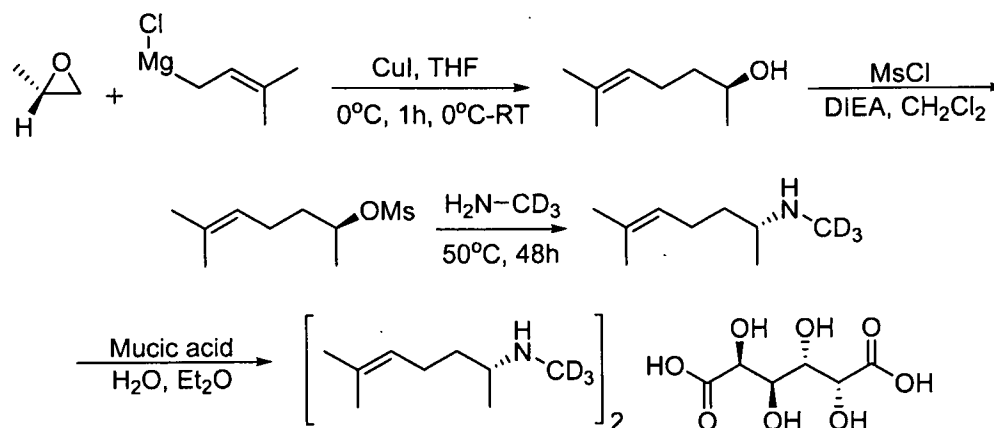
Preparation of the Compounds of the Disclosure

15 In some embodiments, one or more of the compounds, or components to make the compounds, having the formula **1-54**, or a pharmaceutically acceptable salt, tautomer, solvate, enantiomer, diastereomer, or prodrug of any of the foregoing compounds, are commercially available, for example from commercial sources such as
Sigma-Aldrich® of St. Louis, Missouri, USA; TCI America, Portland, Oregon, USA;
20 and Acros Organics, Geel, Belgium; among others.

In some embodiments, one or more of the compounds having the formula **1-54**, or a pharmaceutically acceptable salt, tautomer, enantiomer, diastereomer, solvate, or prodrug of any of the foregoing compounds, are prepared from commercially available reagents by routine methods in synthetic organic chemistry.

25 For example, compounds **8** and **26** are synthesized as described in WO2014/113734, incorporated herein by reference.

In some embodiments, as illustrated in Scheme 1, a deuterated version of the mucate salt of compound 8, ((R)-isomethene-D₃ mucate) is prepared.



Scheme 1

As illustrated in Scheme 1, above, 3-Methylbut-2-enylmagnesium chloride, 0.50 M in
 5 THF (760 mL, 380 mmol), is transferred to a 2 liter, flame-dried round-bottom flask. After cooling to 4 °C, CuI (7.62 g, 40 mmol) is added to give a dark suspension, and (S)-2-methyl-oxirane 99% (14 mL, 200 mmol) in anhydrous THF (12 mL) is slowly added to the stirred reaction mixture via syringe pump at a rate of 110 mL/h at 4 °C to give a dark suspension which is allowed to slowly warm to room temperature in the
 10 ice bath. After stirring at room temperature for 16 hours, thin-layer chromatography and ¹H NMR show (S)-sulcatol ((S)-6-Methyl-hept-5-en-2-ol) and a more polar, more volatile side product. The reaction mixture is poured into saturated aqueous NH₄Cl (600 mL) to give a blue aqueous suspension and an organic layer with pH 9. This mixture is stirred for 30 minutes, and the mixture is extracted three times with Et₂O
 15 (800 mL, 400 mL, and 400 mL). The organic extracts are combined, washed with water (200 mL), brine (200 mL), dried with MgSO₄, and stripped of solvent *in vacuo* (30 mmHg) at 35 °C to give 31.8 grams of a yellow oil which is purified three times by distillation *in vacuo* at 15-20 mmHg. The higher boiling fractions, bp. 80 °C, contain the (S)-sulcatol. The yield of (S)-sulcatol is 13.68 g. R_f in 3:1 hexanes/ethyl acetate: sulcatol: 0.35, impurity: 0.3.
 20

^1H NMR (CDCl_3): δ 5.14 (m, 1H), 3.81 (m, 1H), 2.08 (m, 1H), 1.69 (s, 3H), 1.62 (s, 2H), 1.48 (m, 2H), 1.19 (d, 3H, $J = 6$ Hz).

Alternatively, (S)-sulcatol ((S)-6-Methyl-hept-5-en-2-ol) is synthesized by generating the 3-methylbut-2-enylmagnesium halide Grignard reagent *in situ* from 1-halo-3-methylbut-2-ene (e.g., 1-chloro-3-methylbut-2-ene) and magnesium metal in the presence of (S)-methyloxirane.

In an alternative method, (S)-sulcatol is isolated as follows: (S)-sulcatol and the major impurity (3-methyl-2-buten-1-ol) are treated with a selective oxidant, manganese dioxide (MnO_2) to form a mixture of (S)-sulcatol and 3-methyl-2-butenal. Treatment of this mixture with sodium bisulfite (NaHSO_3) forms a mixture of (S)-sulcatol and sodium 1-hydroxy-3-methylbut-2-ene-1-sulfonate. The sodium 1-hydroxy-3-methylbut-2-ene-1-sulfonate is removed through extraction with water. Removal of water from the organic layer with sodium sulfate yields a solution of (S)-sulcatol in Me-THF.

As shown in Scheme 1, (S)-6-Methyl-hept-5-en-2-ol (2.64 g, 20.58 mmol) and DIEA (6.45 mL, 37.0 mmol) are then dissolved in anhydrous CH_2Cl_2 (28 mL), the reaction mixture is cooled to 5°C , mesyl chloride (1.91 mL, 24.7 mmol) is added dropwise, and the reaction mixture is allowed to slowly warm to room temperature. After 18 hours at room temperature, the reaction mixture is diluted with CH_2Cl_2 (100 mL), washed with water (3 x 35 mL), brine (35 mL), and dried with MgSO_4 , and the solvent is concentrated to give a dark oil which is purified by SiO_2 flash chromatography using hexanes-EtOAc to give (S)-methanesulfonic acid 1,5-dimethyl-hex-4-enyl ester ((S)-sulcatol-O-mesylate) as an oil (3.213 g, 76%). R_f hexanes: CH_2Cl_2 :EtOAc, 40:40:20:0.70.

^1H NMR (CDCl_3): δ 5.08 (m, 1H), 4.80 (m, 1H), 2.99 (s, 3H), 2.10 (m, 2H), 1.75 (m, 1H), 1.69 (s, 3H), 1.62 (m, 1H), 1.61 (s, 3H), 1.43 (d, 3H, $J = 6.5$ Hz).

Optionally, for larger scale preparations, the dark oil may be used in the next step (reaction with methylamine) without silica chromatography, or dissolved in hexanes:CH₂Cl₂:EtOAc, 40:40:20, filtered through silica to remove baseline impurities, and stripped of solvent. Below is the description of a method of synthesis of a larger amount of (S)-methanesulfonic acid 1,5-dimethyl-hex-4-enyl ester (19.8 g).

In an alternative embodiment, the (S)-sulcatol (13.68 g) from the above section is converted to (S)-methanesulfonic acid 1,5-dimethyl-hexyl-4-enyl ester as described above. However, instead of using chromatography, the product is purified by filtering a CH₂Cl₂ solution through silica gel in a filtration funnel (6 cm height x 9.5 cm inside diameter, 60 Å 220-240 mesh silica) and removing under vacuum. The yield of (S)-methanesulfonic acid 1,5-dimethyl-hexyl-4-enyl ester is 19.8 g. This material shows no side products by ¹H NMR.

In the next step (Scheme 1), a 100 mL 3-necked round bottom flask is charged with 40 mL water, weighed, and fitted with a septum and a sintered glass bubbler attached to a lecture bottle containing methylamine-D₃ (10 g), controlled by a regulator. The remaining neck is attached to a dry ice/acetone-cooled condenser fitted with an empty balloon to prevent too much pressure from building in the system. The methylamine-D₃ is slowly bubbled into the water over the course of 25 minutes at ambient temperature. The flask is weighed again and found to contain 9.0 g of methylamine-D₃.

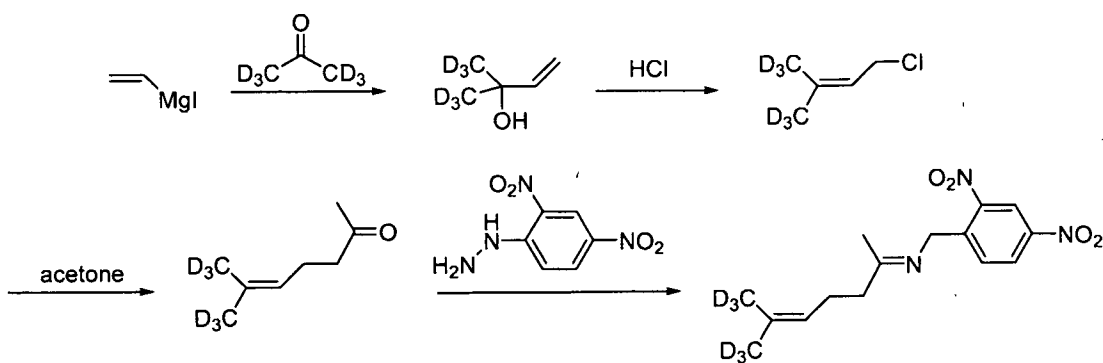
(S)-Sulcatol-*O*-mesylate (3.0 g, 14.54 mmoles) is dissolved in dimethylacetamide (40 mL) in a 200 mL thick walled glass pressure vessel. The aqueous solution of methylamine-D₃ (~48 mL of solution, 9 g, 370.4 mmol) is added. The pressure vessel is sealed and heated at 50 °C for 48 hours while stirring with a magnetic stirbar. The reaction mixture is cooled to 5 °C for 15 minutes and then diluted with ether (300 mL), washed with water (3 x 100 mL) and saturated aqueous NaCl (100 mL), dried over Na₂SO₄, and evaporated under mild vacuum (30 mmHg, 25 °C). Mild vacuum is used because of the volatility of the product. The yield is 2.4 grams of crude product as a

colorless oil ((R)-isomethheptene-D₃), which is used without further purification for the next reaction.

A 250 mL round-bottomed flask is charged with mucic acid (1.6815 g, 8 mmol) and water (80 mL). To this mixture, (R)-isomethheptene-D₃ (2.4 g from the previous
5 reaction, < 16.6 mmoles) in diethyl ether (32 mL) is added dropwise with rapid stirring. Stirring is continued for 18 hours at ambient temperature. The aqueous layer is separated from the organic layer. The aqueous layer is extracted with 3 x 100 mL of toluene and the water is removed under high vacuum (35-40 °C). The resulting white solid is dissolved in methanol (25 mL), and acetonitrile (80 mL) is added slowly
10 dropwise via an addition funnel to give a white suspension. The suspension is filtered and washed with acetonitrile (2 x 20 mL) and dried *in vacuo* (0.1 mmHg) at room temperature in a dessicator for 15 hours to give a white powder. To remove excess mucic acid from this crude material, it is stirred with 12 mL of methanol, filtered, and stripped of solvent. The resulting powder is dissolved in 25 mL methanol, and treated
15 with 75 mL acetonitrile. The white crystalline precipitate is dried *in vacuo*. Yield of the D₃ mucate of compound **8**: 1.25 grams, 2.51 mmol, 34.5% based on (S)-sulcatol-O-mesylate (Scheme 1).

¹H NMR (D₂O) δ 5.23 (m, 2H), 4.50 (s, 2H), 4.0 (s, 2H), 3.24 (m, 2H), 2.12 (m, 4H),
1.78 (m, 2H), 1.7 (s, 6H), 1.65 (s, 6H), 1.6 (m, 2H), 1.28 (d, *J* = 6.5 Hz, 6H). In the
20 ¹H NMR, no peak is observed at or near 2.65 ppm for the D₃-labelled material, in contrast to the ¹H NMR of unlabeled isomethheptene mucate. Positive ion MS: 145.4 [M+H], calculated 144.27 for D₃-isomethheptene. Negative ion MS 209.0 [M-H], calculated 210.14 for D₃-isomethheptene mucate.

In some embodiments, as illustrated in Schemes 2 and 3, a deuterated version of the
25 mucate salt of compound **8**, ((R)-6,7-D₆-isomethheptene mucate) is prepared.



Scheme 2

As shown in Scheme 2, to a solution of acetone- D_6 (6.15 mL, 83.6 mmol) in 150 mL anhydrous THF at -78°C under argon, 1 M vinyl magnesium bromide in THF (100 mL, 100 mmol) is added dropwise through a syringe pump. After completion, the reaction is stirred at -78°C for an additional two hours, then warmed slowly up to room temperature. 15 mL ice water is added to quench the reaction, followed by 100 mL saturated ammonium chloride. The THF layer is separated and the aqueous layer is extracted with diethyl ether (50 mL x 2). The combined organic layers are washed with water and dried with sodium sulfate. After removing the solvent, 6.79 g crude 2-(D_3)methyl(1,1,1- D_3)but-3-en-2-ol is obtained. Purity by ^1H NMR is ~60%, and contaminants also contain vinyl group protons.

^1H NMR (499 MHz, CDCl_3) of major product δ 5.96 (dd, $J = 11, 17.5$ Hz), 5.17 (dd, $J = 1.2, 17.5$ Hz), 4.96 (dd, $J = 1, 11$ Hz). Impurity peaks are observed at 5.95-6.03, 5.20-5.40, and 4.98 - 5.10 ppm.

To a solution of crude 2-(D_3)methyl(1,1,1- D_3)but-3-en-2-ol (3.68 g, 40 mmol) in 30 mL THF, 15 mL 37% aqueous HCl solution is then added dropwise at 4°C . After addition is complete, the reaction is stirred at 4°C for 30 minutes, then it is slowly warmed up to room temperature and stirred for 3 hours. 20 mL water is added and the reaction solution is extracted with diethyl ether (30 mL x 3) and the combined organic layers are washed with water and dried with sodium sulfate. The solvent is removed by distillation at atmospheric pressure at 60°C to remove the ether. At 80°C a

fraction containing the desired 1-chloro-3-(D₃)methyl(4,4,4-D₃)but-2-ene, THF, and 2-(D₃)methyl(1,1,1-D₃)but-3-en-2-ol is obtained. The desired product 1-chloro-3-(D₃)methyl(4,4,4-D₃)but-2-ene is obtained in higher level of purity in the fraction distilled at 130 °C at atmospheric pressure. Yield of this purest fraction was 800 mg
5 (7.2 mmol, 18%).

¹H NMR (499 MHz, CDCl₃) δ 5.42 (t, 1H), 4.06 (d, 2H).

Optionally, a longer reaction time can be used, and the reaction mixture can be combined with methanol before distilling off solvent at 60 °C and 80 °C to take advantage of an azeotrope between methanol and tetrahydrofuran. After removing
10 solvent, the product may be distilled using a slight vacuum (200 to 400 mmHg) and reduced temperature to prevent the decomposition observed at 130 °C. After removal of solvents by distillation at 60 °C and 80 °C atmospheric pressure, dissolve residue in pentane and filter through silica to remove polar contaminants such as THF, 2-(D₃)methyl(1,1,1-D₃)but-3-en-2-ol, and methanol (if the azeotrope is used).

15 In the next step (Scheme 2) to a solution of sodium hydroxide (0.54 g, 13.5 mmol) in 2 mL water is added acetone (0.66 mL, 0.53 g, 9.1 mmol), followed by C16N+Me3Br (0.16 g, 0.44 mmol). 1-chloro-3-(D₃)methyl(4,4,4-D₃)but-2-ene (0.25 g) is then added slowly to the above solution at room temperature. After addition, the reaction is heated to 60 °C and stirred for 4 hours. Then the reaction is cooled to room
20 temperature and 5 mL water is added and the mixture is extracted with diethyl ether (8 mL x 2). The combined organic layers are dried with sodium sulfate and concentrated at 15 mmHg. The ¹H NMR of the crude product is consistent with desired product 6-(D₃)methyl(7,7,7-D₃)hept-5-en-2-one, with precursors acetone, 1-chloro-3-(D₃)methyl(4,4,4-D₃)but-2-ene, and solvent diethyl ether as major contaminants.

25 ¹H NMR (499 MHz, CDCl₃) δ 5.1 (m, 1H), 2.45 (m, 2H), 2.3 (m, 2H), 2.13 (s, 3H).

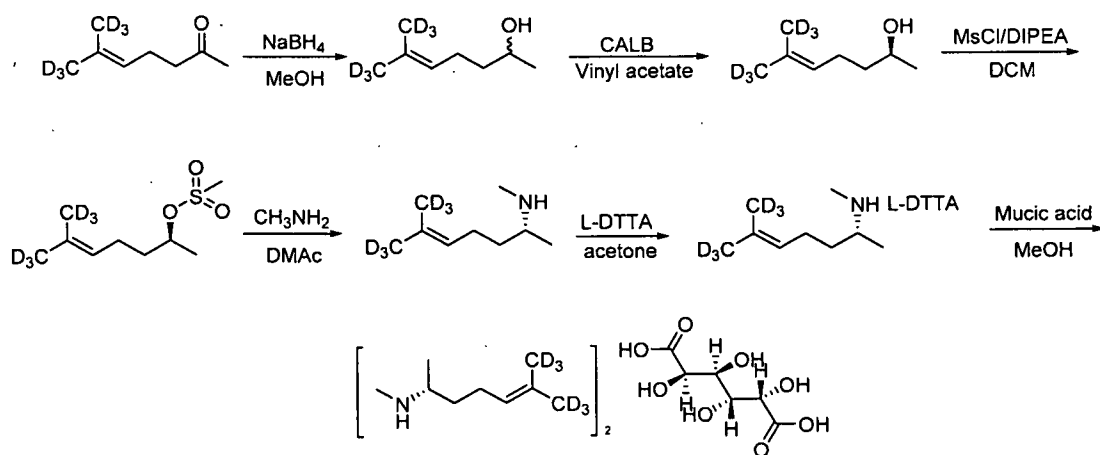
In the next step of Scheme 2, dinitrophenylhydrazones are then formed from the crude product of the previous reaction and purified to ensure that it contained 6-

(D₃)methyl(7,7,7-D₃)hept-5-en-2-one. The crude product is dissolved in 20 mL diethyl ether. 50% (10 mL) of this solution is stripped of solvent at 25 °C. 0.2 g 2,4-DNPH is dissolved in 2 mL methanol and 0.2 mL concentrated H₂SO₄ is added slowly dropwise over 10 minutes the crude ketone in 1 mL methanol. Stir at 25 °C for 2
5 hours. TLC 20% EtOAc:hexane R_f 0.3 for sulcatone and R_f 0.5 for sulcatone hydrazine. Concentrate to remove most of the methanol and dissolve residue in 5 mL CH₂Cl₂ and wash with 2 x 3 mL water. CH₂Cl₂ layer is dried over Na₂SO₄. Remove solvent and purify product by silica chromatography (100% hexane to 70% ethyl acetate:hexane). (E)-1-(2,4-dinitrophenyl)-2-[6-(D₃)methyl(7,7,7-D₃)hept-5-en-2-ylidene]hydrazine (Scheme 2) elutes at 22% EtOAc:hexane and side product 1-(2,4-
10 dinitrophenyl)-2-(propan-2-ylidene)hydrazine elutes at 29% EtOAc:hexane. The product is an orange solid. Mass calculated for C₁₄H₁₈N₄O₄: 312.36. ESI MS negative ion 311.2 (M - H⁻), positive ion 335.3 (M + Na⁺). The side product 1-(2,4-dinitrophenyl)-2-(propan-2-ylidene)hydrazine is also identified by ¹H NMR and mass
15 spectrometry and is the only other dinitrophenylhydrazone formed.

¹H NMR (499 MHz, CDCl₃) δ 11.05 (s, 1H), 9.1 (m, 1H), 8.3 (m, 1H), 7.95 (d, 1H), 5.21 (m, 1H), 2.45 (m, 2H), 2.35 (m, 2H), 2.05 (s, 3H).

The procedure for the conversion of 6-(D₃)methyl(7,7,7-D₃)hept-5-en-2-one to 6,7-D₆ isomethene mucate is illustrated in Scheme 3.

20



Scheme 3

6-(D₃)methyl(7,7,7-D₃)hept-5-en-2-one is reduced with sodium borohydride to form 6-(²H₃)methyl(7,7,7-²H₃)hept-5-en-2-ol (sulcatol). 6-(²H₃)methyl(7,7,7-²H₃)hept-5-en-2-ol is combined with vinyl acetate in the presence of CALB (candida albicans lipase B) to form a mixture of (2S)-6-(D₃)methyl(7,7,7-D₃)hept-5-en-2-ol, (D₆-S-sulcatol), and (2R)-6-(D₃)methyl(7,7,7-D₃)hept-5-en-2-yl acetate. The (2S)-6-(D₃)methyl(7,7,7-D₃)hept-5-en-2-ol is combined with mesyl chloride and DIPEA to form (2S)-6-(D₃)methyl(7,7,7-D₃)hept-5-en-2-yl methanesulfonate, which is reacted with methylamine and DMAc to form methyl[(2R)-6-(D₃)methyl(7,7,7-D₃)hept-5-en-2-yl]amine. Methyl[(2R)-6-(D₃)methyl(7,7,7-D₃)hept-5-en-2-yl]amine is mixed with (-)-di-*p*-tolyl-L-tartaric acid (L-DTTA) to form methyl[(2R)-6-(D₃)methyl(7,7,7-D₃)hept-5-en-2-yl]amine·L-DTTA. Methyl[(2R)-6-(D₃)methyl(7,7,7-D₃)hept-5-en-2-yl]amine·L-DTTA is combined with mucic acid in a 2:1 ratio to form 6,7-D₆ isometheptene mucate {IUPAC name: (2R,3S,4R,5S)-2,3,4,5-tetrahydroxyhexanedioic acid; bis(methyl[(2R)-6-(²H₃)methyl(7,7,7-²H₃)hept-5-en-2-yl]amine)}.

Exemplification

The inventions now being generally described, it will be more readily understood by reference to the following examples, which are included merely for purposes of illustration of certain aspects and embodiments of this disclosure, and are not intended

to limit this disclosure. For example, the particular constructs and experimental design disclosed herein represent exemplary tools and methods for validating proper function. As such, it will be readily apparent that any of the disclosed specific constructs and experimental plan can be substituted within the scope of this disclosure.

5 **Example 1** Evaluation of the affinity of compounds for the peripheral imidazoline-1 (I₁) receptor in bovine adrenal medulla glands determined in a radioligand binding assay

This protocol is adapted from: Molderings, G.J., Moura, D., Fink, K., Bonisch, H. and Gothert, M. (1993), Binding of [³H]clonidine to I₁-imidazoline sites in bovine adrenal medullary membranes, Naun.-Sch. Arch. Pharm., 348: 70, incorporated herein by
10 reference.

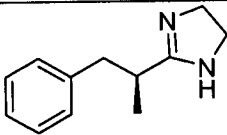
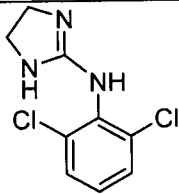
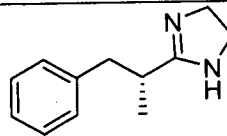
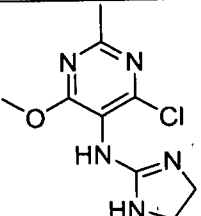
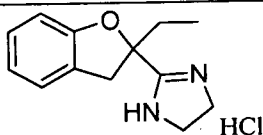
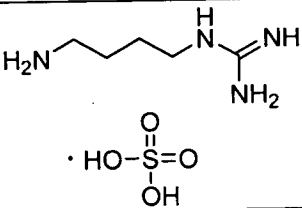
Membrane homogenates of adrenal medulla glands (200 µg protein) are incubated for 60 minutes with 10 nM [³H]clonidine in the absence or presence of a test compound selected from a compound having the formula 1-54, or a mixture thereof, or a
15 pharmaceutically acceptable salt, free base form, enantiomer, diastereomer, tautomer, solvate, or prodrug, or a mixture thereof, of any of the foregoing compounds, in a buffer containing 137 mM NaCl, 2.68 mM NaCl, 2.68 mM KCl, 0.5 mM MgCl₂, 8.1 mM Na₂HPO₄, 1.47 mM KH₂PO₄, 0.5 mM EGTA, 0.5 mM EDTA, 0.5% ascorbic acid and 0.1% BSA (pH 7.4). The buffer also contains 10 µM RX821002 to block the
20 α₂-adrenergic receptors. Nonspecific binding is determined in the presence of 10 µM rilmendine.

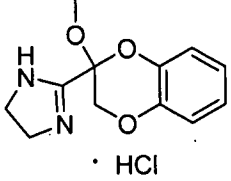
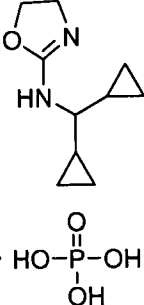
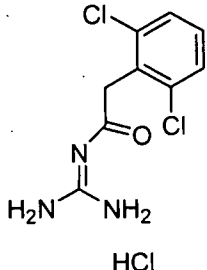
Following the incubation, the samples are filtered rapidly under vacuum through glass fiber filters (GF/B, Packard) presoaked with 0.3% PEI and rinsed several times with ice-cold 50 mM Tris-HCl using a 96-sample cell harvester (Unifilter, Packard). The
25 filters are dried and then counted for radioactivity in a scintillation counter (Topcount, Packard) using a scintillation cocktail (Microscint 0, Packard).

The results are expressed as a percent inhibition of the control radioligand specific binding (Table 1). The standard reference compound is rilmenidine, which is tested in each experiment at several concentrations to obtain a competition curve from which its IC_{50} was calculated.

5

Table 1

Cpd ID	Structure	% inhibition 2 μ M	% inhibition 10 μ M	IC_{50} μ M (approximate)	K_i (nM)
2	 oxalate salt	--	--	--	324
25	 HCl	--	--	--	190
32	 oxalate salt	--	--	--	315
34		5	18	>10	3,880
37	 HCl	--	--	--	10,000
39	 \cdot HO-S(=O)(OH)	14	16	>10	--

46	 · HCl	13	10	>10	--
53	 · HO-P(=O)(OH)-OH	--	--	--	440
54	 HCl	--	--	--	3,943

Example 2 Assays of compound affinity with the Imidazoline-1 (I₁) receptor

This protocol is adapted from: Steffen, G., Dendorfer, A., and Dominiak, P., Imidazoline binding sites on PC-12 cells and bovine chromaffin cells. *Ann. N.Y. Acad. Sci.* **763**: 157-162 (1995), incorporated herein by reference, with modifications, and

5 Piletz, J.E., Zhu, H.E., and Chikkala, D.N., Comparison of Ligand Binding Affinities at Human Imidazoline Binding Sites and the High Affinity State of Alpha-2 Adrenergic Subtypes. *JPET.* **279**: 694-7002 (1996), incorporated herein by reference.

Membrane homogenates of PC-12 cells in 50 mM Tris-HCl (pH 7.4), 5 mM EDTA, 5 mM EGTA, 5 mM MgCl₂, and 30 μM norepinephrine are incubated with 2.0 nM 1100

10 Ci/mmol [¹²⁵I]iodoclonidine in the absence or presence of a test compound selected from a compound having the formula **1-54**, or a mixture thereof, or a pharmaceutically acceptable salt, free base form, enantiomer, diastereomer, tautomer, solvate, or prodrug, or a mixture thereof, of any of the foregoing compounds, or a test

composition selected from any of the compositions disclosed herein for 60 minutes at room temperature. The reaction is terminated by rapid vacuum filtration onto glass fiber filters. Radioactivity trapped onto the filters is determined and compared to control values in order to ascertain any interactions of the test compounds with the I₁ receptor binding site.

Nonspecific binding is determined in the presence of 10 μM iodoclonidine.

The results are expressed as a percent inhibition of the control radioligand specific binding. The standard reference compound is iodoclonidine, which is tested in each experiment at several concentrations to obtain a competition curve from which its IC₅₀ is calculated.

For compound **8** mucate salt, (R)-isometheptene mucate, the K_i is 18 nM for the I₁ receptor and 2300 nM for the α-adrenergic receptor. For compound **26** mucate salt, (S)-isometheptene mucate, the K_i is 1100 nM for the I₁ receptor and 2700 nM for the α-adrenergic receptor.

Example 3 Evaluation of the affinity of compounds for the central imidazoline receptor in the rat cerebral cortex determined in a radioligand binding assay

This protocol is adapted from: Brown, C.M., MacKinnon, A.C., McGrath, J.C., Spedding, M. and Kilpatrick, A.T. (1990), α₂-adrenoceptor subtypes and imidazoline-like binding sites in the rat brain, Brit. J. Pharmacol., **99**:803, incorporated herein by reference.

Membrane homogenates of cerebral cortex (1 mg protein) are incubated for 30 minutes at 22 °C with 2 nM [³H]idazoxan in the absence or presence of the test compound selected from a compound having the formula **1-54**, or a mixture thereof, or a pharmaceutically acceptable salt, free base form, enantiomer, diastereomer, tautomer, solvate, or prodrug, or a mixture thereof, of any of the foregoing compounds,

or a test composition selected from any of the compositions disclosed herein in a buffer containing 50 mM Tris-HCl (pH 7.4), 0.5 mM EDTA and 3 μ M yohimbine.

Nonspecific binding is determined in the presence of 10 μ M cirazoline.

5 Following incubation, the samples are filtered rapidly under vacuum through glass fiber filters (Filtermat B, Wallac) presoaked with 0.3% PEI and rinsed several times with an ice-cold buffer containing 50 mM Tris-HCl and 150 mM NaCl using a 48-sample cell harvester (Mach II, Tomtec). The filters are dried then counted for radioactivity in a scintillation counter (Betaplate 1204, Wallac) using a solid scintillator (Meltilex B/HS, Wallac).

10 The results are expressed as a percent inhibition of the control radioligand specific binding. The standard reference compound is idazoxan, which is tested in each experiment at several concentrations to obtain a competition curve from which its IC₅₀ is calculated.

15 **Example 4** Evaluation of test compounds for analgesic activity using the Formalin Test, late phase (licking score) in a mouse

The method, which detects analgesic/anti-inflammatory activity, follows that described by Wheeler-Aceto, *et al.* (Psychopharmacology, 104. 35-44, 1991), incorporated herein by reference.

20 Mice are given an intraplantar injection of 5% formalin (25 μ L) into one posterior hindpaw. This treatment induces paw licking in control animals. Mice are briefly observed at one minute intervals between 15 and 50 minutes after the injection of formalin and the number of occasions that the mice are observed licking the injected paw is recorded.

10 mice are studied per group. The test is performed partially blind.

The test substances selected from a compound having the formula 1-54, or a mixture thereof, or a pharmaceutically acceptable salt, free base form, enantiomer, disastereomer, tautomer, solvate, or prodrug, or a mixture thereof, of any of the foregoing compounds, or a test composition selected from any of the compositions disclosed herein are evaluated at three doses, administered p.o. 15 minutes before the test i.e. immediately before formalin, and compared with a vehicle control group.

Morphine (32 mg/kg p.o.), 60 minutes before the test i.e. 45 minutes before formalin, is used as a reference substance.

The experiment included eight groups. Because of the number of animals, the experiment is divided into two sub-experiments (n=5 mice/group/day).

Inter-group comparison is performed for the test substance using a Ktuskaii-Waflls test, followed by Mann-Whitney U tests in case of significant group effect. For the reference substance, the treated group is compared with vehicle control using Mann-Whitney U test.

Data for compound 8 mucate salt, (R)-isomethptene mucate, and compound 26 mucate salt, (S)-isomethptene mucate, are shown in Figure 1. Both compounds 8 and 26 lead to a reduction in licking score compared to mice injected only with vehicle, demonstrating an analgesic effect with these compounds. One mouse died after treatment with 100 mg/kg (S)-isomethptene, suggesting this isomer might have issues with toxicity. The analgesic effect of (S)-isomethptene is difficult to determine due to toxicity of the compound.

Example 5 Evaluation of test compounds for analgesic activity using the Hot Plate Test in a mouse

The method, which detects analgesic activity, follows that described by Eddy and Leimbach (J. Pharmacol. Exp. Ther., 107, 385-393, 1953), incorporated herein by reference.

Mice are placed onto a hot metal plate maintained at 54 °C surrounded by a Plexiglas cylinder (height: 13 cm; diameter: 19 cm). The latency to the first foot-lick is measured (maximum: 30 seconds).

10 mice are studied per group. The test is performed partially blind.

- 5 The test substances selected from a compound having the formula **1-54**, or a mixture thereof, or a pharmaceutically acceptable salt, free base form, enantiomer, diastereomer, tautomer, solvate, or prodrug, or a mixture thereof, of any of the foregoing compounds, or a test composition selected from any of the compositions disclosed herein are evaluated at three doses (10, 30 and 100 mg/kg), administered p.o.
- 10 15 minutes before the test, and compared with a vehicle control group.

Morphine (32 mg/kg p.o.) administered 60 minutes before the test, is used as reference substance. The experiment includes 8 groups.

- 15 Data with the test substance are analyzed by comparing treated groups with vehicle control using ANOVA followed by post-hoc Dunnett's tests. Data with the reference substance are analyzed using unpaired Student's t tests.

- 20 Data for compound **8** mucate salt, (R)-isomethptene mucate, and compound **26** mucate salt, (S)-isomethptene mucate, are shown in Figure 8. Both compounds **8** and **26** lead to longer foot-licking latency times compared to mice injected only with vehicle, demonstrating an analgesic effect with these compounds. One mouse died after treatment with 100 mg/kg (R)-isomethptene.

Example 6 Evaluation of test substances for analgesic activity using the Tail-flick Test in the mouse

The method, which detects analgesic activity, follows that described by D'Amour and Smith (J. Pharmacol. Exp. Ther., 1, 74-79, 1941), incorporated herein by reference.

The mouse's tail is heated by means of a thermal light source (20 volts). The latency before the animal withdraws its tail is measured (maximum: 15 seconds).

Ten mice are studied per group. The test is performed partially blind.

5 The test substances selected from a compound having the formula **1-54**, or a mixture thereof, or a pharmaceutically acceptable salt, free base form, enantiomer, diastereomer, solvate, tautomer, or prodrug, or a mixture thereof, of any of the foregoing compounds, or a test composition selected from any of the compositions disclosed herein are evaluated at three doses (10, 30, and 100 mg), administered p.o. 15 minutes before the test, and compared with a vehicle control group.

10 Morphine (32 mg/kg p.o.) 60 minutes before the test, is used as reference substance. The experiment includes eight groups.

Data with the test substances are analyzed by comparing treated groups with vehicle control using ANOVA followed by post-hoc Dunnett's tests. Data with the reference substance are analyzed using unpaired Student's t tests.

15 Data for compound **8** mucate salt, (R)-isometheptene mucate, and compound **26** mucate salt, (S)-isometheptene mucate, are shown in Figure 2. Both compounds **8** and **26** lead to longer tail flick latency times compared to mice injected only with vehicle, demonstrating an analgesic effect with these compounds. Compound **8** at 100 mg/kg p.o. shows activity similar to that of morphine at 32 mg/kg. Two mice died after
20 treatment with 100 mg/kg (S)-isometheptene, suggesting this isomer might have issues with toxicity. The analgesic effect of (S)-isometheptene is difficult to determine due to toxicity of the compound.

Example 7 **Testing of compounds in TAAR1 cAMP Assay**

25 The cAMP Hunter cell line expressing human TAAR1 is expanded from freezer stocks according to standard procedures. Cells are seeded in a total volume of 20 μ L

into white walled, 384-well microplates and incubated at 37 °C for the appropriate time prior to testing. cAMP modulation is determined using the DiscoverX HitHunter cAMP XS+ assay. For agonist determination, cells are incubated with samples selected from a compound having the formula 1-54, or a mixture thereof, or a pharmaceutically acceptable salt, free base form, enantiomer, diastereomer, tautomer, solvate, or prodrug, or a mixture thereof, of any of the foregoing compounds, or a test composition selected from any of the compositions disclosed herein to induce response. Media is aspirated from cells and replaced with 15 µL 2:1 HBSS/10 mM Hepes:cAMP XS+ Ab reagent. Intermediate dilution of sample stocks is performed to generate 4x sample in assay buffer. 4.5 µL of 4x sample is added to cells and incubated at 37 °C or room temperature for 30 or 60 minutes. Final assay vehicle concentration is 1%. After appropriate compound incubation, assay signal is generated through incubation with 20 µL cAMP XS+ ED/CL lysis cocktail for one hour followed by incubation with 20 µL cAMP XS+ EA reagent for three hours at room temperature. Microplates are read following signal generation with a PerkinEimer Envision™ instrument for chemiluminescent signal detection. Compound activity is analyzed using the CBIS data analysis suite (ChemInnovation, CA). For Gs agonist mode assays, percentage activity is calculated using the following formula: % Activity=100% x (mean RLU of test sample – mean RLU of vehicle control) / (mean RLU of MAX control – mean RLU of vehicle control).

Data for compound 8 mucate salt, (R)-isometheptene mucate, and compound 26 mucate salt, (S)-isometheptene mucate, are shown in Figures 3A-B. For compound 8 mucate salt, (R)-isometheptene mucate, the EC₅₀ is 29.45 µM and for compound 26 mucate salt, (S)-isometheptene mucate, the EC₅₀ is 21.12 µM. Compound 26 more potently activates TAAR1 than compound 8.

Example 8 Testing of compounds in spontaneous trigeminal allodynia (STA) rats

Protocols are adapted from Oshinsky, M.L., *et al.*, Spontaneous Trigeminal Allodynia in Rats: A Model of Primary Headache, *Headache*, 2012, **52**: 1336-1349, incorporated

herein by reference. Spontaneous trigeminal allodynia (STA) rats are rats with the inherited trait of spontaneously changing trigeminal von Frey thresholds. Oshinsky *et al.* describes these rats as a novel model of spontaneous headache and can be used as a model of primary headache.

- 5 STA rats and litter mates without the trait are injected with compounds selected from a compound having the formula 1-54 (0.1 – 200 mg/kg), or a mixture thereof, or a pharmaceutically acceptable salt, free base form, tautomer, enantiomer, diastereomer, solvate, or prodrug, or a mixture thereof, of any of the foregoing compounds, or a test composition selected from any of the compositions disclosed herein on days when
10 their thresholds in spontaneous allodynia rats are 4 g or below for STA rats. Testing days for each of the compounds are separated by at least one week. Tactile sensory thresholds are recorded prior to and following injections at 0.5 hours, 1.5 hours, 2.5 hours, 3.5 hours, and 24 hours.

Tactile sensory testing

- 15 Rats are trained and acclimated to a plastic tube restraint and entered uncoaxed. This restrainer allows the rats to undergo sensory testing.

Periorbital, hind-paw, and jaw-pressure thresholds are determined by applying von Frey monofilaments (Stoelting Co., Wood Dale, IL, USA). Each monofilament is identified by manufacturer-assigned force values (26, 15, 10, 8, 6, 4, 2, 1.4, 1, 0.6, 0.4,
20 0.07 g). For trigeminal testing, the filaments are tested on both the left and right sides of the face, over the rostral portion of the eye for periorbital testing, and on the skin over the masseter muscle for jaw testing. The vibrissae are not touched during testing. For the hind-paw testing, the filaments are applied to the mid-plantar region of the left and right hind paws, avoiding the less sensitive foot pads. For the hind-paw testing,
25 the maximum value tested is 26 g; the rats that did not respond to this stimulus are assigned this value. Left and right threshold data are recorded separately. The von Frey stimuli are presented in sequential order, either ascending or descending, as necessary, to determine the threshold of response. After a positive response, a weaker

stimulus is presented, and after a negative response, a stronger stimulus is presented. Results are presented either as the threshold in grams \pm standard error of the mean (SEM), or as a percent change from baseline on the side that has the lowest value. The threshold is defined as a positive response to 2 of 3, or in some cases 3 of 5 trials of a
5 single von Frey monofilament. The value of the von Frey filament that elicits head withdrawal in 2 of 3 repetitions of the stimulus is designated as that day's threshold. Several behaviors are considered a positive head-withdrawal response, including when the rat vigorously strokes its face with the ipsilateral forepaw and quickly recoils its head away from the stimulus or vocalizes. For the periorbital von Frey testing, rats
10 that did not respond to the 10 g stimulus are assigned 10 g as their threshold.

Data for compound **8** mucate salt, (R)-isomethoptene mucate, and compound **26** mucate salt, (S)-isomethoptene mucate, are shown in Figures 4, 15, and 17. Figures 4 and 15 show data collected using STA rats after treatment with 30 mg/kg of the (R)-isomer or (S)-isomer of isomethoptene mucate. Figure 17 shows data collected using
15 STA rats after treatment with 1 mg/kg of the (R)-isomer or (S)-isomer of isomethoptene mucate. No significant changes in trigeminal sensitivity are observed when rats are treated with 1 mg/kg of the (R)-isomer or (S)-isomer of isomethoptene mucate. The data illustrate that treatment with 30 mg/kg of the (R)-isomer of
20 isomethoptene mucate significantly increases trigeminal thresholds at the 0.5 hr (7.8-fold), 1.5 hr (4.3-fold), 2.5 hr (4.5-fold), 3.5 hr (8.5-fold), and 24 hr (8.2-fold) time points. In contrast, treatment with 30 mg/kg of the (S)-isomer, has no effect on trigeminal sensitivity. STA rats treated with greater than 1 mg/kg compound **8** mucate salt show a dramatic increase in threshold values versus STA rats treated with
25 compound **26** mucate salt or the control rats, demonstrating the analgesic effect of compound **8** mucate salt.

Example 9 Impact of compounds on arterial blood pressure (BP) and heart rate effects *in vivo*

Rats are anesthetized with Inactin® (sodium thiobutabarbital 100 to 150 mg/kg i.p.) and prepared for the recording of the following parameters: 1) Mean, systolic and

diastolic arterial blood pressure (mmHg), via a pressure transducer introduced into the left carotid artery and 2) Heart rate (beats/min), derived from pulse blood pressure.

The parameters measured are allowed to stabilize for a period of at least 20 minutes before the test substance selected from a compound having the formula 1-54, or a
5 mixture thereof, or a pharmaceutically acceptable salt, enantiomer, diastereomer, free base form, tautomer, solvate, or prodrug, or a mixture thereof, of any of the foregoing compounds, or a test composition selected from any of the compositions disclosed herein is administered.

10 Measurements are performed before and then 30 seconds, 1, 2, 5, 10 and 15 minutes after the end of each i.v. bolus administration.

Results are expressed in absolute values and as maximal change from pre-dose.

Six rats are studied per group and each test compound is evaluated at three doses (0.05, 0.5 and 5 mg/kg), administered via i.v. as a 30-second bolus, at intervals of 15 minutes, and compared with a time-matched vehicle control group. The experiment
15 therefore includes four groups. Inter-group comparison on maximal absolute changes from pre-dose (each test substance versus vehicle, and each isomer versus racemate) is performed using an unpaired Student's t test.

Data for compound 8 mucate salt, (R)-isomethheptene mucate, and compound 26 mucate salt, (S)-isomethheptene mucate, are shown in Figures 5A-D and 18-21.

20 Isomethheptene mucate USP (0.05, 0.5 and 5 mg/kg), administered as a 30-second i.v. bolus to anesthetized rats, only induces a slight but dose-dependent hypertension from 0.5 mg/kg when comparing the amplitude of the response to that observed in the time-matched vehicle control group. The increase occurs shortly following the administration and reaches a maximum of 4.0 ± 0.6 mmHg from pre-dose for mean
25 blood pressure (BP) at 0.05 mg/kg (NS), 10.5 ± 0.9 mmHg from pre-dose at 0.5 mg/kg (NS) and 11.7 ± 2.8 mmHg from pre-dose at 5 mg/kg ($p < 0.05$). Isomethheptene mucate USP induces a clear and rapid dose-dependent tachycardia that reaches a maximum of

19.0±4.3 bpm from respective pre-dose at 0.05 mg/kg (NS), 40.8±4.0 bpm at 0.5 mg/kg ($p<0.001$) and 57.8±8.6 bpm at 5 mg/kg ($p<0.001$).

Compound **26** mucate salt, isometheptene mucate isomer 1 (0.05, 0.5 and 5 mg/kg), administered as a 30-second i.v. bolus to anesthetized rats, induces a dose-dependent hypertension, but also only from 0.5 mg/kg when comparing the amplitude of the response to that observed in the time-matched vehicle control group. The increase occurs shortly following the administration and reaches a maximum of 2.7±0.8 mmHg max from pre-dose for mean BP at 0.05 mg/kg (NS), 10.3±4.0 mmHg max from pre-dose at 0.5 mg/kg (NS) and 34.7±7.6 mmHg max from pre-dose at 5 mg/kg ($p<0.01$).

Compound **26** mucate salt also causes a clear and rapid dose-dependent tachycardia that reaches a maximum of 23.8±3.2 bpm from respective pre-dose at 0.05 mg/kg ($p<0.01$), 70.3±9.1 bpm at 0.5 mg/kg ($p<0.001$) and 76.5±8.2 bpm at 5 mg/kg ($p<0.001$).

Compound **8** mucate salt, isometheptene mucate isomer 2 (0.05, 0.5 and 5 mg/kg), administered as a 30-second i.v. bolus to anesthetized rats, induces a slight but dose-dependent hypertension, but only from 0.5 mg/kg when comparing the amplitude of the response to that observed in the time-matched vehicle control group. The increase occurs shortly following the administration and reaches a maximum of 3.0±0.9 mmHg max from pre-dose for mean BP at 0.05 mg/kg (NS), 7.5±1.5 mmHg max from pre-dose for mean BP at 0.5 mg/kg (NS) and 19.2±4.4 mmHg max from pre-dose at 5 mg/kg ($p<0.01$). Compound **8** mucate salt also causes a clear and rapid dose-dependent tachycardia that reaches a maximum of 24.7±5.6 bpm from respective pre-dose at 0.05 mg/kg ($p<0.05$), 49.5±9.2 bpm at 0.5 mg/kg ($p<0.001$) and 72.2±5.9 bpm at 5 mg/kg ($p<0.001$).

Although the maximum increase in arterial blood pressure observed following the administration of compound **26** mucate salt at 5 mg/kg is higher than that observed with compound **8** mucate salt (34.7±7.6 mmHg versus 19.2±4.4 mmHg), there is no statistical difference between the two isomers. A trend for systolic blood pressure is

however observed ($p=0.0762$). The tachycardia observed following compound **8** mucate salt and compound **26** mucate salt administration is not statistically different.

These results suggest that isometheptene mucate (the racemate), compound **8** mucate salt, and compound **26** mucate salt (0.05, 0.5 and 5 mg/kg), administered as a bolus of
5 30-second i.v. bolus to anesthetized rats, induce a dose-dependent hypertension. Both compound **8** mucate salt and compound **26** mucate salt induce a more pronounced hypertension than that induced by the racemate, and compound **26** mucate salt clearly induces (although not statistically significant) a more pronounced hypertension than
10 compound **8** mucate salt. The racemate and the two isomers induce a dose-dependent tachycardia that is not statistically different, although that observed following the administration of 0.5 mg/kg compound **26** mucate salt is slightly higher.

Example 10 Evaluation of test compounds for analgesic efficacy in a rat chronic constrictive nerve injury (CCI) model of neuropathic pain

Animals

15 Male Sprague Dawley rats (Harlan) are used in the study. Upon receipt, rats are assigned unique identification numbers and group housed with 2-3 per cage in standard cages. Rats are allowed to acclimate for at least one week prior to dosing. All rats are examined and weighed prior to initiation of the study to assure adequate health and suitability. During the course of the study, 12/12 light/dark cycles are
20 maintained. The room temperature is maintained between 20 °C and 23 °C with a relative humidity maintained around 50%. Chow and water are provided *ad libitum* for the duration of the study. All testing is performed during the animals' light cycle phase. Rats are single housed after surgery.

Test compounds

25 Gabapentin (100 mg/kg) is dissolved in saline and administered p.o. at a dose volume of 1 mL/kg 60 minutes prior to test.

(S)-Isometheptene mucate (mucate salt of compound **26**) and (R)-isometheptene mucate (mucate salt of compound **8**) (10, 30, and 100 mg/kg; free base) are dissolved in water and administered orally at a dose volume of 10 mg/kg 15 minutes prior to test.

- 5 In addition to compounds **8** and **26** mucate salts, the test compounds can be selected from a compound having the formula **1-54**, or a mixture thereof, or a pharmaceutically acceptable salt, free base form, enantiomer, diastereomer, tautomer, solvate, or prodrug, or a mixture thereof, of any of the foregoing compounds or a test composition selected from any of the compositions disclosed herein.

10 ***Chronic constrictive surgery of the sciatic nerve***

This surgery is performed according to Bennett and Xie (1988). Specifically, rats are anesthetized with isoflurane (2% in air). The left hind flank is shaved and sterilized and the rat positioned on its side on a sterile surgical field. The pelvic bone ridge is palpated and a vertical incision is made perpendicular to the long axis of the spine.

- 15 The first layer of muscle is cut to expose the sciatic nerve. Retractors are used to widen the incision, centering the portion of the sciatic nerve to be ligated. The exposed nerve is carefully teased apart from the second layer of muscle, removing fascia lining. Using 5 cm lengths of 4.0 chromic gut suture (pre-soaked in saline), three loose ligations are made around the sciatic nerve, spaced at 0.5 cm intervals.
- 20 Sutures are positioned superior to the point where the nerve branches. The incision is then closed in layers, using 4.0 silk sutures, and the skin closed using sterile autoclips. Topical antibiotic ointment is applied to the closed incision. Each rat is monitored until awake and moving freely around the recovery chamber. Animals are single-housed for the entire duration of the study.

25 ***Evaluation of mechanical allodynia***

Paw withdrawal from a mechanical stimulus is measured by applying von Frey filaments of ascending bending force to the plantar surface of the hind paws (ipsilateral and contralateral). Baseline and post-treatment withdrawal threshold

values for non-noxious mechanical sensitivity are evaluated using von Frey filaments (Semmes-Weinstein filaments, Stoelting, Wood Dale, IL, USA) of varying stiffness (0.4, 0.7, 1.2, 2.0, 3.6, 5.5, 8.5, 10, 15, 26 g). Animals are placed on a perforated metallic platform and allowed to acclimate to their surroundings for a minimum of 15 minutes before each test session. Each filament is presented perpendicular to the plantar surface with sufficient force to cause slight buckling against the paw, then held until a positive response was noted (paw sharply withdrawn). Confirmation of threshold is tested by examining the filament above and below the threshold withdrawal response. Each filament is applied three times.

Prior to CCI surgery, rats are tested for baseline threshold using the von Frey filaments. Rats with a paw withdrawal threshold (PWT) less than 12 g are not included in the study. Rats are balanced based on their post injury PWT measured two weeks after surgery. On test day rats are administered vehicle, gabapentin, or test compounds and PWT is assessed 15 minutes after administration for vehicle or test compounds and 60 minutes for gabapentin.

Data are analyzed by analysis of variance (ANOVA), followed by post-hoc comparisons when appropriate. An effect is considered significant if $p < 0.05$.

As shown in Figures 6A-D and 26, gabapentin, (R)-isometheptene mucate (100 mg/kg), and (S)-isometheptene mucate (100 mg/kg) significantly increase PWT compared to the vehicle-treated rats. In addition, (S)-isometheptene mucate (30 mg/kg) shows a non-significant trend to also increasing PWT.

Example 11 Evaluation of test compounds in the rat model of bortezomib-induced neuropathy

Animals

Male Sprague Dawley rats (Harlan) are used in the study. Upon receipt, rats are assigned unique identification numbers and group housed with 2-3 per cage in standard cages. Rats are allowed to acclimate for at least one week prior to dosing.

All rats are examined and weighed prior to initiation of the study to assure adequate health and suitability. During the course of the study, 12/12 light/dark cycles are maintained. The room temperature is maintained between 20 °C and 23 °C with a relative humidity maintained around 50%. Chow and water are provided *ad libitum* for the duration of the study. All testing is performed during the animals' light cycle phase. Rats are approximately 300 grams at the start of the study. Rats are balanced by body weight and paw withdrawal threshold prior to and following BTZ injection.

Test compounds

Bortezomib (BTZ; 0.5 mg/kg; Selleck Chemicals) is dissolved in 5% Tween80, 5% ethanol in 90% saline and injected i.p. at a dose volume of 1 mL/kg.

Gabapentin (100 mg/kg) is dissolved in saline and administered p.o. at a dose volume of 1 mL/kg 60 minutes prior to test.

(S)-isometheptene mucate (compound 26 mucate salt) and (R)-isometheptene mucate (compound 8 mucate salt) (10, 30, and 100 mg/kg; free base) are dissolved in water and administered orally at a dose volume of 10 mg/kg 15 minute prior to test.

In addition to compounds 8 and 26 mucate salts, the test compounds can be selected from a compound having the formula 1-54, or a mixture thereof, or a pharmaceutically acceptable salt, free base form, tautomer, enantiomer, diastereomer, solvate, or prodrug, or a mixture thereof, of any of the foregoing compounds or a test composition selected from any of the compositions disclosed herein.

BTZ-Induced Neuropathic Pain

Prior to commencing BTZ or vehicle injections, rats are tested for their paw withdrawal threshold (PWT). Baseline and post-treatment PWT values for non-noxious mechanical sensitivity are evaluated using von Frey (VF) filaments (Semmes-Weinstein filaments, Stoelting) of varying stiffness (0.4, 0.7, 1.2, 2.0, 3.6, 5.5, 8.5, 10, 15, 26 g) starting with the middle filament (3.6 g). Each filament is presented perpendicular to the plantar surface with sufficient force to cause slight buckling

against the paw, then held for approximately six seconds or until a positive response is noted. A positive response is defined as withdrawal from the von Frey filament. Confirmation of threshold is tested by examining the filament above and below the withdrawal response in a modified up-down method paradigm. If a response is positive, the next descending filament is tested. If the response is negative, the next ascending filament is tested. The responses from both hind paws are averaged at each time point.

Rats that had a baseline (pre-BTZ injection) PWT less than 12 g are not included in the study. Rats are subsequently balanced by body weight and by the baseline PWT values. Rats are injected with either bortezomib (0.5 mg/kg; ip) or vehicle (5% Tween80, 5% ethanol in saline; i.p.) and post BTZ injection PWT is assessed 12 days after injection. On test day, compounds are administered 15 minutes prior to test except gabapentin which is administered 60 minutes prior to test.

Data are analyzed by analysis of variance (ANOVA), followed by post-hoc comparisons when appropriate. An effect is considered significant if $p < 0.05$.

As shown in Figures 7A-D and 27, Acute BTZ (0.5 mg/kg; ip) administration causes chemical-induced neuropathy as observed by significant lower paw withdrawal thresholds (PWT) as compared to vehicle-treated controls. Gabapentin, (R)-isometheptene mucate (100 mg/kg), and (S)-isometheptene mucate (30 and 100 mg/kg) significantly increase PWT as compared to the BTZ-treated control group suggesting potential analgesic efficacy of these compounds on BTZ-induced neuropathic pain.

25

Example 12 Establishment of a stable CHO cell line expressing human imidazoline-1 (I₁) receptor for compound screening

Establishment of the cell line

Materials and instruments

- 5 Materials include: Lentiviruses 4 plasmid system, pLenti PGK-I₁R-puro (construct by Genscript), lipofectamine LTX and plus TM Reagent (Invitrogen, Cat. No. 15338100), F12 medium (Invitrogen, Cat. No. 11765-054), DMEM medium (Invitrogen, Cat. No. 11995065), Opti-MEM (Invitrogen, Cat. No. 31985-062), Trypsin /EDTA (Invitrogen, 25200-056, FBS (Hyclone, Cat. No. SH30084.03), Hycromycin B (Invitrogen, Cat. No. 10843555001), and Puromycin (Invitrogen, Cat. No. A1113803)
- 10

Cell lines used are: 293T (Bioduro) in DMEM + 10% FBS and CHO (Bioduro) in DMEM + 10% FBS.

Instruments used are an inverted microscope (Olympus, CKX41).

Methods

15 *Construct generation*

Human full length I₁ receptor is cloned into pLenti PGK vector by Genescript. The final construct is confirmed by sequencing and restriction digestion.

Stable cell line generation

Day 1: Plated 293T cells

- 20 293T cells are plated before transfection onto a 10 cm dish to reach 20-30% confluency (3×10^6 cells /10 cm dish) on the day of transfection, and the cells are incubated at 37 °C, 5% CO₂.

Day 2: Transfect 293T cells

Lentiviruses 4 plasmid system

Plasmid	Ug
Target plasmid	4
RRE	4.2
VSVG	3.1
REV	2.1
Total	13.4

Change 293T cell medium to 5 mL Opti-MEM (FBS free). Mix 750 μ L Opti-MEM, 13.4 μ g target DNA (4 plasmids), and 26.8 μ L plus TM Reagent and incubate at room temperature for 15 minutes.

Mix 750 μ L Opti-MEM and 40 μ L lipofectamine and incubate at room temperature for 15 minutes.

The lipofectamine and plasmids mixtures are then combined and incubated at room temperature for 15 minutes. After this time, 1.5 mL of the mixture is added to the plate containing 5 mL Opti-MEM.

Plates are replenished with 7 mL serum-containing DMEM media after five hours.

Day 3: Change medium of 293T cell and plate CHO cells

Provide 8 mL of fresh serum-containing DMEM to 293T cells, and incubate at 37 °C, 5% CO₂.

Plate 2×10^6 CHO cells in a 10 cm dish (20-30% confluent), and incubate at 37 °C, 5% CO₂.

Day 4: Collect virus and first virus infection

Collect virus from 293T cells and then filter with a 0.45 µm syringe filter. Replace 293T medium with fresh medium for the second virus collection. Collect the medium (conditional medium) from CHO cells and store at 4 °C. Add 8 mL of viral supernatant with 8 µg/mL polybrene to CHO cells. After eight hours the virus supernatant is removed and the conditioned medium is added.

Day 5: Collect 72 hour virus and second virus infection

Collect second virus infection medium and filter with a 0.45 µm syringe filter. Repeat the infection with the second virus supernatant. Change to fresh medium eight hours after the second infection.

Day 7: Replace with Puromycin-Selective culture medium.

Replace fresh medium containing 12.5 µg/mL puromycin for each cell line and culture for 3 weeks.

Cloning and confirmation

After three weeks of selection, single clones are picked and cultured in 24 well plates. Cell cultures are expanded for frozen stocks and positive clones are confirmed by RT-PCR. Constructs are confirmed by restriction digestion with XhoI (Figure 9A).

Detection of I₁ receptor in CHO/ I₁ receptor stable cell lines by RT-PCR

Materials and instruments

Materials used include: QIAamp RNA Mini Kit (# 52304, QIAGEN), TaqMan Reverse Transcription Reagents (# N8080234, Life Technology), TaKaRa Taq™ (#R001B, TaKaRa), and TaKaRa LA Taq® (#RR52A, TaKaRa).

Primers:

Forward primer	Reverse primer	Length
----------------	----------------	--------

		(bp)
CCTGCATCAGGTGGAGAT AAG	TTCATCGAGGTTGCTGAG AAG	111

Cell lines used are CHO (Bioduro) in DMEM + 10% FBS and CHO/ I₁ receptor (Bioduro) in DMEM + 10% FBS + 12.5 µg/mL puromycin.

Instruments used include: inverted microscope (Olympus, CKX41), gradient PCR meter (Biometra, 070-851), electrophoresis meter (DYY, 6C), and gel imaging meter
5 (Alphamager, DE-500)

Methods

1. Total RNA Extraction

Total RNA is isolated from cells using a QIAamp RNA Mini Kit, following the manufacture's protocol. The concentration of mRNA is determined with a Nanodrop.

10 2. Reverse Transcription

Set up RT-Reaction Mixtures on ice:

Component	20 µl Reaction
Nuclease-free water	to 20 µl
10x TaqMan RT Buffer	2 µl
Deoxy NTPs mixture	4 µl
Random Hexamers	1 µl
RNAse Inhibitor	0.4 µl

RNA Sample	1 µg
25 mM MgCl ₂	4.4µl
MultiScribe Reverse Transcriptase (50U/µl)	0.5µl

Used the following program for the RT-Reactions:

Cycle step	Temp	Time
Incubation	25 °C	10 min
Reverse Transcription	48 °C	30 min
Transcriptase Inactivation	95 °C	5min

Set up the PCR-Reaction Mixtures on ice:

Component	50 µl Reaction	Final Concentration
Nuclease-free water	to 50 µl	
10x buffer	5 µl	1x
Forward primer (10 µM)	1 µl	Optimal
Reverse primer (10 µM)	1 µl	Optimal
dNTP mixture (2.5 mM)	2 µl	
Taq	1 µl	10 to 100 ng
cDNA sample	2 µl	10 to 100 ng

PCR procedure:

Cycle step		Temp	Time
Initial denaturation		95 °C	3 min
	Denaturation	95 °C	1 min
Cycle (30 cycles)	Annealing	55 °C	1 min
	Extension	72 °C	1 min
Final extension		72 °C	10 min

For analysis by electrophoresis, use 10 μ L of PCR reaction mixture, 2% agarose gel, 100 V, 20 minutes.

Results

5 RT-PCR result from the transient transfection of I₁ receptor/CHO cells indicates that I₁ receptor is expressed in the transfected cells (Figure 9B).

Example 13 Establishment of a functional assay for the imidazoline-1 (I₁) receptor in PC-12 cells or an I₁ receptor stable cell line to evaluate the impact of I₁ receptor agonists and antagonists on forskolin-stimulated cAMP induction

10 *Materials and Instruments*

Materials used include: PC-12 cell line (adherent ATCC®-CRL1721.1, suspension ATCC®-CRL1721), DMEM (Gibco, Cat. #11965), RPMI-1640 (Gibco, Cat. #72400), FBS (Gibco, Cat. #10099), Horse serum (Gibco, Cat. #26050), NGF (Sigma, Cat. #N0513), Collagen (Gibco, Cat. #A10483-01), Forskolin (FSK) (Sigma, Cat. #F6886), 96-well plate (Corning, Cat. #3599), 384-well plate (Greiner, Cat. #784075),
 15 and cAMP dynamic 2 kit (Cisbio, Cat #62AM4PEB).

Instruments used include: EnVision® Multilabel Reader (PerkinElmer, #2104-0010).

Methods

Day 1

5 Coat 96 well plate with 40 μ L/well collagen (50 μ g/mL, dilute from 3 mg/mL collagen stock in 0.02 M acetic acid), incubate at room temperature for one hour, rinse with PBS three times, and air dry.

PC-12 (adherent) cells are cultured in RPMI-1640 medium supplemented with 10% FBS.

10 Cells are collected and centrifuged at 1000 rpm for five minutes, and resuspended in RPMI-1640 medium supplemented with 1% FBS, 50 ng/mL NGF.

Plate 2000 cells/well in a 96 well plate coated with collagen, and incubate at 37 °C with 5% CO₂ for 48 hours.

I₁ receptor/CHO stable cell line is plated at 3500 cells/well in DMEM + 10% FBS.

Day 3

15 Prepare serial dilutions of benazoline and efaroxan, and add 20 μ L benazoline, efaroxan, or medium to each well. Optionally, test compounds selected from a compound having the formula 1-54, or a mixture thereof, or a pharmaceutically acceptable salt, free base form, tautomer, enantiomer, diastereomer, solvate, or prodrug, or a mixture thereof, of any of the foregoing compounds, or a test
20 composition selected from any of the compositions disclosed herein can be added to the cells at the same time.

Spin cells at 1000 rpm for one minute and then incubate at room temperature for 30 minutes.

Add 20 μ l forskolin mix (10 μ M forskolin + 100 μ M IBMX) or medium (medium + IBMX) to each well according to the plate map, spin cells at 1000 rpm for one minute, then incubate at room temperature for 30 minutes.

5 Discard 60 μ L supernatant from each well, and add 20 μ L lysis buffer to each well, shake for two minutes, and transfer 18 μ L from each well to 384-well plate.

Add 1 μ L cAMP-d2 to each well (except negative control), add 1 μ L lysis buffer to negative control well, and spin cells at 1000 rpm for one minute.

Add 1 μ L Cryptate to each well, mix, spin cells at 1000 rpm for one minute, and incubate at room temperature for 30 minutes.

10 Read plate with Envision and analyze data using the fluorescence ratio (665 nm/615 nm).

Results

Both benazoline and efaroxan inhibit forskolin-stimulated cAMP in PC-12 cells. The IC_{50} of each compound is similar to reports in the literature (Figure 10A). The
15 inhibitory effect of benazoline on forskolin induced cAMP is antagonized by clonidine (compound **25** mucate salt).

To evaluate the I_1 receptor function, the cAMP assay is carried out in CHO cells transiently transfected with I_1 receptor expression vector. Both efaroxan and benazoline show an inhibitory effect on forskolin-induced cAMP in I_1 receptor/CHO
20 cells, but not in the parent CHO cell line. This result suggests functional I_1 receptor is expressed in transiently transfected CHO cells (Figures 10B-C).

Example 14 Pharmacokinetic studies of compounds and compositions of the disclosure

Studies

Pharmacokinetic (PK) studies in dogs, rats, and humans are conducted with
5 isometheptene mucate USP and compound **8** mucate salt, (R)-isometheptene mucate.
A test compound can also be selected from a compound having the formula **1-54**, or a
mixture thereof, or a pharmaceutically acceptable salt, free base form, enantiomer,
disastereomer, tautomer, solvate, or prodrug, or a mixture thereof, of any of the
foregoing compounds or a test composition selected from any of the compositions
10 disclosed herein.

Dog studies

Dosing

For IV solutions, the vehicle is saline 0.9% NaCl for Injection, USP, and for PO, the
vehicle is deionized tap water. On the day of dosing, the test compounds are mixed
15 with vehicle to achieve the desired concentrations. A salt factor of 1.74 is used for
calculation of the test compound amount as the dose is calculated as the free base of
the compound **8** mucate salt or of racemic isometheptene mucate.

Test system

The animals used are beagles (dogs) from the MPI Research Colony (MPI Research
20 Study Number 999-407). The dogs are at least five months of age and the males
weighed 5.5 to 12.0 kg and the females weighed 5.0 to 10.0 kg at arrival, as measured
within three days of arrival. The study uses four males and four females. The dogs
are acclimated for at least one week prior to testing and are acclimated to a sling
restraint for at least three times for a period of at least 20 minutes each time. Prior to
25 dose initiation, animals are acclimated to the oral gavage dosing procedure at least

three times. A fixed dose volume of 10 mL/animal of tap water is administered on each occasion.

Study design

Group	Treatment	Route	Dose Level** (mg/kg)	Dose Volume (mL/kg)	Dose Concentration (mg/mL)	Number of Animals	
						Males	Females
1	Isometheptene Mucate USP	IV	1	2.5	0.4	2	2
2	Compound 8	IV	0.5	2.5	0.2	2	2
1	Isometheptene Mucate USP	PO	10	5	2	*	*
2	Compound 8	PO	5	5	1	*	*
*Animal were dosed via IV on Day 1; After a 7-day washout period, the same dogs were used for dosing via oral gavage.							
**Dose was calculated as free base, a salt factor of 1.74 was used to weigh out the test compounds.							

5 Compounds are administered via oral gavage or intravenous injection. The test compound is administered once intravenously on Day 1. After a 7-day washout period the test article is administered once via oral gavage. For oral gavage (PO) the test compound is withdrawn from stirred formulations and dosed via oral gavage. Individual doses are based on the most recent body weights. After each dose, and
 10 prior to removal of the gavage tube, the tube is flushed with 5 to 10 mL of tap water. The oral route is the intended route of administration of compound 8 mucate salt in humans.

For intravenous (IV), the test compound is administered via the cephalic or other suitable vein. Individual doses are based on the most recent body weights. The dose
 15 is administered by bolus injection, unless otherwise indicated. If a catheter is used for dosing, the catheter is flushed with approximately 1 mL of sterile 0.9% Sodium Chloride for Injection, USP following dosing. The intravenous route is used for pharmacodynamic studies in nonclinical species and for calculation of absolute bioavailability.

Sample collection and analysis

Animals are monitored at least twice daily and observed for mortality, injury, and availability of food and water. Any animals in poor health were identified for further monitoring and possible euthanasia. Body weights are collected within three days of transfer and on the day prior to and the day following each dose.

0.5 mL samples are collected from the jugular or other suitable vein. The anticoagulant used is K₂EDTA. Samples are centrifuged and the plasma stored frozen (-60 to -90 °C). The plasma is analyzed for (R)-isomethoptene mucate and (S)-isomethoptene mucate. Interconversion between (R)-isomethoptene mucate and (S)-isomethoptene mucate is not observed (Table 2).

Rat studies

Dosing

For IV solutions, the vehicle is saline 0.9% NaCl for Injection, USP, and for PO, the vehicle is deionized tap water. On the day of dosing, the test compounds are mixed with vehicle to achieve the desired concentrations. A salt factor of 1.74 is used for calculation of the test compound amount as the dose is calculated as the free base of the compound **8** mucate salt or of racemic isomethoptene mucate.

Test system

The animals used are CD[®] rats [CrI:CD[®](SD)] from Charles River Laboratories. The rats are six weeks of age at arrival and the males weigh 130 to 210 g and the females weigh 100 to 170 g at arrival, as measured within three days of arrival. The study uses 20 males and 20 females. The rats are acclimated for at least one week prior to testing. During this acclimation period, all animals are observed daily for any clinical signs of disease, and all animals are given a detailed clinical examination prior to selection for study.

The week prior to dose initiation, all animals (including animals potentially designated for PO and IV administration) are administered a sham dose of tap water via oral gavage on at least two occasions in the same manner and at the same volume intended for PO use during the study period.

5 *Study design*

Group	Treatment	Route	Dose Level** (mg/kg)	Dose Volume (mL/kg)	Dose Concentration (mg/mL)	Number of Animals	
						Males	Females
1	Isometheptene Mucate USP	IV	1	5	0.2	5	5
2	Compound 8	IV	0.5	5	0.1	5	5
3	Isometheptene Mucate USP	PO	10	10	1	5	5
4	Compound 8	PO	5	10	0.5	5	5

**Dose was calculated as free base, a salt factor of 1.74 was used to weigh out the test compounds.

Compounds are administered via oral gavage or intravenous injection. The test compound is administered once on Day 1. For oral gavage (PO) the test compound is withdrawn from stirred formulations and dosed via oral gavage. Individual doses are based on the most recent body weights. The oral route is the intended route of administration of compound 8 mucate in humans.

For intravenous (IV), the test compound is administered via the tail vein. Individual doses are based on the most recent body weights. The dose is administered by bolus injection, unless otherwise indicated. The intravenous route is used for pharmacodynamic studies in nonclinical species and for calculation of absolute bioavailability.

Sample collection and analysis

Animals are monitored at least twice daily and observed for mortality, injury, and availability of food and water. Any animals in poor health are identified for further

monitoring and possible euthanasia. Body weights are collected within three days of transfer and on the day prior to and the day following each dose.

0.5 mL samples are collected from the sublingual or other suitable vein. The anticoagulant used is K₂EDTA. Samples are centrifuged and the plasma stored frozen (-60 to -90 °C). The plasma is analyzed for (R)-isomethoptene mucate and (S)-isomethoptene mucate. Interconversion between (R)-isomethoptene mucate and (S)-isomethoptene mucate is not observed (Table 2).

Table 2

Species, Test Article (Route)	Dose, mg/kg	C _{max} , ng/mL		AUC, ng.h/mL		T _{max} , h		T _{1/2} , h	
		R-IMH	S-IMH	R-IMH	S-IMH	R-IMH	S-IMH	R-IMH	S-IMH
Dog, IMH (IV)	1	354	330	351	306	0.016	0.016	1.6	1.5
Dog, IMH (PO)	10	1380	1220	4901	3885	0.48	0.48	2.7	2.5
Dog, Cpd 8 (IV)	0.5	222	NC	179	NC	0.016	NC	1.1	NC
Dog, Cpd 8 (PO)	5	776	NC	1755	NC	0.39	NC	1.5	NC
Rat, IMH (IV)	1	165	175	62	66	0.16	0.16	0.37	0.38
Rat, IMH (PO)	10	16.1	46.5	8.8	80	0.25	0.37	0.55	0.79
Rat, Cpd 8 (IV)	0.5	198	NC	76	NC	0.16	NC	0.47	NC
Rat, Cpd 8 (PO)	5	12.5	NC	NC	NC	0.33	NC	NC	NC

10 *Human studies*

Study design and methodology

The study is a single-center, randomized, double-blind, placebo-controlled, single ascending dose, safety and tolerability study of compound 8 mucate salt capsules in healthy volunteers. Four successive cohorts are planned with doses of compound 8 mucate salt ((R)-isomethoptene mucate) capsules, 35 mg, 70 mg, 140 mg, and 280 mg, respectively. Each cohort consists of 15 subjects, and subjects are randomly assigned in a 3:1:1 ratio to compound 8 mucate salt, racemic isomethoptene, or placebo capsules:

- Cohort 1: compound **8** mucate salt, 35 mg (n=9); Racemic isometheptene, 70 mg (n=3); Placebo (n=3)
- Cohort 2: compound **8** mucate salt, 70 mg (n=9); Racemic isometheptene, 70 mg (n=3); Placebo (n=3)
- 5 • Cohort 3: compound **8** mucate salt, 140 mg (n=9); Racemic isometheptene, 70 mg (n=3); Placebo (n=3)
- Cohort 4: compound **8** mucate salt, 280 mg (n=9); Racemic isometheptene, 70 mg (n=3); Placebo (n=3)

Unless otherwise modified based on safety review following each cohort, all subjects
10 in Cohorts 1, 2, and 3 took 4 capsules and subjects in Cohort 4 take 8 capsules.

All subjects are screened for eligibility. After re-confirming that subjects meet the inclusion and none of the exclusion criteria, eligible subjects are admitted on Day 1 (Visit 1) to the clinic at least 10 hours before dosing. The following morning on Day 1 after all pre-dose assessments are complete, subjects receive a single dose of study
15 drug (4 or 8 capsules depending on the cohort). Following dosing, subjects are confined for close monitoring over 48 hours. Post-dose safety monitoring and blood collection for PK analysis occur periodically during the 48-hour period. Once all 48-hour post-dose assessments are completed, the subject is discharged with a follow-up visit in 7 days (Day 10 ± 1 day) for their final study visit (Visit 2). Preliminary data
20 are shown in Figures 11A-D for cohorts 1 and 2 and in Figures 12A-D for cohort 3. Interconversion between (R)-isometheptene and (S)-isometheptene is not observed. For cohort 3, the data suggest that there are slow, normal, and fast metabolizers of (R)-isometheptene and (S)-isometheptene.

Additionally, a dose dependent decrease of side effects is observed during the study.
25 Subjects participating in clinical trials of experimental medicines can have anxiety in connection with ingesting a test article that may contain an experimental medicine or experience white coat syndrome in a medical environment, which can lead to elevated blood pressure and other side effects.. Subjects receiving 140 mg of (R)-isometheptene report no side effects. One subject receiving 70 mg of (R)-
30 isometheptene reports side effects. Three subjects receiving 35 mg of (R)-

isometheptene report side effects. Four subjects in the placebo group report side effects. Since the placebo group had the highest number of subjects reporting side effects, these results suggest that increased amounts of (R)-isometheptene can reduce side effects and that (R)-isometheptene appears to have a calming effect. In some
5 embodiments, compounds or compositions of this disclosure can be used in the treatment of white coat syndrome, anxiety, or anxiety and tension associated with dementias such as Alzheimer's disease.

Example 15 Inflammatory soup model studies of compounds and compositions of the disclosure

10 Rats can be used in an inflammatory soup (IS) model of migraine. Inflammatory soup, composed of a mixture of prostaglandin E2, serotonin, bradykinin, and histamine, has frequently been used in the migraine literature to study activation of nociceptors and as a model of migraine. Activity of the compounds described herein can be evaluated using the inflammatory soup model.

15 To assess trigeminal allodynia, periorbital von Frey microfilament thresholds are measured throughout the treatment period in rats receiving infusions of saline (n = 10) or IS (n = 10) three days/week. Rats receiving infusions of IS transition to a more sensitive state, as seen as a decrease in their periorbital thresholds, whereas rats receiving saline infusions do not transition to a more sensitive state. Rats that
20 transition to chronic periorbital sensitivity have thresholds of < 2.0g. Naive or non-transitioned rats do not respond to any pressure less than 8-10g. Data are shown in Figure 16.

The effects of R- and S-enantiomers of isometheptene mucate (compounds 8 and 26
25 mucate salts, 1 mg/kg, 30 mg/kg, and 100 mg/kg i.p.) on trigeminal sensitivity in the IS model (closely mimics the symptoms of chronic migraine) are tested. A test compound could also be selected from a compound having the formula 1-54, or a mixture thereof, or a pharmaceutically acceptable salt, free base form, enantiomer, diastereomer, tautomer, solvate, or prodrug, or a mixture thereof, of any of the

foregoing compounds or a test composition selected from any of the compositions disclosed herein.

Dosing rats with 1 mg/kg of either the R- or S-enantiomers of isometheptene mucate has no significant effect on trigeminal thresholds during the 0.5 hour, 1.5 hour, 2.5 hour, 3.5 hour, and 24 hour time points (Fig. 13).

By contrast, treatment with 30 mg/kg of the R-enantiomer of isometheptene has an analgesic effect starting at the 0.5 hour time point, illustrated by a 2.3 ± 0.3 -fold increase in trigeminal thresholds ($p < 0.01$, ANOVA) (Fig. 14). This analgesic effect continued during the 1.5 hour (3.0 ± 0.4 -fold, $p < 0.01$, ANOVA), 2.5 hour (2.9 ± 0.4 -fold, $p < 0.001$, ANOVA), and 3.5 hour (1.7 ± 0.2 -fold, $p < 0.05$, ANOVA) time points (Fig. 14). Trigeminal thresholds return to baseline levels at the 24 hour time point. The saline control group has no change in trigeminal thresholds over the time-course of the experiment (Fig. 14).

Treatment with 30 mg/kg of the S-enantiomer of isometheptene has no analgesic effect during the 0.5 hour ($p = 0.56$, ANOVA), 1.5 hour ($p = 0.70$, ANOVA), 2.5 hour ($p = 0.59$, ANOVA), 3.5 hour ($p = 0.32$, ANOVA), and 24 hour ($p = 0.54$, ANOVA) time points (Fig. 14).

Therefore, while 1 mg/kg of the R- or S-enantiomer of isometheptene mucate has no effect on trigeminal sensitivity of IS rats, 30 mg/kg of the R-enantiomer mucate significantly decreases trigeminal sensitivity at the 0.5 hour, 1.5 hour, 2.5 hour, and 3.5 hour time points. Baseline thresholds return to baseline levels at the 24 hour time point. Similar to the results found in STA rats (Example 8), the 30 mg/kg dose of the S-enantiomer has no effect on trigeminal sensitivity at any of the time points. No significant changes in trigeminal sensitivity are seen when IS rats are treated with 1 mg/kg R- or S-isometheptene mucate. (Fig. 13, $n = 8$ IS rats/group). Rats receiving saline treatment have no change in sensory thresholds over the course of the experimental timeline. (Fig. 14, $n = 8$ IS rats/group, $*p < 0.05$, $**p < 0.01$, $***p < 0.001$).

Example 16 Dose-response activation of test compounds on phospho-ERK expression of 293T cells transiently transfected with I₁ receptor

I₁ receptors are coupled to activation of phosphatidylcholine selective phospholipase C (PC-PLC), liberation of arachidonic acid (AA), generation of diacylglycerol (DAG),
 5 activation of protein kinase C (PKC) isoforms (PKC β _{II} and PKC ζ) and mitogen-activated protein kinase (MAPK); extracellular-regulated kinase (ERK); and c-jun kinase (JNK) (Figure 22). Studies are conducted with 293T cells transiently transfected with I₁ and compounds of this disclosure to determine if treatment of the cells with the compounds leads to activation of ERK.

10 **A. Materials and reagents**

1. Materials

1.1 Cell line

Cell Line	Source	Culture Medium
293T	ATCC	DMEM + 10%FBS 15

1.2 Reagents

- a) Lipofectamine LTX and plus TM Reagent (Invitrogen , Cat #: 15338100)
 b) Plasmid: I₁R (constructed by Genscript)
 c) Opti-mem (Invitrogen, Cat #: 31985-062)
 20 d) DMEM medium (Invitrogen - Cat #: 11995065)
 e) FBS (Hyclone, Cat #: SH30084.03)
 f) 10× Cell Lysis Buffer (Cell Signalling, Cat #:9803)
 Add Protease Inhibitor Cocktail Tablets (Roche, Cat#:04693132001) and
 phosphatase inhibitor Cocktail Tablets (Roche, Cat #:04906837001)
 25 g) 5× Sample loading Buffer(ShangHai Beyotime Biotechnology, Cat #: P0015L)
 h) PBST (PBS with 0.1% Tween-20)
 i) Prestained Protein Ladder (BIO-RAD, Cat #:161-0374)
 j) BCA protein assay kit(ShangHai Beyotime Biotechnology, Cat #:P0010)
 k) Chemiluminescent HRP substrate (Millipore, Cat #:WBKL 50500)
 30 l) PVDF membrane (Millipore)
 m) Antibodies:

Antibodies	Supplier	Cat.	MW(KD)	Dilution	Isotype
Anti Phospho-p44/42 MAPK (Erk1/2)	CST	9106s	42,44	1:2000	Mouse mAb
Anti – p44/42 MAPK (Erk1/2)	CST	9102s	42,44	1:1000	Rabbit mAb
Anti – Nischarin antibody(C-16)	Santa Cruz	sc-47236	190	1:200	goat IgG
Anti-mouse IgG, HRP-linked Antibody	Promega	W4021		1:4000	
Anti-rabbit IgG, HRP-linked Antibody	Promega	W4011		1:4000	
Anti-goat IgG, HRP-linked Antibody	Beyotime	TA-08		1:2000	

2. Equipment

CO₂ Water Jacketed Incubator, Thermo (USA)

Inverted Microscope – Olympus - IX71

5 Vertical electrophoresis systems and Blotting Module (Bio-Rad)

Biolmaging systems: UVP-Biospectrum AC chemi HR 410

B. Methods

1. Day 1: Set up 293T cells

10 Cells are cultured in DMEM medium with L-glutamine, supplemented with 10% FBS at 37 °C, 5% CO₂ atmosphere. Cells used are 80% confluent. Cells are trypsinized and collected. 0.5×10^6 /2 mL 293T cells are seeded in 6-well plate.

2. Day 2: Transfect 293T cells

Transient transfection with 2.5 µg I₁R plasmid, 2.5 µL plus and 5 µL LTX/well:

- 15
- A : OPTI-MEM 125 µL and target plasmid 2.5 µg and PLUS 2.5 µL are mixed at room temperature and incubated for 5 minutes.
 - A': OPTI-MEM 125 µL and lipofectamine 5 µL are mixed at room temperature and incubated for 5 minutes.
 - A+A' are mixed at room temperature and incubated for 5 minutes.
 - d) 250 µL of each mix is added into the desired wells.

- 3. Day 3 : Change medium to 1%FBS according to the platemap**
- 4. Day 4: Treat 293T/I₁ receptor expressing cells with different concentration compounds for 30 minutes according to the platemap, then collect and lyse cells.**
- 5 a) Prepare 1000x stocks of (S)-isometheptene mucate (compound 26 mucate salt) and (R)-isometheptene mucate (compound 8 mucate salt) diluted with water or DMSO. In addition to compounds 8 and 26 mucate salts, the test compounds can be selected from a compound having the formula 1-54, or a mixture thereof, or a pharmaceutically acceptable salt, free base form, tautomer, enantiomer,
- 10 disastereomer, solvate, or prodrug, or a mixture thereof, of any of the foregoing compounds or a test composition selected from any of the compositions disclosed herein.
- b) Prepare 10x stock of test compounds solution diluted with 1% FBS DMEM.
- c) Treat 293T/I₁ receptor expressing cells with 200 µl 10x test compounds
- 15 solution for 30 minutes according to the platemap.
- d) Cells are collected, spun at 1000 rpm for 4 minutes, washed with ice-cold PBS, and 50 µl of ice-cold 1×lysis buffer (supplemented with protease inhibitors and phosphatase inhibitors) is added to the cells to precipitate lysates. The mixture is vortexed and incubated on ice for 10 minutes.
- 20 e) Transfer cell lysates to Eppendorf tubes and spin at 13,000 rpm, 4 °C for 10 minutes.
- f) Remove a small volume of the lysate to perform a protein assay. Determine the protein concentration for each cell lysate using a BCA protein assay kit.
- g) To the remaining volume of cell lysate, adjust the lysate to the same protein
- 25 concentration with lysis buffer, and then add 1/4 volume of 5× Sample Loading Buffer.
- h) Boil each cell lysate at 100 °C for 5 minutes.
- 5. Day 5-6 :Western blot**
- a) Load equal amounts 40 µg cell lysate onto 10% SDS-PAGE gels using gel
- 30 loading tips, along with molecular weight markers.

- b) Run the samples on a 10% SDS-PAGE gel at 300V for 25 minutes until the dye reached the bottom of the gel.
- c) Transfer protein onto PVDF membrane by Bio-Rad Mini Trans-Blot® Electrophoretic Transfer Cell, at 300mA for 2.5 hours.
- 5 d) After the transfer, remove the membrane from the blotting cassette and mark the orientation of the gel. Rinse briefly with TBST.
- e) Block non-specific binding on the membrane in TBST and 5% nonfat dried milk for 1 hour on a shaking platform at room temperature.
- f) Incubate the membrane with a specific primary antibody diluted in TBST and 5% nonfat dried milk with gentle agitation at 4 °C overnight.
- 10 g) Wash three times for 5 minutes each with TBST.
- h) Incubate with HRP-conjugated secondary antibody in TBST-5% nonfat dried milk for 30 minutes at room temperature.
- i) Wash three times again for 5 minutes each with TBST prior to addition of chemiluminescence reagents.
- 15 j) Remove excess chemiluminescence reagent and acquire image using BioImaging systems system (Biospectrum AC chemi HR 410).

An increase in phospho-ERK is observed after treatment of the human I₁ receptor transfected 293T cells with (R)-isometheptene mucate (compound **8** mucate salt) at 0.002, 0.02, 0.2, and 2 μM (Figure 23). A similar increase in phospho-ERK is not observed after treatment with (S)-isometheptene mucate (compound **26** mucate salt).

20

Example 17 Evaluation of test compound in the precipitated withdrawal (Saelens) test in the mouse

In this study, the analgesic potential of (R)-isometheptene (compound **8** mucate salt) and (S)-isometheptene (compound **26** mucate salt) is evaluated using an opiate-like dependence model with the Naloxone-precipitated Withdrawal (Saelens) Test in mice. Typically, when opiate-pretreated mice are administered the opiate antagonist naloxone, they demonstrate jumping behavior as a pain response to opiate withdrawal

25

symptoms. The analgesic activity of (R)-isometheptene and (S)-isometheptene is assessed in this study by measuring whether isometheptene administration can reduce this naloxone-induced jumping activity. In addition to compounds **8** and **26** mucate salts, the test compounds can be selected from a compound having the formula **1-54**,
5 or a mixture thereof, or a pharmaceutically acceptable salt, free base form, tautomer, enantiomer, diastereomer, solvate, or prodrug, or a mixture thereof, of any of the foregoing compounds or a test composition selected from any of the compositions disclosed herein.

One hundred and ten male NMRI mice, bred by Janvier Labs and group housed in
10 enriched conditions, are split into 11 different experimental groups (8 treatment groups, 3 control), each consisting of 10 mice and identified by indelible tail markings. Mice receive 7 administrations of morphine (32 mg/kg i.p.) over 2 consecutive days; 5
administrations on the first day at 9:00, 10:00, 11:00, 13:00 and 15:00, and 2
administrations on the second day at 9:00 and 11:00. Two hours following the last
15 injection on the D2, the mice receive i.p. naloxone injection (10 mg/kg) and are individually placed in an inverted Plexiglas container so the number of jumps is recorded for the 10 minutes immediately following injection. The effects of (R)-
isometheptene and (S)-isometheptene are each evaluated at two doses (10 mg/kg and
30 mg/kg), administered i.p. 30 minutes before naloxone or physiological saline and
20 compared with the appropriate vehicle control group. A third control group is included for additional reference, where mice are administered saline in place of
morphine and receive only the drug-free vehicle injection on D2. Because of the
number of animals, the experiment is divided into 2 sub-experiments (n=5
mice/group/day) (Figure 28).

25 All data is entered into calculation sheets and compared to the raw data by two people and thus completely verified prior to data analysis. Mann-Whitney U-test analysis is used to compare treated groups with the appropriate controls. Differences are considered statistically significant when the null hypothesis can be rejected at a risk of less than 0.05.

Example 18 Evaluation of rat models of osteoarthritis (OA)

In this study, two experiments are conducted using a monosodium iodacetate (MIA) induced model of osteoarthritic pain in adult male SD rats to assess the analgesic potential of the test compounds. In the first experiment, MIA is injected to induce
5 osteoarthritic pain which manifested as a shift in hindlimb weight distribution. The analgesic potential of (R)-isometheptene (compound **8** mucate salt) and (S)-isometheptene (compound **26** mucate salt) are thus assessed by evaluating their respective abilities to reverse these shifts, using Diclofenoc as a reference substance (positive control) (Figures 29-31). In addition to compounds **8** and **26** mucate salts,
10 the test compounds can be selected from a compound having the formula **1-54**, or a mixture thereof, or a pharmaceutically acceptable salt, free base form, enantiomer, diastereomer, tautomer, solvate, or prodrug, or a mixture thereof, of any of the foregoing compounds or a test composition selected from any of the compositions disclosed herein. Weight bearing chambers are first used to assess baseline weight
15 distribution, after which animals receive intraarticular (i.ar.) injections of MIA (3 or 4.8 mg) or saline. Fourteen days after injection (D14), animals receive either isometheptene (R)-isometheptene or (S)-isometheptene at 10, 30, or 100 mg/kg i.v.), diclofenac (30 mg/kg p.o.), or vehicle injections and weight-bearing is re-measured every 30 minutes for 2-3 hours. In total, 3 conditions are evaluated (MIA 3 mg, 4.8 mg,
20 vehicle) in 8 groups ((R)-isometheptene and (S)-isometheptene at 3 doses each, diclofenac, vehicle) with 12 animals per group for a total of 288 rats.

For the second experiment, the analgesic potential of the test compounds is assessed using a post-MIA conditioned place preference (CPP) paradigm in adult male SD rats. Animals are acclimated to the CPP apparatus by allowing them to explore all 3
25 chambers for 30 minutes/day for 3 days and on day 13 (D13), baseline time spent in each chamber is assessed for 15 minutes. On D14, animals receive either an i.v. vehicle or i.ar. saline treatment and are confined in 1 chamber for 30 minutes in the morning. Four hours later, they are injected with an optimal dose of either (R)-isometheptene (compound **8** mucate salt), (S)-isometheptene (compound **26** mucate

salt), vehicle, or lidocaine (positive control) and confined in the opposite chamber for 30 minutes. On day 15 (D15), the animals are allowed to explore all 3 chambers again for 15 minutes and the Difference Score of time spent in the drug-paired chamber (day 15 – baseline) is calculated to indicate potential analgesic relief. In total, 2 conditions
5 are evaluated (MIA, vehicle) in 4 groups ((R)-isometheptene, (S)-isometheptene, lidocaine, vehicle) with 20 animals per group for a total of 160 rats.

Example 19 Evaluation of the test compounds on modulation of opioid withdrawal

To assess the efficacy of the test compounds in alleviating naloxone-precipitated withdrawal in chronic morphine-treated rats, male SD rats are implanted with
10 morphine pellets (2 x 75 mg, s.c.). Seven days later, baseline body weight and hot plate latency is assessed. The animals then receive systemic administration of the vehicle or varying doses of the test compounds, followed by naloxone (3 mg/kg i.p.) or saline. The jumping frequency, the existence of diarrhea, and wet dog shaking symptoms are recorded during the first 30 minutes post-naloxone administration. Hot
15 plate latency and body weight are re-assessed 30 minutes post-naloxone/saline. In total, 2 pre-treatment groups (naloxone, vehicle) are evaluated in 7 groups ((R)-isometheptene (compound 8 mucate salt) and (S)-isometheptene (compound 26
mucate salt) at 10, 30, and 100 mg/kg + vehicle) with 8 rats per group for a total of 112 rats. In addition to compounds 8 and 26 mucate salts, the test compounds can be
20 selected from a compound having the formula 1-54, or a mixture thereof, or a pharmaceutically acceptable salt, free base form, enantiomer, diastereomer, tautomer, solvate, or prodrug, or a mixture thereof, of any of the foregoing compounds or a test composition selected from any of the compositions disclosed herein (Figures 32-38).

Example 20 Evaluation of Nitric Oxide Donor Induced Model in Rats

25 To assess the efficacy of the test compounds for the reversal of cutaneous allodynia, sumatriptan-induced medication overuse headache (MOH) are triggered by nitric oxide (NO) donors in rats so the rescue efficacy of isometheptene can be assessed. Baseline paw withdrawal thresholds (PWT) are assessed for each animal, before

receiving s.c. sumatriptan (0.6 mg/24 hours) or saline delivered by osmotic minipump for 7 days. The animals are then housed drug-free for 14 days and on day 21 (D21) sodium nitroprusside (SNP; 3mg/kg i.p.) is injected and facial and hindpaw tactile thresholds are assessed at 1 and 2 hours post-SNP. Rats that successfully develop tactile hypersensitivity at 2 hours post SNP are treated with varying doses of the isometheptene isomers or vehicle controls. Facial and hindpaw allodynia is further assessed using von Frey filaments at appropriate time points until 5 hours post-SNP to determine the efficacy of the isometheptene compounds in reversal of cutaneous allodynia precipitated by NO donor (Figures 24 and 25). In total, two pre-treatment conditions (sumatriptan or saline pump) are evaluated in 7 groups ((R)-isometheptene (compound 8 mucate salt) and (S)-isometheptene (compound 26 mucate salt) at 10, 30 and 100 mg/kg + vehicle), with 12 rats per group for a total of 168 rats. In addition to compounds 8 and 26 mucate salts, the test compounds can be selected from a compound having the formula 1-54, or a mixture thereof, or a pharmaceutically acceptable salt, free base form, tautomer, enantiomer, diastereomer, solvate, or prodrug, or a mixture thereof, of any of the foregoing compounds or a test composition selected from any of the compositions disclosed herein.

Incorporation by Reference

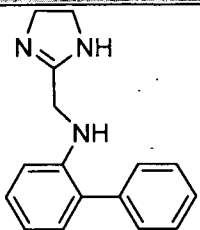
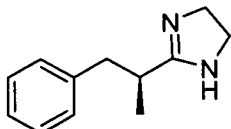
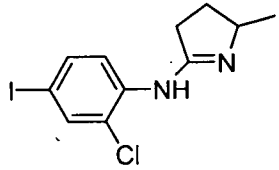
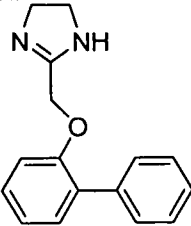
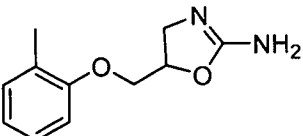
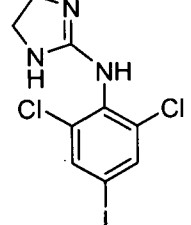
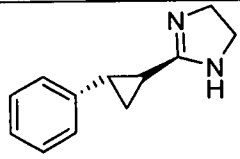
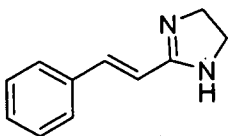
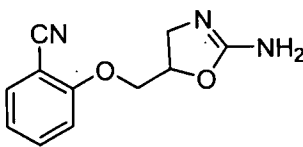
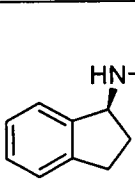
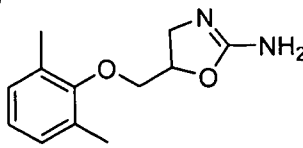
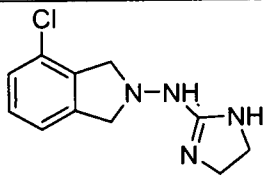
All references cited in this specification, and their references, are incorporated by reference herein in their entirety where appropriate for teachings of additional or alternative details, features, and/or technical background.

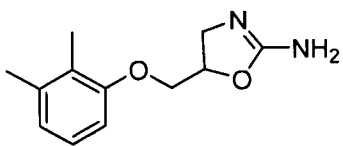
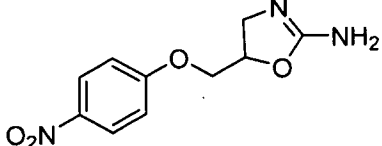
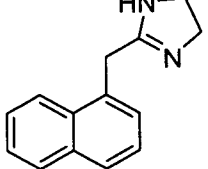
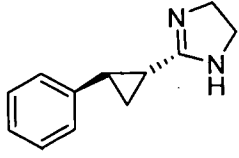
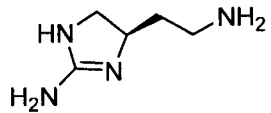
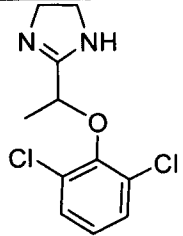
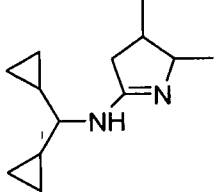
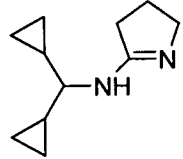
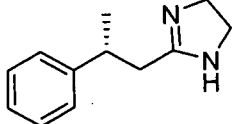
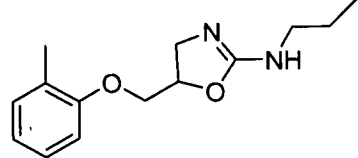
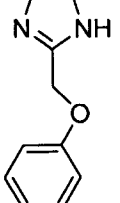

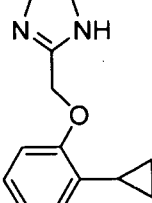
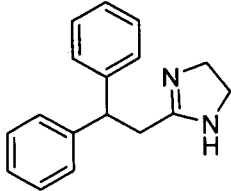
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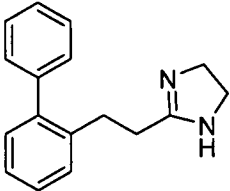
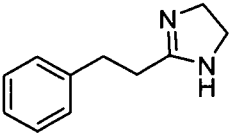
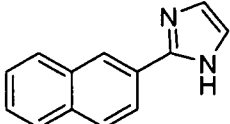
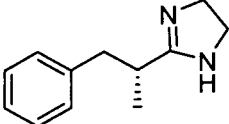
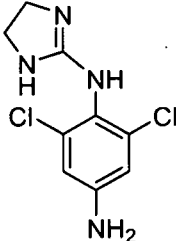
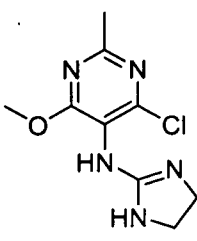
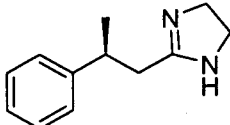
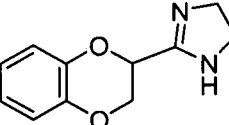
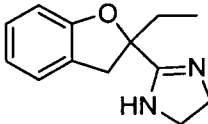
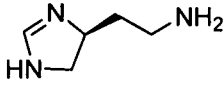
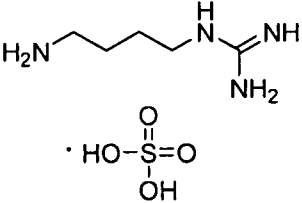
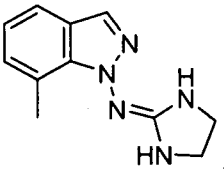
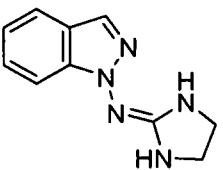
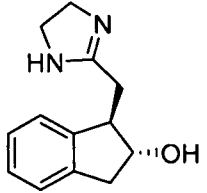
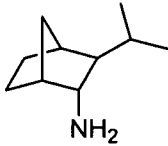
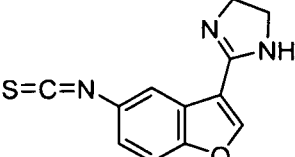
While the invention has been particularly shown and described with reference to particular embodiments, it will be appreciated that variations of the above-disclosed and other features and functions, or alternatives thereof, may be desirably combined into many other different systems or applications. Also, that various presently unforeseen or unanticipated alternatives, modifications, variations or improvements therein may be subsequently made by those skilled in the art which are also intended to be encompassed by the following claims.

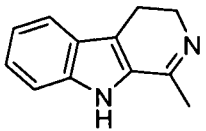
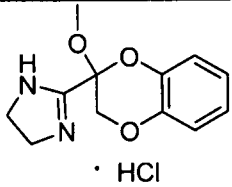
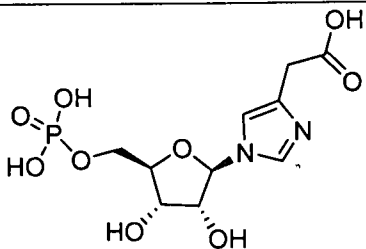
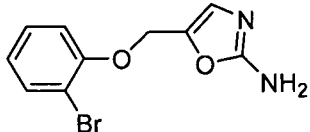
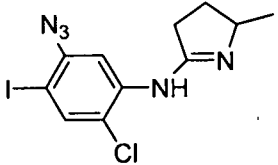
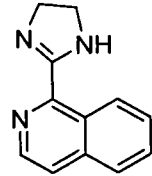
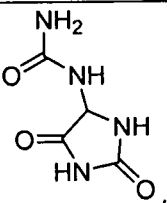
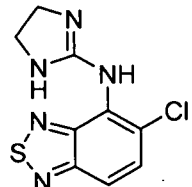
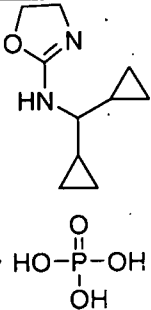
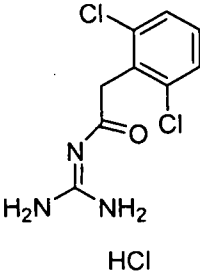
Some embodiments of this disclosure are:

1. A compound for use as an analgesic, the compound having the formula:

Cpd ID	Structure	Cpd ID	Structure
1		2	
3		4	
5		6	
7		9	
10		11	
12		13	

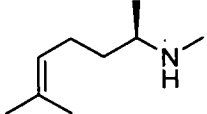
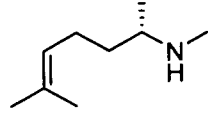
14		15	
16		17	
18		19	
20		21	
22		23	
24		25	
27		28	

29		30	
31		32	
33		34	
35		36	
37		38	
39		40	
41		42	
43		44	

45		46	 · HCl
47		48	
49		50	
51		52	
53	 · HO-P(=O)(OH) ₂ , or	54	 HCl

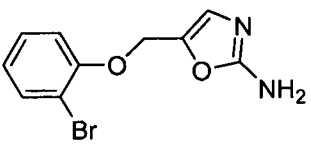
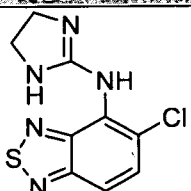
or a mixture thereof, or a pharmaceutically acceptable salt, free base form, enantiomer, diastereomer, tautomer, solvate, or prodrug, or a mixture thereof, of any of the foregoing compounds.

2. A compound for use as an analgesic, the compound having the formula:

Cpd ID	Structure	Cpd ID	Structure
8	 or	26	

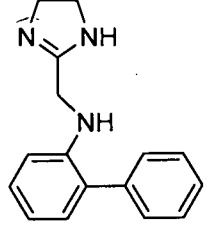
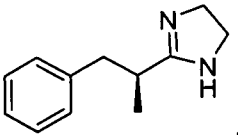
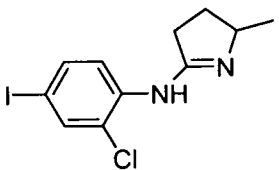
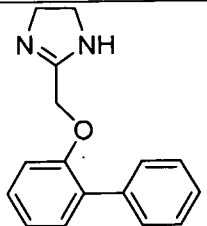
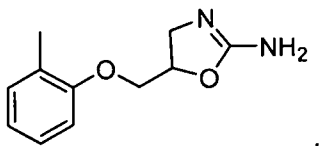
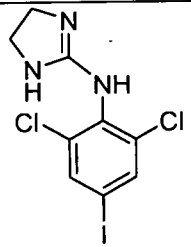
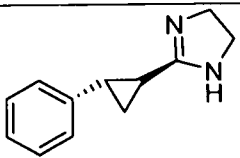
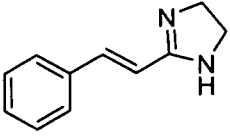
or a mixture thereof, or a pharmaceutically acceptable salt, solvate, or prodrug, or a mixture thereof, of any of the foregoing compounds.

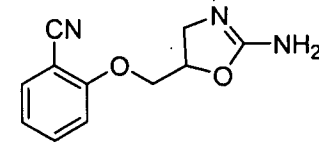
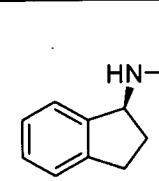
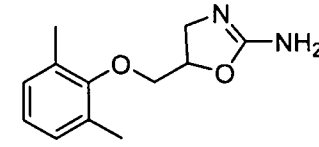
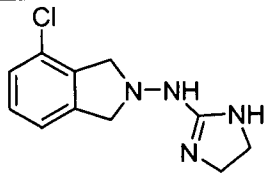
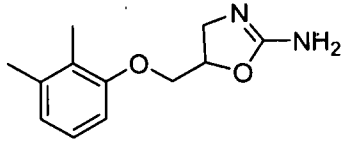
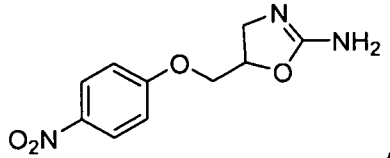
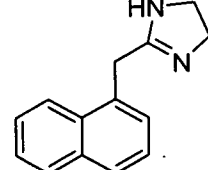
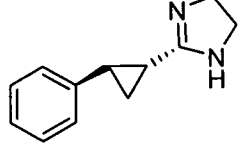
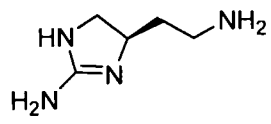
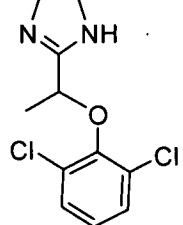
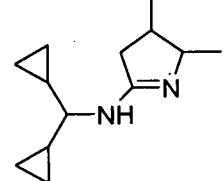
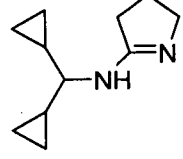
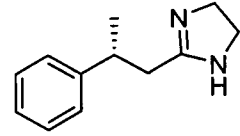
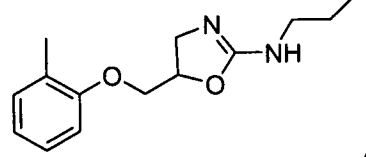
3. A compound for use as an analgesic, the compound having the formula:

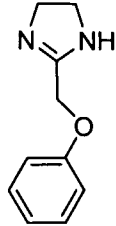
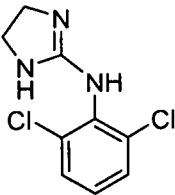
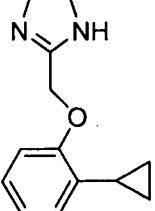
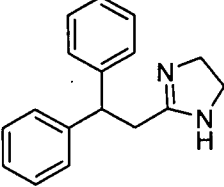
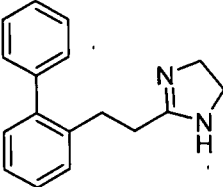
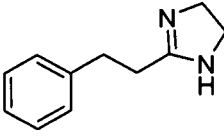
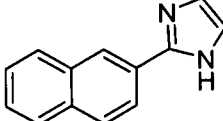
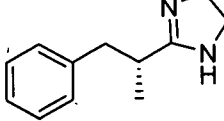
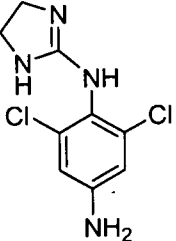
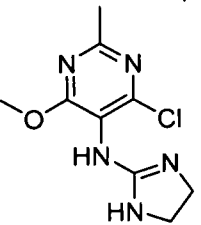
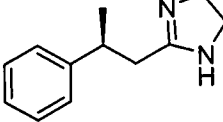
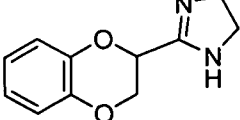
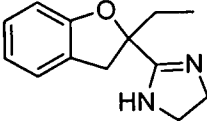
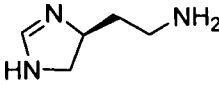
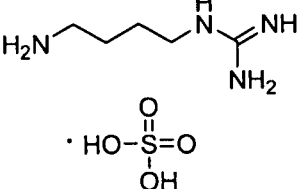
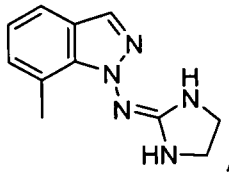
Cpd ID	Structure	Cpd ID	Structure
48	 or	52	

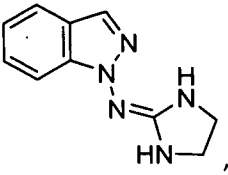
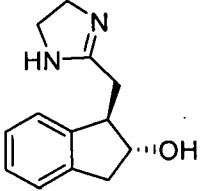
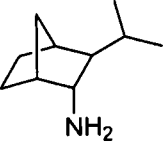
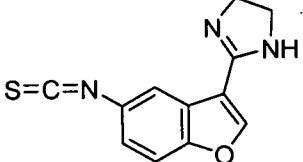
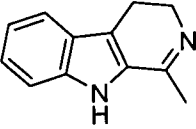
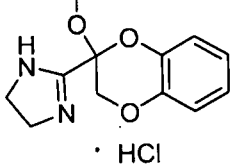
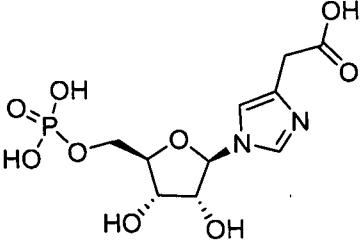
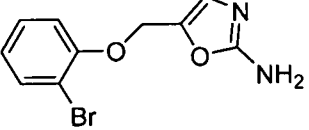
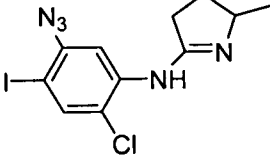
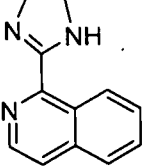
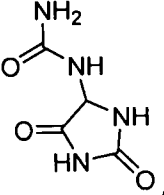
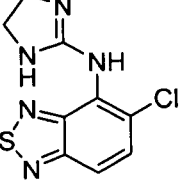
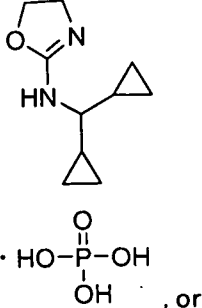
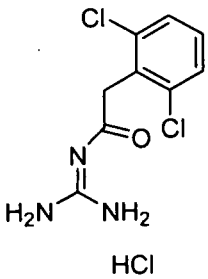
or a mixture thereof, or a pharmaceutically acceptable salt, tautomer, solvate, or prodrug, or a mixture thereof, of any of the foregoing compounds.

4. A pharmaceutical composition comprising as an active ingredient a therapeutically effective amount of a compound having the formula:

Cpd ID	Structure	Cpd ID	Structure
1		2	
3		4	
5		6	
7		9	

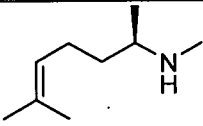
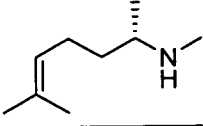
10		11	
12		13	
14		15	
16		17	
18		19	
20		21	
22		23	

24		25	
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31		32	
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35		36	
37		38	
39		40	

41		42	
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51		52	
53		54	

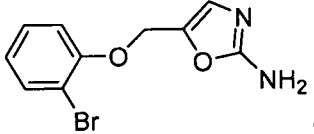

or a mixture thereof, or a pharmaceutically acceptable salt, free base form, enantiomer, diastereomer, tautomer, solvate, or prodrug or a mixture thereof, of any of the foregoing compounds.

5. The pharmaceutical composition of embodiment 4, further comprising at least one pharmaceutically acceptable excipient, carrier, or diluent.
6. Use of the pharmaceutical composition of embodiment 4 or 5 as an analgesic.
7. A pharmaceutical composition comprising as an active ingredient a therapeutically effective amount of a compound having the formula:

Cpd ID	Structure	Cpd ID	Structure
8	 or	26	

or a mixture thereof, or a pharmaceutically acceptable salt, solvate, or prodrug, or a mixture thereof, of any of the foregoing compounds.

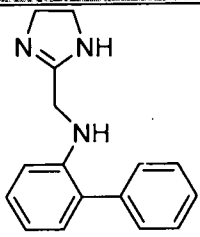
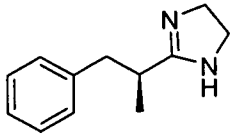
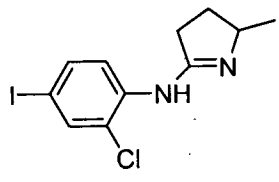
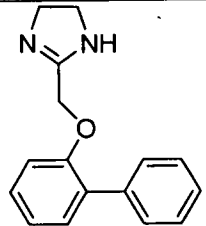
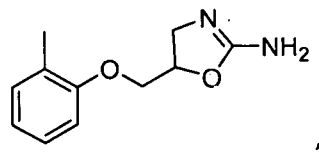
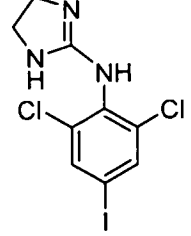
8. The pharmaceutical composition of embodiment 7, further comprising at least one pharmaceutically acceptable excipient, carrier, or diluent.
9. Use of the pharmaceutical composition of embodiment 7 or 8 as an analgesic.
10. A pharmaceutical composition comprising as an active ingredient a therapeutically effective amount of a compound having the formula:

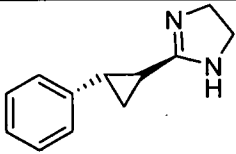
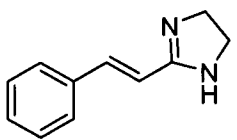
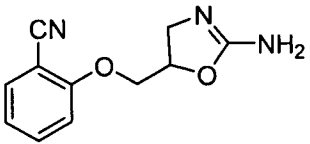
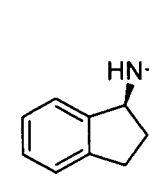
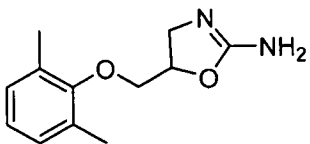
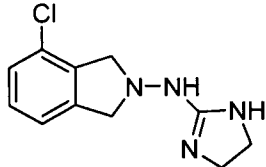
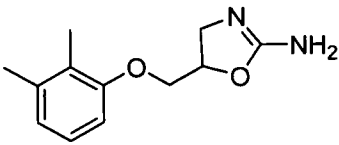
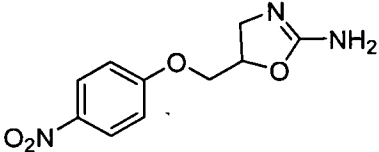
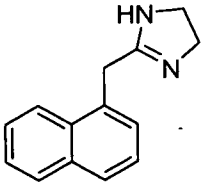
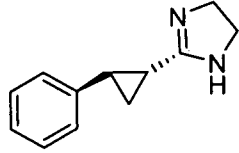
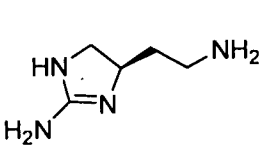
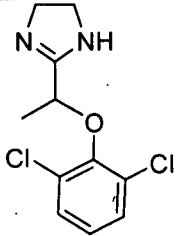
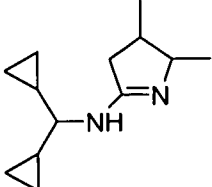
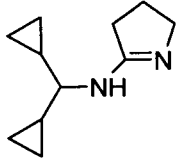
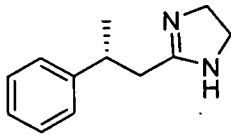
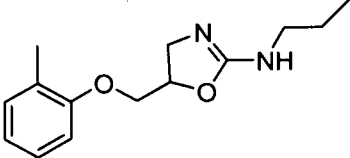
Cpd ID	Structure	Cpd ID	Structure
48	 or	52	

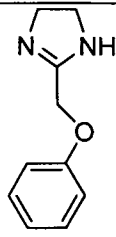
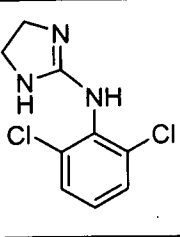
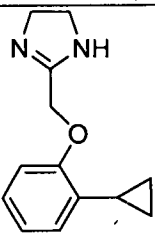
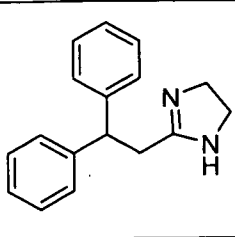
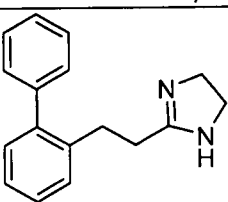
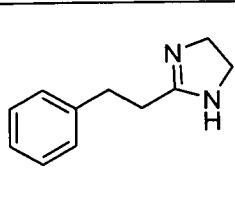
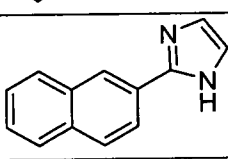
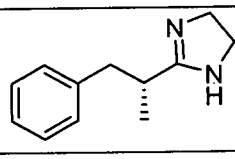

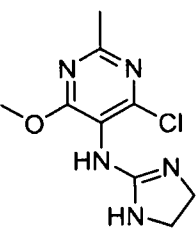
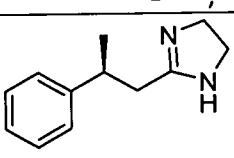
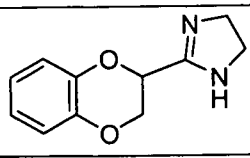
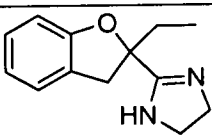
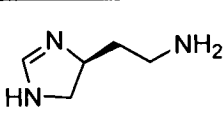
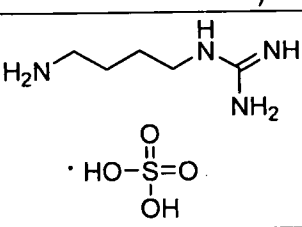
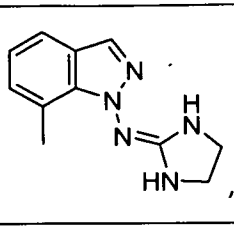
or a mixture thereof, or a pharmaceutically acceptable salt, tautomer, solvate, or prodrug, or a mixture thereof, of any of the foregoing compounds.

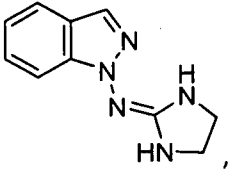
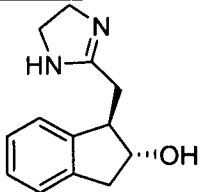
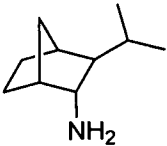
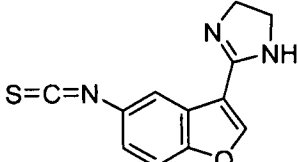
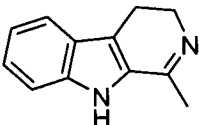
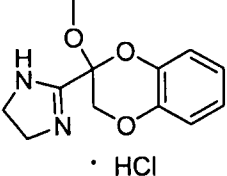
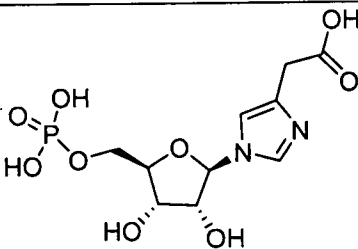
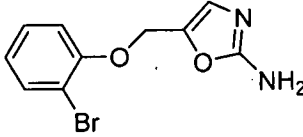
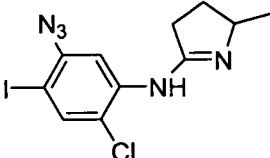

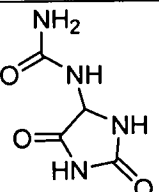
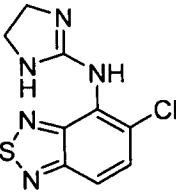
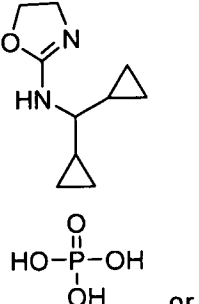
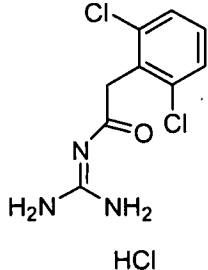
11. The pharmaceutical composition of embodiment 10, further comprising at least one pharmaceutically acceptable excipient, carrier, or diluent.
12. Use of the pharmaceutical composition of embodiment 10 or 11 as an analgesic.

13. A method of treating or preventing one or more conditions selected from the group consisting of: pain; psychic pain; psychological pain; psychiatric pain; depression; allodynia; fibromyalgia; fibromyalgia-ness; central sensitization; centralization; regional pain syndrome; temporomandibular joint syndrome (TMJ); lower back pain; interstitial cystitis; Gulf War syndrome; visceral pain; phantom limb pain; kidney stones; gout; neuropathic pain; post-herpetic neuralgia; diabetic neuropathy; sickle cell pain; priapism; nociceptive pain; post-operative pain; orthopedic injury pain; bunionectomy; dental extraction; pain after severed spinal cord injury; osteoarthritis; rheumatoid arthritis; Lyme disease; Parkinson's disease; pain associated with cancer; opioid-induced constipation; an opioid withdrawal symptom; and pain associated with post-traumatic stress disorder (PTSD), in a patient in need thereof, comprising administering to said patient a therapeutically effective amount a compound having the formula:

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7		9	
10		11	
12		13	
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18		19	
20		21	
22		23	

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39		40	

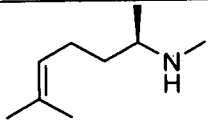
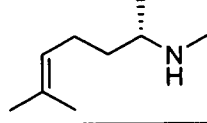
41		42	
43		44	
45		46	 <p>HCl</p>
47		48	
49		50	
51		52	
53	 <p>HO-P(=O)(OH)₂, or</p>	54	 <p>HCl</p>

or a mixture thereof, or a pharmaceutically acceptable salt, free base form, enantiomer, diastereomer, tautomer, solvate, or prodrug, or a mixture thereof, of any of the foregoing compounds.

14. The method of embodiment **13**, wherein the condition is depression.
15. The method of embodiment **13**, wherein the condition is Parkinson's disease.
16. The method of embodiment **13**, wherein the condition is visceral pain.
17. The method of embodiment **13**, wherein the condition is allodynia.
18. The method of embodiment **13**, wherein the condition is fibromyalgia.
19. The method of embodiment **13**, wherein the condition is rheumatoid arthritis.
20. The method of embodiment **13**, wherein the condition is neuropathic pain.
21. The method of embodiment **13**, wherein the condition is nociceptive pain.
22. The method of embodiment **13**, wherein the condition is central sensitization.
23. The method of embodiment **13**, wherein the condition is pain.
24. The method of embodiment **13**, wherein the condition is psychic pain.
25. The method of embodiment **13**, wherein the condition is psychological pain.
26. The method of embodiment **13**, wherein the condition is psychiatric pain.
27. The method of embodiment **13**, wherein the condition is phantom limb pain.
28. The method of embodiment **13**, wherein the condition is opioid-induced constipation.
29. The method of embodiment **13**, wherein the condition is an opioid withdrawal symptom.
30. The method of any one of embodiments **13-29**, wherein the compound is administered simultaneously, separately, or sequentially with one or more substances selected from the group consisting of acetaminophen, a non-steroidal anti-inflammatory drug (NSAID), ibuprofen, naprosyn, a cyclooxygenase-2 inhibitor, aspirin, caffeine, dichloralphenazone, a triptan, an antidepressant, a serotonin-norepinephrine reuptake inhibitor (SNRI), and a gabapentinoid.
31. The method of any one of embodiments **13-29**, wherein the compound is administered simultaneously, separately, or sequentially with one or more

additional therapeutics selected from the group consisting of a chemotherapeutic drug; an antiproliferative agent, an anti-inflammatory agent, a corticosteroid, an anti-asthmatic agent, an anti-allergic agent, an immunosuppressive agent, an immunomodulatory agent, a cardiovascular disease treatment agent, an anti-diabetic agent, a blood disorder treatment agent, a nerve growth factor receptor antagonist, a sodium channel blocker, a CYP2D6 inhibitor, and a TNF-alpha inhibitor.

32. The method of embodiment **31**, wherein the additional therapeutic is a CYP2D6 inhibitor.
33. The method of any one of embodiments **13-29**, wherein the compound is administered simultaneously, separately, or sequentially with one or more opiates.
34. A method of treating or preventing one or more conditions selected from the group consisting of: pain; psychic pain; psychological pain; psychiatric pain; allodynia; fibromyalgia; fibromyalgia-ness; central sensitization; centralization; regional pain syndrome; temporomandibular joint syndrome (TMJ); lower back pain; interstitial cystitis; Gulf War syndrome; visceral pain; phantom limb pain; kidney stones; gout; neuropathic pain; post-herpetic neuralgia; diabetic neuropathy; sickle cell pain; priapism; nociceptive pain; , post-operative pain; orthopedic injury pain; bunionectomy; dental extraction; pain after severed spinal cord injury; osteoarthritis; rheumatoid arthritis; Lyme disease; Parkinson's disease; pain associated with cancer; opioid-induced constipation; an opioid withdrawal symptom; and pain associated with post-traumatic stress disorder (PTSD), in a patient in need thereof, comprising administering to said patient a therapeutically effective amount a compound having the formula:

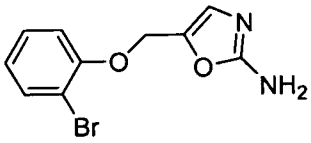

Cpd ID	Structure	Cpd ID	Structure
8	 or	26	

or a mixture thereof, or a pharmaceutically acceptable salt, solvate, or prodrug, or a mixture thereof, of any of the foregoing compounds.

35. The method of embodiment **34**, wherein the condition is Parkinson's disease.
36. The method of embodiment **34**, wherein the condition is visceral pain.
37. The method of embodiment **34**, wherein the condition is allodynia.
38. The method of embodiment **34**, wherein the condition is fibromyalgia.
39. The method of embodiment **34**, wherein the condition is rheumatoid arthritis.
40. The method of embodiment **34**, wherein the condition is neuropathic pain.
41. The method of embodiment **34**, wherein the condition is nociceptive pain.
42. The method of embodiment **34**, wherein the condition is central sensitization.
43. The method of embodiment **34**, wherein the condition is pain.
44. The method of embodiment **34**, wherein the condition is psychic pain.
45. The method of embodiment **34**, wherein the condition is psychological pain.
46. The method of embodiment **34**, wherein the condition is psychiatric pain.
47. The method of embodiment **34**, wherein the condition is phantom limb pain.
48. The method of embodiment **34**, wherein the condition is opioid-induced constipation.
49. The method of embodiment **34**, wherein the condition is an opioid withdrawal symptom.
50. The method of any one of embodiments **34-49**, wherein the compound is administered simultaneously, separately, or sequentially with one or more substances selected from the group consisting of acetaminophen, a non-steroidal anti-inflammatory drug (NSAID), ibuprofen, naprosyn, a cyclooxygenase-2 inhibitor, aspirin, caffeine, dichloralphenazone, a triptan, an antidepressant, a serotonin-norepinephrine reuptake inhibitor (SNRI), and a gabapentinoid.
51. The method of any one of embodiments **34-49**, wherein the compound is administered simultaneously, separately, or sequentially with one or more additional therapeutics selected from the group consisting of a chemotherapeutic drug, an antiproliferative agent, an anti-inflammatory agent,

a corticosteroid, an anti-asthmatic agent, an anti-allergic agent, an immunosuppressive agent, an immunomodulatory agent, a cardiovascular disease treatment agent, an anti-diabetic agent, a blood disorder treatment agent, a nerve growth factor receptor antagonist, a sodium channel blocker, a CYP2D6 inhibitor, and a TNF-alpha inhibitor.

52. The method of embodiment **51**, wherein the additional therapeutic is a CYP2D6 inhibitor.
53. The method of any one of embodiments **34-49**, wherein the compound is administered simultaneously, separately, or sequentially with one or more opiates.
54. A method of treating or preventing one or more conditions selected from the group consisting of: pain; psychic pain; psychological pain; psychiatric pain; depression; allodynia; fibromyalgia; fibromyalgia-ness; central sensitization; centralization; regional pain syndrome; temporomandibular joint syndrome (TMJ); lower back pain; interstitial cystitis; Gulf War syndrome; visceral pain; phantom limb pain; kidney stones; gout; neuropathic pain; post-herpetic neuralgia; diabetic neuropathy; sickle cell pain; priapism; nociceptive pain; post-operative pain; orthopedic injury pain; bunionectomy; dental extraction; pain after severed spinal cord injury; osteoarthritis; rheumatoid arthritis; Lyme disease; Parkinson's disease; pain associated with cancer; opioid-induced constipation; an opioid withdrawal symptom; and pain associated with post-traumatic stress disorder (PTSD), in a patient in need thereof, comprising administering to said patient a therapeutically effective amount a compound having the formula:

Cpd ID	Structure	Cpd ID	Structure
48	 or	52	

or a mixture thereof, or a pharmaceutically acceptable salt, tautomer, solvate, or prodrug, or a mixture thereof, of any of the foregoing compounds.

55. The method of embodiment 54, wherein the condition is depression.
56. The method of embodiment 54, wherein the condition is Parkinson's disease.
57. The method of embodiment 54, wherein the condition is visceral pain.
58. The method of embodiment 54, wherein the condition is allodynia.
59. The method of embodiment 54, wherein the condition is fibromyalgia.
60. The method of embodiment 54, wherein the condition is rheumatoid arthritis.
61. The method of embodiment 54, wherein the condition is neuropathic pain.
62. The method of embodiment 54, wherein the condition is nociceptive pain.
63. The method of embodiment 54, wherein the condition is central sensitization.
64. The method of embodiment 54, wherein the condition is pain:
65. The method of embodiment 54, wherein the condition is psychic pain.
66. The method of embodiment 54, wherein the condition is psychological pain.
67. The method of embodiment 54, wherein the condition is psychiatric pain.
68. The method of embodiment 54, wherein the condition is phantom limb pain.
69. The method of embodiment 54, wherein the condition is opioid-induced constipation.
70. The method of embodiment 54, wherein the condition is an opioid withdrawal symptom.
71. The method of any one of embodiments 54-70, wherein the compound is administered simultaneously, separately, or sequentially with one or more substances selected from the group consisting of acetaminophen, a non-steroidal anti-inflammatory drug (NSAID), ibuprofen, naprosyn, a cyclooxygenase-2 inhibitor, aspirin, caffeine, dichloralphenazone, a triptan, an antidepressant, a serotonin-norepinephrine reuptake inhibitor (SNRI), and a gabapentinoid.
72. The method of any one of embodiments 54-70, wherein the compound is administered simultaneously, separately, or sequentially with one or more additional therapeutics selected from the group consisting of a chemotherapeutic drug, an antiproliferative agent, an anti-inflammatory agent, a corticosteroid, an anti-asthmatic agent, an anti-allergic agent, an

immunosuppressive agent, an immunomodulatory agent, a cardiovascular disease treatment agent, an anti-diabetic agent, a blood disorder treatment agent, a nerve growth factor receptor antagonist, a sodium channel blocker, a CYP2D6 inhibitor, and a TNF-alpha inhibitor.

73. The method of embodiment 72, wherein the additional therapeutic is a CYP2D6 inhibitor.
74. The method of any one of embodiments 54-70, wherein the compound is administered simultaneously, separately, or sequentially with one or more opiates.
75. A method of treating or preventing one or more conditions selected from the group consisting of: pain; psychic pain; psychological pain; psychiatric pain; depression; allodynia; fibromyalgia; fibromyalgia-ness; central sensitization; centralization; regional pain syndrome; temporomandibular joint syndrome (TMJ); lower back pain; interstitial cystitis; Gulf War syndrome; visceral pain; phantom limb pain; kidney stones; gout; neuropathic pain; post-herpetic neuralgia; diabetic neuropathy; sickle cell pain; priapism; nociceptive pain; post-operative pain; orthopedic injury pain; bunionectomy; dental extraction; pain after severed spinal cord injury; osteoarthritis; rheumatoid arthritis; Lyme disease; Parkinson's disease; pain associated with cancer; opioid-induced constipation; an opioid withdrawal symptom; and pain associated with post-traumatic stress disorder (PTSD), in a patient in need thereof, comprising administering to said patient a therapeutically effective amount of the pharmaceutical composition of embodiment 4.
76. The method of embodiment 75, wherein the condition is depression.
77. The method of embodiment 75, wherein the condition is Parkinson's disease.
78. The method of embodiment 75, wherein the condition is visceral pain.
79. The method of embodiment 75, wherein the condition is allodynia.
80. The method of embodiment 75, wherein the condition is fibromyalgia.
81. The method of embodiment 75, wherein the condition is rheumatoid arthritis.
82. The method of embodiment 75, wherein the condition is neuropathic pain.

83. The method of embodiment 75, wherein the condition is nociceptive pain.
84. The method of embodiment 75, wherein the condition is central sensitization.
85. The method of embodiment 75, wherein the condition is pain.
86. The method of embodiment 75, wherein the condition is psychic pain.
87. The method of embodiment 75, wherein the condition is psychological pain.
88. The method of embodiment 75, wherein the condition is psychiatric pain.
89. The method of embodiment 75, wherein the condition is phantom limb pain.
90. The method of embodiment 75, wherein the condition is opioid-induced constipation.
91. The method of embodiment 75, wherein the condition is an opioid withdrawal symptom.
92. The method of any one of embodiments 75-91, wherein the pharmaceutical composition is administered simultaneously, separately, or sequentially with one or more substances selected from the group consisting of acetaminophen, a non-steroidal anti-inflammatory drug (NSAID), ibuprofen, naprosyn, a cyclooxygenase-2 inhibitor, aspirin, caffeine, dichloralphenazone, a triptan, an antidepressant, a serotonin–norepinephrine reuptake inhibitor (SNRI), and a gabapentinoid.
93. The method of any one of embodiments 75-91, wherein the pharmaceutical composition is administered simultaneously, separately, or sequentially with one or more additional therapeutics selected from the group consisting of a chemotherapeutic drug, an antiproliferative agent, an anti-inflammatory agent, a corticosteroid, an anti-asthmatic agent, an anti-allergic agent, an immunosuppressive agent, an immunomodulatory agent, a cardiovascular disease treatment agent, an anti-diabetic agent, a blood disorder treatment agent, a nerve growth factor receptor antagonist, a sodium channel blocker, a CYP2D6 inhibitor, and a TNF-alpha inhibitor.
94. The method of embodiment 93, wherein the additional therapeutic is a CYP2D6 inhibitor.

95. The method of any one of embodiments 75-91, wherein the pharmaceutical composition is administered simultaneously, separately, or sequentially with one or more opiates.
96. A method of treating or preventing one or more conditions selected from the group consisting of: pain; psychic pain; psychological pain; psychiatric pain; allodynia; fibromyalgia; fibromyalgia-ness; central sensitization; centralization; regional pain syndrome; temporomandibular joint syndrome (TMJ); lower back pain; interstitial cystitis; Gulf War syndrome; visceral pain; phantom limb pain; kidney stones; gout; neuropathic pain; post-herpetic neuralgia; diabetic neuropathy; sickle cell pain; priapism; nociceptive pain; post-operative pain; orthopedic injury pain; bunionectomy; dental extraction; pain after severed spinal cord injury; osteoarthritis; rheumatoid arthritis; Lyme disease; Parkinson's disease; pain associated with cancer; opioid-induced constipation; an opioid withdrawal symptom; and pain associated with post-traumatic stress disorder (PTSD), in a patient in need thereof, comprising administering to said patient a therapeutically effective amount of the pharmaceutical composition of embodiment 7.
97. The method of embodiment 96, wherein the condition is Parkinson's disease.
98. The method of embodiment 96, wherein the condition is visceral pain.
99. The method of embodiment 96, wherein the condition is allodynia.
100. The method of embodiment 96, wherein the condition is fibromyalgia.
101. The method of embodiment 96, wherein the condition is rheumatoid arthritis.
102. The method of embodiment 96, wherein the condition is neuropathic pain.
103. The method of embodiment 96, wherein the condition is nociceptive pain.
104. The method of embodiment 96, wherein the condition is central sensitization.
105. The method of embodiment 96, wherein the condition is pain.

106. The method of embodiment **96**, wherein the condition is psychic pain.
107. The method of embodiment **96**, wherein the condition is psychological pain.
108. The method of embodiment **96**, wherein the condition is psychiatric pain.
109. The method of embodiment **96**, wherein the condition is phantom limb pain.
110. The method of embodiment **96**, wherein the condition is opioid-induced constipation.
111. The method of embodiment **96**, wherein the condition is an opioid withdrawal symptom.
112. The method of any one of embodiments **96-111**, wherein the pharmaceutical composition is administered simultaneously, separately, or sequentially with one or more substances selected from the group consisting of acetaminophen, a non-steroidal anti-inflammatory drug (NSAID), ibuprofen, naprosyn, a cyclooxygenase-2 inhibitor, aspirin, caffeine, dichloralphenazone, a triptan, an antidepressant, a serotonin–norepinephrine reuptake inhibitor (SNRI), and a gabapentinoid.
113. The method of any one of embodiments **96-111**, wherein the pharmaceutical composition is administered simultaneously, separately, or sequentially with one or more additional therapeutics selected from the group consisting of a chemotherapeutic drug, an antiproliferative agent, an anti-inflammatory agent, a corticosteroid, an anti-asthmatic agent, an anti-allergic agent, an immunosuppressive agent, an immunomodulatory agent, a cardiovascular disease treatment agent, an anti-diabetic agent, a blood disorder treatment agent, a nerve growth factor receptor antagonist, a sodium channel blocker, a CYP2D6 inhibitor, and a TNF-alpha inhibitor.
114. The method of embodiment **113**, wherein the additional therapeutic is a CYP2D6 inhibitor.

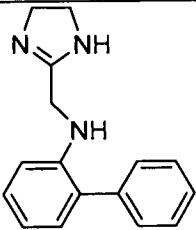
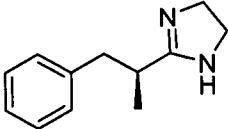
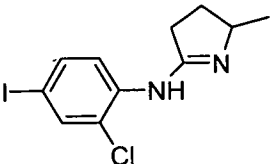
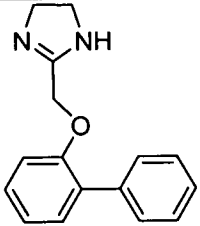
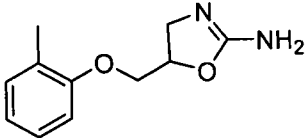

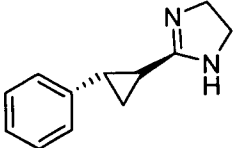
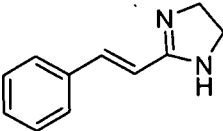
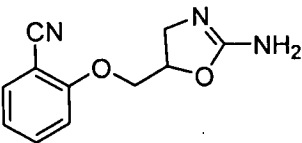
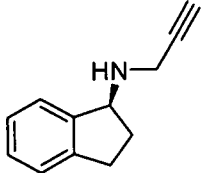
115. The method of any one of embodiments **96-111**, wherein the pharmaceutical composition is administered simultaneously, separately, or sequentially with one or more opiates.
116. A method of treating or preventing one or more conditions selected from the group consisting of: pain; psychic pain; psychological pain; psychiatric pain; depression; allodynia; fibromyalgia; fibromyalgia-ness; central sensitization; centralization; regional pain syndrome; temporomandibular joint syndrome (TMJ); lower back pain; interstitial cystitis; Gulf War syndrome; visceral pain; phantom limb pain; kidney stones; gout; neuropathic pain; post-herpetic neuralgia; diabetic neuropathy; sickle cell pain; priapism; nociceptive pain; post-operative pain; orthopedic injury pain; bunionectomy; dental extraction; pain after severed spinal cord injury; osteoarthritis; rheumatoid arthritis; Lyme disease; Parkinson's disease; pain associated with cancer; opioid-induced constipation; an opioid withdrawal symptom; and pain associated with post-traumatic stress disorder (PTSD), in a patient in need thereof, comprising administering to said patient a therapeutically effective amount of the pharmaceutical composition of embodiment **10**.
117. The method of embodiment **116**, wherein the condition is depression.
118. The method of embodiment **116**, wherein the condition is Parkinson's disease.
119. The method of embodiment **116**, wherein the condition is visceral pain.
120. The method of embodiment **116**, wherein the condition is allodynia.
121. The method of embodiment **116**, wherein the condition is fibromyalgia.
122. The method of embodiment **116**, wherein the condition is rheumatoid arthritis.
123. The method of embodiment **116**, wherein the condition is neuropathic pain.
124. The method of embodiment **116**, wherein the condition is nociceptive pain.

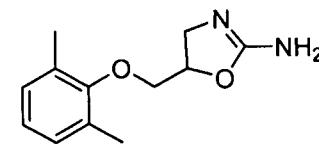
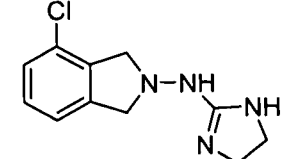
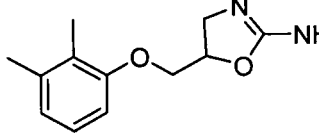
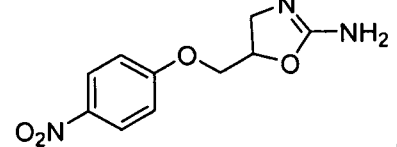
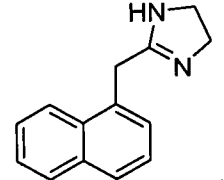
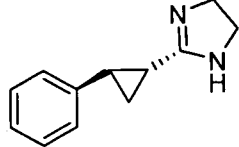
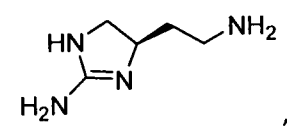
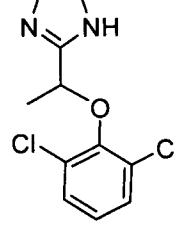
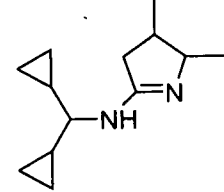
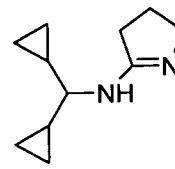
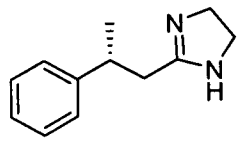
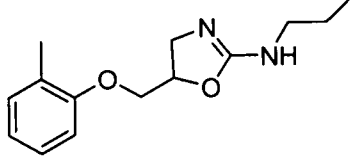
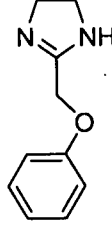
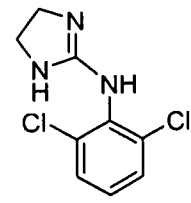
125. The method of embodiment **116**, wherein the condition is central sensitization.
126. The method of embodiment **116**, wherein the condition is pain.
127. The method of embodiment **116**, wherein the condition is psychic pain.
128. The method of embodiment **116**, wherein the condition is psychological pain.
129. The method of embodiment **116**, wherein the condition is psychiatric pain.
130. The method of embodiment **116**, wherein the condition is phantom limb pain.
131. The method of embodiment **116**, wherein the condition is opioid-induced constipation.
132. The method of embodiment **116**, wherein the condition is an opioid withdrawal symptom.
133. The method of any one of embodiments **116-132**, wherein the pharmaceutical composition is administered simultaneously, separately, or sequentially with one or more substances selected from the group consisting of acetaminophen, a non-steroidal anti-inflammatory drug (NSAID), ibuprofen, naprosyn, a cyclooxygenase-2 inhibitor, aspirin, caffeine, dichloralphenazone, a triptan, an antidepressant, a serotonin–norepinephrine reuptake inhibitor (SNRI), and a gabapentinoid.
134. The method of any one of embodiments **116-132**, wherein the pharmaceutical composition is administered simultaneously, separately, or sequentially with one or more additional therapeutics selected from the group consisting of a chemotherapeutic drug, an antiproliferative agent, an anti-inflammatory agent, a corticosteroid, an anti-asthmatic agent, an anti-allergic agent, an immunosuppressive agent, an immunomodulatory agent, a cardiovascular disease treatment agent, an anti-diabetic agent, a blood disorder treatment agent, a nerve growth factor receptor antagonist, a sodium channel blocker, a CYP2D6 inhibitor, and a TNF-alpha inhibitor.

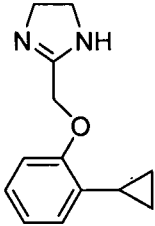
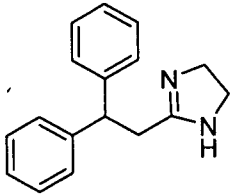
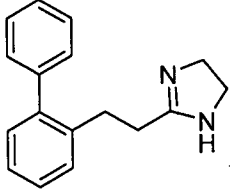
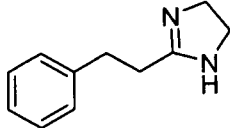
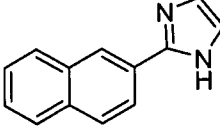
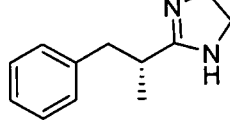

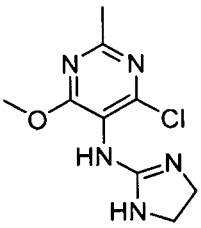
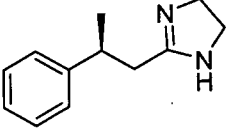
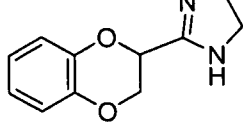
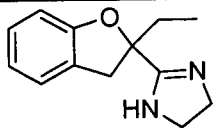
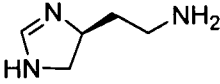
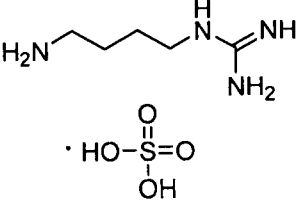
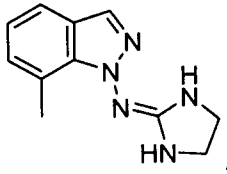
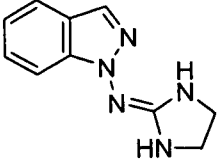
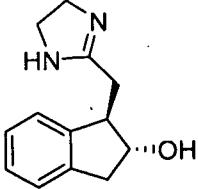
135. The method of embodiment 134, wherein the additional therapeutic is a CYP2D6 inhibitor.

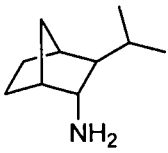
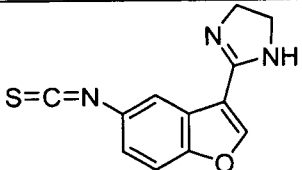
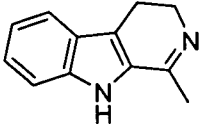
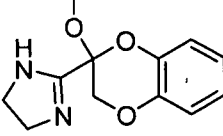
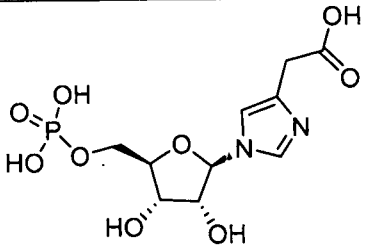
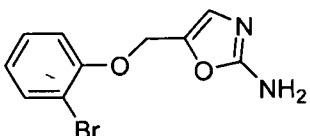
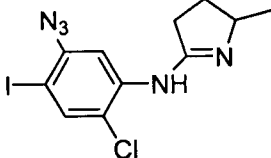
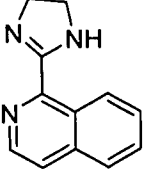
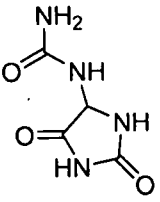

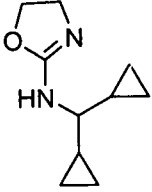
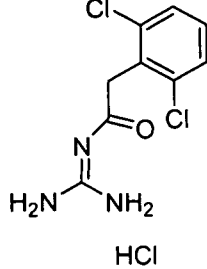
136. The method of any one of embodiments 116-132, wherein the pharmaceutical composition is administered simultaneously, separately, or sequentially with one or more opiates.

137. Use of a compound having the formula:

Cpd ID	Structure	Cpd ID	Structure
1		2	
3		4	
5		6	
7		9	
10		11	

12		13	
14		15	
16		17	
18		19	
20		21	
22		23	
24		25	

27		28	
29		30	
31		32	
33		34	
35		36	
37		38	
39		40	
41		42	

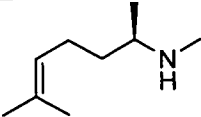
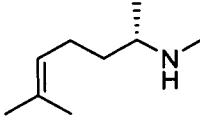
43		44	
45		46	 · HCl
47		48	
49		50	
51		52	
53	 · HO-P(=O)(OH)-OH , or	54	 HCl

or a mixture thereof, or a pharmaceutically acceptable salt, free base form, enantiomer, diastereomer, tautomer, solvate, or prodrug, or a mixture thereof, of any of the foregoing compounds, for the manufacture of a medicament for treating or preventing one or more conditions selected from the group

consisting of: pain; psychic pain; psychological pain; psychiatric pain; depression; allodynia; fibromyalgia; fibromyalgia-ness; central sensitization; centralization; regional pain syndrome; temporomandibular joint syndrome (TMJ); lower back pain; interstitial cystitis; Gulf War syndrome; visceral pain; phantom limb pain; kidney stones; gout; neuropathic pain; post-herpetic neuralgia; diabetic neuropathy; sickle cell pain; priapism; nociceptive pain; post-operative pain; orthopedic injury pain; bunionectomy; dental extraction; pain after severed spinal cord injury; osteoarthritis; rheumatoid arthritis; Lyme disease; Parkinson's disease; pain associated with cancer; opioid-induced constipation; an opioid withdrawal symptom; and pain associated with post-traumatic stress disorder (PTSD).

138. The use of embodiment **137**, wherein the condition is depression.
139. The use of embodiment **137**, wherein the condition is Parkinson's disease.
140. The use of embodiment **137**, wherein the condition is visceral pain.
141. The use of embodiment **137**, wherein the condition is allodynia.
142. The use of embodiment **137**, wherein the condition is fibromyalgia.
143. The use of embodiment **137**, wherein the condition is rheumatoid arthritis.
144. The use of embodiment **137**, wherein the condition is neuropathic pain.
145. The use of embodiment **137**, wherein the condition is nociceptive pain.
146. The use of embodiment **137**, wherein the condition is central sensitization.
147. The use of embodiment **137**, wherein the condition is pain.
148. The use of embodiment **137**, wherein the condition is psychic pain.
149. The use of embodiment **137**, wherein the condition is psychological pain:
150. The use of embodiment **137**, wherein the condition is psychiatric pain.
151. The use of embodiment **137**, wherein the condition is phantom limb pain.

152. The use of embodiment **137**, wherein the condition is opioid-induced constipation.
153. The use of embodiment **137**, wherein the condition is an opioid withdrawal symptom.
154. The use of any one of embodiments **137-153**, wherein the medicament is administered simultaneously, separately, or sequentially with one or more substances selected from the group consisting of acetaminophen, a non-steroidal anti-inflammatory drug (NSAID), ibuprofen, naprosyn, a cyclooxygenase-2 inhibitor, aspirin, caffeine, dichloralphenazone, a triptan, an antidepressant, a serotonin–norepinephrine reuptake inhibitor (SNRI), and a gabapentinoid.
155. The use of any one of embodiments **137-153**, wherein the medicament is administered simultaneously, separately, or sequentially with one or more additional therapeutics selected from the group consisting of a chemotherapeutic drug, an antiproliferative agent, an anti-inflammatory agent, a corticosteroid, an anti-asthmatic agent, an anti-allergic agent, an immunosuppressive agent, an immunomodulatory agent, a cardiovascular disease treatment agent, an anti-diabetic agent, a blood disorder treatment agent, a nerve growth factor receptor antagonist, a sodium channel blocker, a CYP2D6 inhibitor, and a TNF-alpha inhibitor.
156. The use of embodiment **155**, wherein the additional therapeutic is a CYP2D6 inhibitor.
157. The use of any one of embodiments **137-153**, wherein the medicament is administered simultaneously, separately, or sequentially with one or more opiates.
158. Use of a compound having the formula:

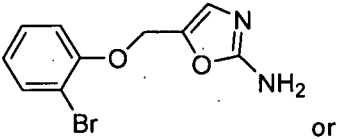
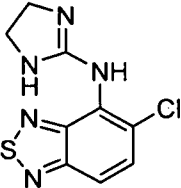
Cpd ID	Structure	Cpd ID	Structure
8	 or	26	

or a mixture thereof, or a pharmaceutically acceptable salt, solvate, or prodrug, or a mixture thereof, of any of the foregoing compounds, for the manufacture of a medicament for treating or preventing one or more conditions selected from the group consisting of: pain; psychic pain; psychological pain; psychiatric pain; allodynia; fibromyalgia; fibromyalgia-ness; central sensitization; centralization; regional pain syndrome; temporomandibular joint syndrome (TMJ); lower back pain; interstitial cystitis; Gulf War syndrome; visceral pain; phantom limb pain; kidney stones; gout; neuropathic pain; post-herpetic neuralgia; diabetic neuropathy; sickle cell pain; priapism; nociceptive pain; post-operative pain; orthopedic injury pain; bunionectomy; dental extraction; pain after severed spinal cord injury; osteoarthritis; rheumatoid arthritis; Lyme disease; Parkinson's disease; pain associated with cancer; opioid-induced constipation; an opioid withdrawal symptom; and pain associated with post-traumatic stress disorder (PTSD).

159. The use of embodiment **158**, wherein the condition is Parkinson's disease.
160. The use of embodiment **158**, wherein the condition is visceral pain.
161. The use of embodiment **158**, wherein the condition is allodynia.
162. The use of embodiment **158**, wherein the condition is fibromyalgia.
163. The use of embodiment **158**, wherein the condition is rheumatoid arthritis.
164. The use of embodiment **158**, wherein the condition is neuropathic pain.
165. The use of embodiment **158**, wherein the condition is nociceptive pain.
166. The use of embodiment **158**, wherein the condition is central sensitization.
167. The use of embodiment **158**, wherein the condition is pain.
168. The use of embodiment **158**, wherein the condition is psychic pain.
169. The use of embodiment **158**, wherein the condition is psychological pain.
170. The use of embodiment **158**, wherein the condition is psychiatric pain.

171. The use of embodiment **158**, wherein the condition is phantom limb pain.
172. The use of embodiment **158**, wherein the condition is opioid-induced constipation.
173. The use of embodiment **158**, wherein the condition is an opioid withdrawal symptom.
174. The use of any one of embodiments **158-173**, wherein the medicament is administered simultaneously, separately, or sequentially with one or more substances selected from the group consisting of acetaminophen, a non-steroidal anti-inflammatory drug (NSAID), ibuprofen, naprosyn, a cyclooxygenase-2 inhibitor, aspirin, caffeine, dichloralphenazone, a triptan, an antidepressant, a serotonin–norepinephrine reuptake inhibitor (SNRI), and a gabapentinoid.
175. The use of any one of embodiments **158-173**, wherein the medicament is administered simultaneously, separately, or sequentially with one or more additional therapeutics selected from the group consisting of a chemotherapeutic drug, an antiproliferative agent, an anti-inflammatory agent, a corticosteroid, an anti-asthmatic agent, an anti-allergic agent, an immunosuppressive agent, an immunomodulatory agent, a cardiovascular disease treatment agent, an anti-diabetic agent, a blood disorder treatment agent, a nerve growth factor receptor antagonist, a sodium channel blocker, a CYP2D6 inhibitor, and a TNF-alpha inhibitor.
176. The use of embodiment **175**, wherein the additional therapeutic is a CYP2D6 inhibitor.
177. The use of any one of embodiments **158-173**, wherein the medicament is administered simultaneously, separately, or sequentially with one or more opiates.
178. Use of a compound having the formula:

Cpd ID	Structure	Cpd ID	Structure
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48		52	
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or a mixture thereof, or a pharmaceutically acceptable salt, tautomer, solvate, or prodrug, or a mixture thereof, of any of the foregoing compounds, for the manufacture of a medicament for treating or preventing one or more conditions selected from the group consisting of: pain; psychic pain; psychological pain; psychiatric pain; depression; allodynia; fibromyalgia; fibromyalgia-ness; central sensitization; centralization; regional pain syndrome; temporomandibular joint syndrome (TMJ); lower back pain; interstitial cystitis; Gulf War syndrome; visceral pain; phantom limb pain; kidney stones; gout; neuropathic pain; post-herpetic neuralgia; diabetic neuropathy; sickle cell pain; priapism; nociceptive pain; post-operative pain; orthopedic injury pain; bunionectomy; dental extraction; pain after severed spinal cord injury; osteoarthritis; rheumatoid arthritis; Lyme disease; Parkinson's disease; pain associated with cancer; opioid-induced constipation; an opioid withdrawal symptom; and pain associated with post-traumatic stress disorder (PTSD).

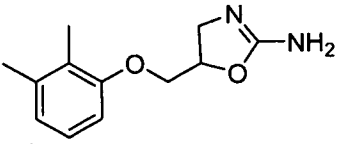
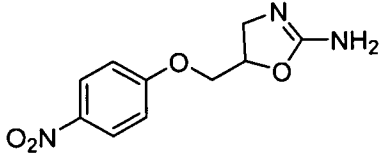
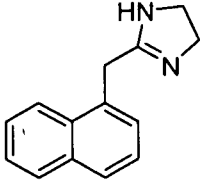
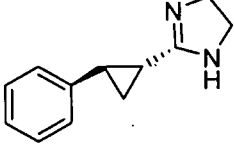
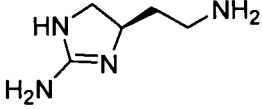
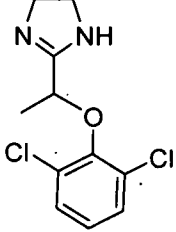
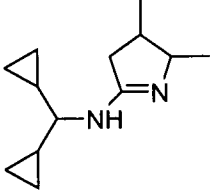
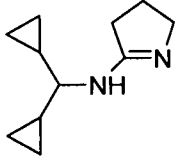
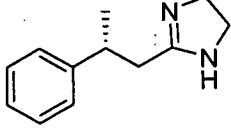
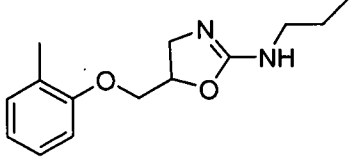
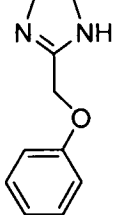
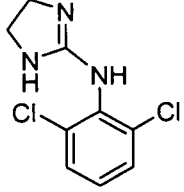
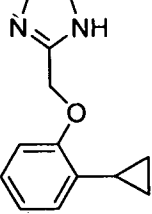
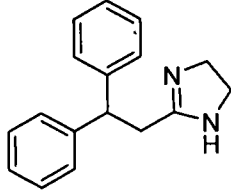
179. The use of embodiment 178, wherein the condition is depression.
180. The use of embodiment 178, wherein the condition is Parkinson's disease.
181. The use of embodiment 178, wherein the condition is visceral pain.
182. The use of embodiment 178, wherein the condition is allodynia.
183. The use of embodiment 178, wherein the condition is fibromyalgia.
184. The use of embodiment 178, wherein the condition is rheumatoid arthritis.
185. The use of embodiment 178, wherein the condition is neuropathic pain.
186. The use of embodiment 178, wherein the condition is nociceptive pain.
187. The use of embodiment 178, wherein the condition is central sensitization.

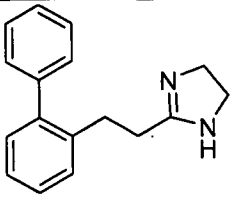
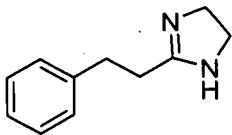
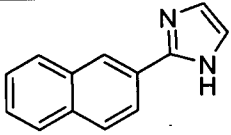
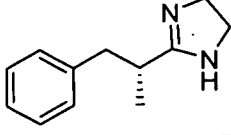
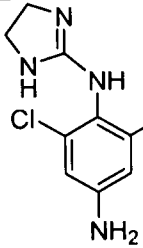
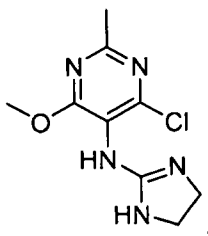
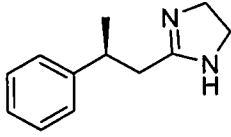
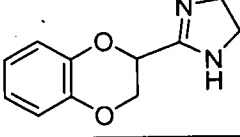
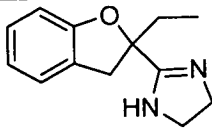
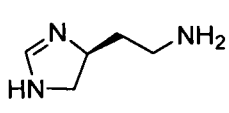
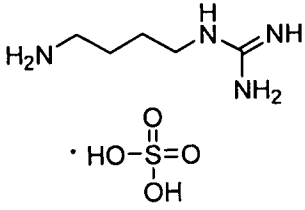
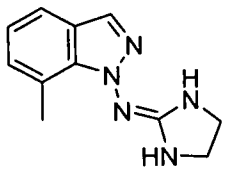
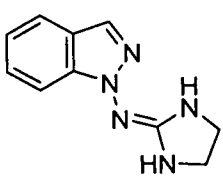
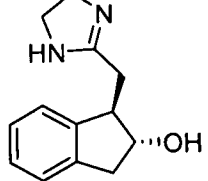
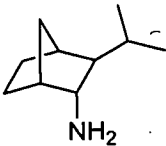
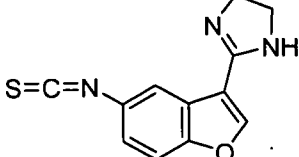
188. The use of embodiment **178**, wherein the condition is pain.
189. The use of embodiment **178**, wherein the condition is psychic pain.
190. The use of embodiment **178**, wherein the condition is psychological pain.
191. The use of embodiment **178**, wherein the condition is psychiatric pain.
192. The use of embodiment **178**, wherein the condition is phantom limb pain.
193. The use of embodiment **178**, wherein the condition is opioid-induced constipation.
194. The use of embodiment **178**, wherein the condition is an opioid withdrawal symptom.
195. The use of any one of embodiments **178-194**, wherein the medicament is administered simultaneously, separately, or sequentially with one or more substances selected from the group consisting of acetaminophen, a non-steroidal anti-inflammatory drug (NSAID), ibuprofen, naprosyn, a cyclooxygenase-2 inhibitor, aspirin, caffeine, dichloralphenazone, a triptan, an antidepressant, a serotonin–norepinephrine reuptake inhibitor (SNRI), and a gabapentinoid.
196. The use of any one of embodiments **178-194**, wherein the medicament is administered simultaneously, separately, or sequentially with one or more additional therapeutics selected from the group consisting of a chemotherapeutic drug, an antiproliferative agent, an anti-inflammatory agent, a corticosteroid, an anti-asthmatic agent, an anti-allergic agent, an immunosuppressive agent, an immunomodulatory agent, a cardiovascular disease treatment agent, an anti-diabetic agent, a blood disorder treatment agent, a nerve growth factor receptor antagonist, a sodium channel blocker, a CYP2D6 inhibitor, and a TNF-alpha inhibitor.
197. The use of embodiment **196**, wherein the additional therapeutic is a CYP2D6 inhibitor.

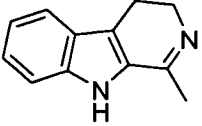
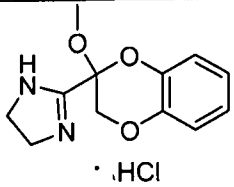
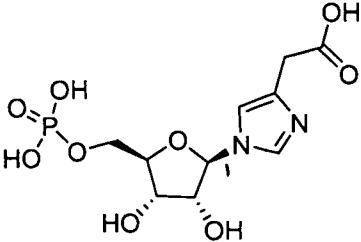
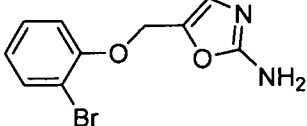
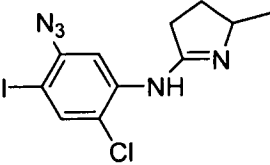
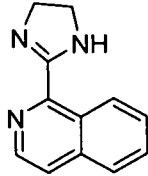
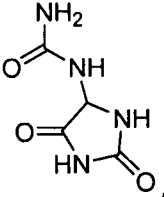
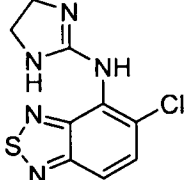
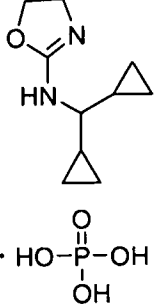
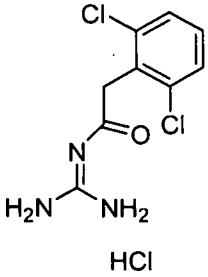
198. The use of any one of embodiments 178-194, wherein the medicament is administered simultaneously, separately, or sequentially with one or more opiates.

199. A compound having the formula:

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7		9	
10		11	
12		13	

14		15	
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18		19	
20		21	
22		23	
24		25	
27		28	

29		30	
31		32	
33		34	
35		36	
37		38	
39		40	
41		42	
43		44	

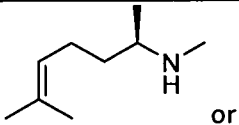
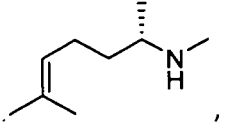
45		46	
47		48	
49		50	
51		52	
53		54	

or a mixture thereof, or a pharmaceutically acceptable salt, free base form, enantiomer, diastereomer, tautomer, solvate, or prodrug, or a mixture thereof, of any of the foregoing compounds, for use in treating or preventing one or more conditions selected from the group consisting of: pain; psychic pain; psychological pain; psychiatric pain; depression; allodynia; fibromyalgia; fibromyalgia-ness; central sensitization; centralization; regional pain syndrome; temporomandibular joint syndrome (TMJ); lower back pain; interstitial cystitis; Gulf War syndrome; visceral pain; phantom limb pain;

kidney stones; gout; neuropathic pain; post-herpetic neuralgia; diabetic neuropathy; sickle cell pain; priapism; nociceptive pain; post-operative pain; orthopedic injury pain; bunionectomy; dental extraction; pain after severed spinal cord injury; osteoarthritis; rheumatoid arthritis; Lyme disease; Parkinson's disease; pain associated with cancer; opioid-induced constipation; an opioid withdrawal symptom; and pain associated with post-traumatic stress disorder (PTSD).

200. The compound of embodiment **199**, wherein the condition is depression.
201. The compound of embodiment **199**, wherein the condition is Parkinson's disease.
202. The compound of embodiment **199**, wherein the condition is visceral pain.
203. The compound of embodiment **199**, wherein the condition is allodynia.
204. The compound of embodiment **199**, wherein the condition is fibromyalgia.
205. The compound of embodiment **199**, wherein the condition is rheumatoid arthritis.
206. The compound of embodiment **199**, wherein the condition is neuropathic pain.
207. The compound of embodiment **199**, wherein the condition is nociceptive pain.
208. The compound of embodiment **199**, wherein the condition is central sensitization.
209. The compound of embodiment **199**, wherein the condition is pain.
210. The compound of embodiment **199**, wherein the condition is psychic pain.
211. The compound of embodiment **199**, wherein the condition is psychological pain.

212. The compound of embodiment **199**, wherein the condition is psychiatric pain.
213. The compound of embodiment **199**, wherein the condition is phantom limb pain.
214. The compound of embodiment **199**, wherein the condition is opioid-induced constipation.
215. The compound of embodiment **199**, wherein the condition is an opioid withdrawal symptom.
216. The compound of any one of embodiments **199-215**, wherein the compound is used simultaneously, separately, or sequentially with one or more substances selected from the group consisting of acetaminophen, a non-steroidal anti-inflammatory drug (NSAID), ibuprofen, naprosyn, a cyclooxygenase-2 inhibitor, aspirin, caffeine, dichloralphenazone, a triptan, an antidepressant, a serotonin–norepinephrine reuptake inhibitor (SNRI), and a gabapentinoid.
217. The compound of any one of embodiments **199-215**, wherein the compound is used simultaneously, separately, or sequentially with one or more additional therapeutics selected from the group consisting of a chemotherapeutic drug, an antiproliferative agent, an anti-inflammatory agent, a corticosteroid, an anti-asthmatic agent, an anti-allergic agent, an immunosuppressive agent, an immunomodulatory agent, a cardiovascular disease treatment agent, an anti-diabetic agent, a blood disorder treatment agent, a nerve growth factor receptor antagonist, a sodium channel blocker, a CYP2D6 inhibitor, and a TNF-alpha inhibitor.
218. The compound of embodiment **217**, wherein the additional therapeutic is a CYP2D6 inhibitor.
219. The compound of any one of embodiments **199-215**, wherein the compound is used simultaneously, separately, or sequentially with one or more opiates.
220. A compound having the formula:

Cpd ID	Structure	Cpd ID	Structure
8	 or	26	

or a mixture thereof, or a pharmaceutically acceptable salt, solvate, or prodrug, or a mixture thereof, of any of the foregoing compounds, for use in treating or preventing one or more conditions selected from the group consisting of: pain; psychic pain; psychological pain; psychiatric pain; allodynia; fibromyalgia; fibromyalgia-ness; central sensitization; centralization; regional pain syndrome; temporomandibular joint syndrome (TMJ); lower back pain; interstitial cystitis; Gulf War syndrome; visceral pain; phantom limb pain; kidney stones; gout; neuropathic pain; post-herpetic neuralgia; diabetic neuropathy; sickle cell pain; priapism; nociceptive pain; post-operative pain; orthopedic injury pain; bunionectomy; dental extraction; pain after severed spinal cord injury; osteoarthritis; rheumatoid arthritis; Lyme disease; Parkinson's disease; pain associated with cancer; opioid-induced constipation; an opioid withdrawal symptom; and pain associated with post-traumatic stress disorder (PTSD).

221. The compound of embodiment **220**, wherein the condition is Parkinson's disease.
222. The compound of embodiment **220**, wherein the condition is visceral pain.
223. The compound of embodiment **220**, wherein the condition is allodynia.
224. The compound of embodiment **220**, wherein the condition is fibromyalgia.
225. The compound of embodiment **220**, wherein the condition is rheumatoid arthritis.
226. The compound of embodiment **220**, wherein the condition is neuropathic pain.
227. The compound of embodiment **220**, wherein the condition is nociceptive pain.

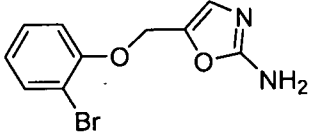
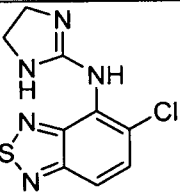
228. The compound of embodiment **220**, wherein the condition is central sensitization.
229. The compound of embodiment **220**, wherein the condition is pain.
230. The compound of embodiment **220**, wherein the condition is psychic pain.
231. The compound of embodiment **220**, wherein the condition is psychological pain.
232. The compound of embodiment **220**, wherein the condition is psychiatric pain.
233. The compound of embodiment **220**, wherein the condition is phantom limb pain.
234. The compound of embodiment **220**, wherein the condition is opioid-induced constipation.
235. The compound of embodiment **220**, wherein the condition is an opioid withdrawal symptom.
236. The compound of any one of embodiments **220-235**, wherein the compound is used simultaneously, separately, or sequentially with one or more substances selected from the group consisting of acetaminophen, a non-steroidal anti-inflammatory drug (NSAID), ibuprofen, naprosyn, a cyclooxygenase-2 inhibitor, aspirin, caffeine, dichloralphenazone, a triptan, an antidepressant, a serotonin–norepinephrine reuptake inhibitor (SNRI), and a gabapentinoid.
237. The compound of any one of embodiments **220-235**, wherein the compound is used simultaneously, separately, or sequentially with one or more additional therapeutics selected from the group consisting of a chemotherapeutic drug, an antiproliferative agent, an anti-inflammatory agent, a corticosteroid, an anti-asthmatic agent, an anti-allergic agent, an immunosuppressive agent, an immunomodulatory agent, a cardiovascular disease treatment agent, an anti-diabetic agent, a blood disorder treatment

agent, a nerve growth factor receptor antagonist, a sodium channel blocker, a CYP2D6 inhibitor, and a TNF-alpha inhibitor.

238. The compound of embodiment 237, wherein the additional therapeutic is a CYP2D6 inhibitor.

239. The compound of any one of embodiments 220-235, wherein the compound is used simultaneously, separately, or sequentially with one or more opiates.

240. A compound having the formula:

Cpd ID	Structure	Cpd ID	Structure
48	 or	52	

or a mixture thereof, or a pharmaceutically acceptable salt, tautomer, solvate, or prodrug, or a mixture thereof, of any of the foregoing compounds, for use in treating or preventing one or more conditions selected from the group consisting of: pain; psychic pain; psychological pain; psychiatric pain; depression; allodynia; fibromyalgia; fibromyalgia-ness; central sensitization; centralization; regional pain syndrome; temporomandibular joint syndrome (TMJ); lower back pain; interstitial cystitis; Gulf War syndrome; visceral pain; phantom limb pain; kidney stones; gout; neuropathic pain; post-herpetic neuralgia; diabetic neuropathy; sickle cell pain; priapism; nociceptive pain; post-operative pain; orthopedic injury pain; bunionectomy; dental extraction; pain after severed spinal cord injury; osteoarthritis; rheumatoid arthritis; Lyme disease; Parkinson's disease; pain associated with cancer; opioid-induced constipation; an opioid withdrawal symptom; and pain associated with post-traumatic stress disorder (PTSD).

241. The compound of embodiment 240, wherein the condition is depression.

242. The compound of embodiment 240, wherein the condition is Parkinson's disease.

243. The compound of embodiment 240, wherein the condition is visceral pain.
244. The compound of embodiment 240, wherein the condition is allodynia.
245. The compound of embodiment 240, wherein the condition is fibromyalgia.
246. The compound of embodiment 240, wherein the condition is rheumatoid arthritis.
247. The compound of embodiment 240, wherein the condition is neuropathic pain.
248. The compound of embodiment 240, wherein the condition is nociceptive pain.
249. The compound of embodiment 240, wherein the condition is central sensitization.
250. The compound of embodiment 240, wherein the condition is pain.
251. The compound of embodiment 240, wherein the condition is psychic pain.
252. The compound of embodiment 240, wherein the condition is psychological pain.
253. The compound of embodiment 240, wherein the condition is psychiatric pain.
254. The compound of embodiment 240, wherein the condition is phantom limb pain.
255. The compound of embodiment 240, wherein the condition is opioid-induced constipation.
256. The compound of embodiment 240, wherein the condition is an opioid withdrawal symptom.
257. The compound of any one of embodiments 240-256, wherein the compound is used simultaneously, separately, or sequentially with one or more substances selected from the group consisting of acetaminophen, a non-steroidal anti-inflammatory drug (NSAID), ibuprofen, naprosyn, a

cyclooxygenase-2 inhibitor, aspirin, caffeine, dichloralphenazone, a triptan, an antidepressant, a serotonin–norepinephrine reuptake inhibitor (SNRI), and a gabapentinoid.

258. The compound of any one of embodiments **240-256**, wherein the compound is used simultaneously, separately, or sequentially with one or more additional therapeutics selected from the group consisting of a chemotherapeutic drug, an antiproliferative agent, an anti-inflammatory agent, a corticosteroid, an anti-asthmatic agent, an anti-allergic agent, an immunosuppressive agent, an immunomodulatory agent, a cardiovascular disease treatment agent, an anti-diabetic agent, a blood disorder treatment agent, a nerve growth factor receptor antagonist, a sodium channel blocker, a CYP2D6 inhibitor, and a TNF-alpha inhibitor.
259. The compound of embodiment **258**, wherein the additional therapeutic is a CYP2D6 inhibitor.
260. The compound of any one of embodiments **240-256**, wherein the compound is used simultaneously, separately, or sequentially with one or more opiates.
261. Use of the pharmaceutical composition of any one of embodiments **4**, **7**, or **10** for the manufacture of a medicament for treating or preventing one or more conditions selected from the group consisting of: pain; psychic pain; psychological pain; psychiatric pain; allodynia; fibromyalgia; fibromyalgia-ness; central sensitization; centralization; regional pain syndrome; temporomandibular joint syndrome (TMJ); lower back pain; interstitial cystitis; Gulf War syndrome; visceral pain; phantom limb pain; kidney stones; gout; neuropathic pain; post-herpetic neuralgia; diabetic neuropathy; sickle cell pain; priapism; nociceptive pain; post-operative pain; orthopedic injury pain; bunionectomy; dental extraction; pain after severed spinal cord injury; osteoarthritis; rheumatoid arthritis; Lyme disease; Parkinson's disease; pain associated with cancer; opioid-induced constipation; an opioid withdrawal symptom; and pain associated with post-traumatic stress disorder (PTSD).

262. The use of embodiment **261**, wherein the condition is Parkinson's disease.
263. The use of embodiment **261**, wherein the condition is visceral pain.
264. The use of embodiment **261**, wherein the condition is allodynia.
265. The use of embodiment **261**, wherein the condition is fibromyalgia.
266. The use of embodiment **261**, wherein the condition is rheumatoid arthritis.
267. The use of embodiment **261**, wherein the condition is neuropathic pain.
268. The use of embodiment **261**, wherein the condition is nociceptive pain.
269. The use of embodiment **261**, wherein the condition is central sensitization.
270. The use of embodiment **261**, wherein the condition is pain.
271. The use of embodiment **261**, wherein the condition is psychic pain.
272. The use of embodiment **261**, wherein the condition is psychological pain.
273. The use of embodiment **261**, wherein the condition is psychiatric pain.
274. The use of embodiment **261**, wherein the condition is phantom limb pain.
275. The use of embodiment **261**, wherein the condition is opioid-induced constipation.
276. The use of embodiment **261**, wherein the condition is an opioid withdrawal symptom.
277. The use of any one of embodiments **261-276**, wherein the medicament is administered simultaneously, separately, or sequentially with one or more substances selected from the group consisting of acetaminophen, a non-steroidal anti-inflammatory drug (NSAID), ibuprofen, naprosyn, a cyclooxygenase-2 inhibitor, aspirin, caffeine, dichloralphenazone, a triptan, an antidepressant, a serotonin-norepinephrine reuptake inhibitor (SNRI), and a gabapentinoid.

278. The use of any one of embodiments **261-276**, wherein the medicament is administered simultaneously, separately, or sequentially with one or more additional therapeutics selected from the group consisting of a chemotherapeutic drug, an antiproliferative agent, an anti-inflammatory agent, a corticosteroid, an anti-asthmatic agent, an anti-allergic agent, an immunosuppressive agent, an immunomodulatory agent, a cardiovascular disease treatment agent, an anti-diabetic agent, a blood disorder treatment agent, a nerve growth factor receptor antagonist, a sodium channel blocker, a CYP2D6 inhibitor, and a TNF-alpha inhibitor.
279. The use of embodiment **278**, wherein the additional therapeutic is a CYP2D6 inhibitor.
280. The use of any one of embodiments **261-276**, wherein the medicament is administered simultaneously, separately, or sequentially with one or more opiates.
281. The pharmaceutical composition of any one of embodiments **4, 7, or 10** for use in treating or preventing one or more conditions selected from the group consisting of: pain; psychic pain; psychological pain; psychiatric pain; allodynia; fibromyalgia; fibromyalgia-ness; central sensitization; centralization; regional pain syndrome; temporomandibular joint syndrome (TMJ); lower back pain; interstitial cystitis; Gulf War syndrome; visceral pain; phantom limb pain; kidney stones; gout; neuropathic pain; post-herpetic neuralgia; diabetic neuropathy; sickle cell pain; priapism; nociceptive pain; post-operative pain; orthopedic injury pain; bunionectomy; dental extraction; pain after severed spinal cord injury; osteoarthritis; rheumatoid arthritis; Lyme disease; Parkinson's disease; pain associated with cancer; opioid-induced constipation; an opioid withdrawal symptom; and pain associated with post-traumatic stress disorder (PTSD).
282. The pharmaceutical composition of embodiment **281**, wherein the condition is Parkinson's disease.

283. The pharmaceutical composition of embodiment **281**, wherein the condition is visceral pain.
284. The pharmaceutical composition of embodiment **281**, wherein the condition is allodynia.
285. The pharmaceutical composition of embodiment **281**, wherein the condition is fibromyalgia.
286. The pharmaceutical composition of embodiment **281**, wherein the condition is rheumatoid arthritis.
287. The pharmaceutical composition of embodiment **281**, wherein the condition is neuropathic pain.
288. The pharmaceutical composition of embodiment **281**, wherein the condition is nociceptive pain.
289. The pharmaceutical composition of embodiment **281**, wherein the condition is central sensitization.
290. The pharmaceutical composition of embodiment **281**, wherein the condition is pain.
291. The pharmaceutical composition of embodiment **281**, wherein the condition is psychic pain.
292. The pharmaceutical composition of embodiment **281**, wherein the condition is psychological pain.
293. The pharmaceutical composition of embodiment **281**, wherein the condition is psychiatric pain.
294. The pharmaceutical composition of embodiment **281**, wherein the condition is phantom limb pain.
295. The pharmaceutical composition of embodiment **281**, wherein the condition is opioid-induced constipation.
296. The pharmaceutical composition of embodiment **281**, wherein the condition is an opioid withdrawal symptom.
297. The pharmaceutical composition of any one of embodiments **281-296**, wherein the pharmaceutical composition is used simultaneously, separately, or

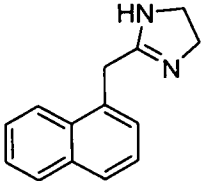
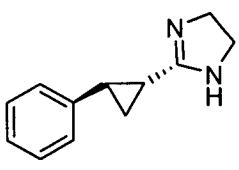
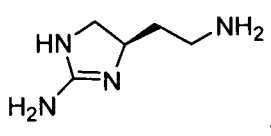
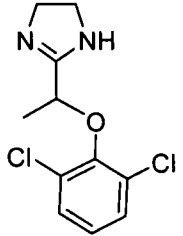
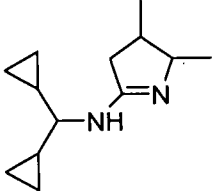
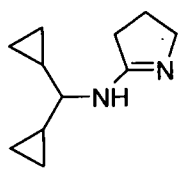
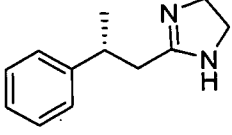
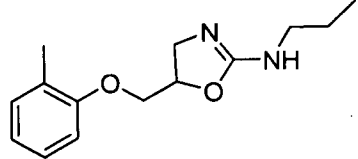
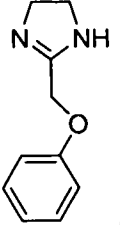
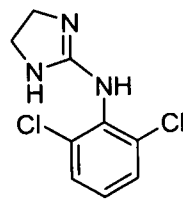
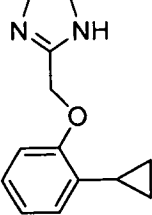
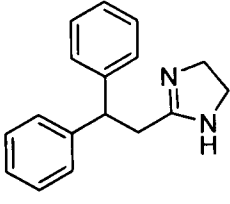
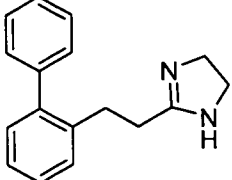
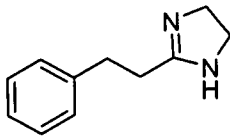
sequentially with one or more substances selected from the group consisting of acetaminophen, a non-steroidal anti-inflammatory drug (NSAID), ibuprofen, naprosyn, a cyclooxygenase-2 inhibitor, aspirin, caffeine, dichloralphenazone, a triptan, an antidepressant, a serotonin–norepinephrine reuptake inhibitor (SNRI), and a gabapentinoid.

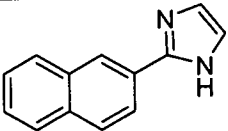
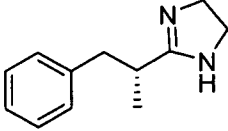
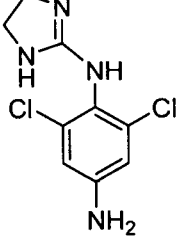
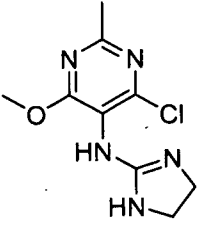
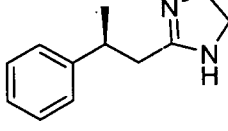
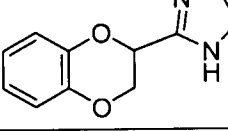
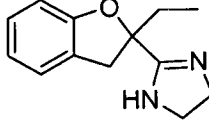
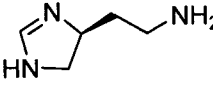
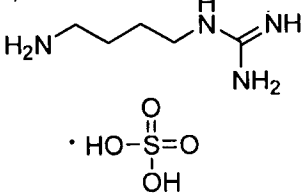
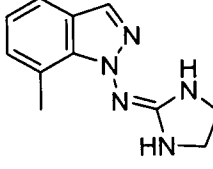
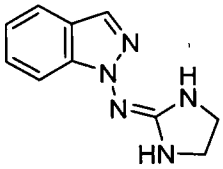
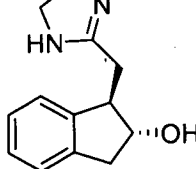
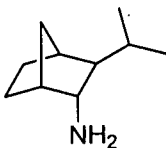
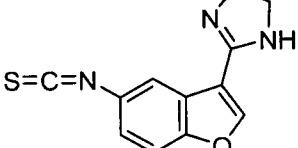
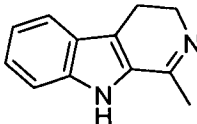
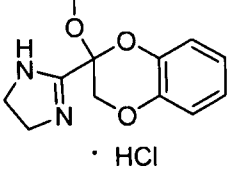
298. The pharmaceutical composition of any one of embodiments **281-296**, wherein the pharmaceutical composition is used simultaneously, separately, or sequentially with one or more additional therapeutics selected from the group consisting of a chemotherapeutic drug, an antiproliferative agent, an anti-inflammatory agent, a corticosteroid, an anti-asthmatic agent, an anti-allergic agent, an immunosuppressive agent, an immunomodulatory agent, a cardiovascular disease treatment agent, an anti-diabetic agent, a blood disorder treatment agent, a nerve growth factor receptor antagonist, a sodium channel blocker, a CYP2D6 inhibitor, and a TNF-alpha inhibitor.
299. The pharmaceutical composition of embodiment **298**, wherein the additional therapeutic is a CYP2D6 inhibitor.
300. The pharmaceutical composition of any one of embodiments **281-296**, wherein the pharmaceutical composition is used simultaneously, separately, or sequentially with one or more opiates.

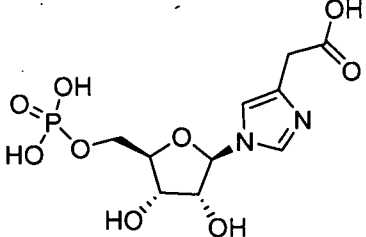
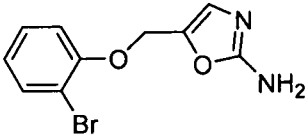
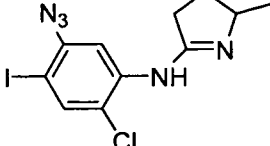
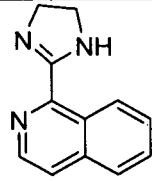
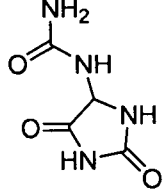
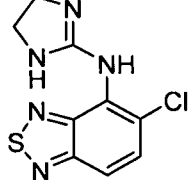
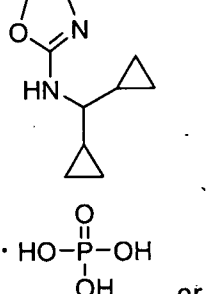
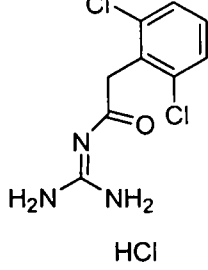
Claims:

1. A compound for use as an analgesic, the compound having the formula:

Cpd ID	Structure	Cpd ID	Structure
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10		11	
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14		15	

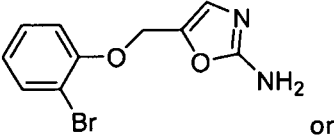
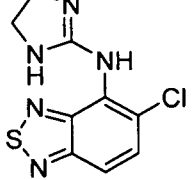
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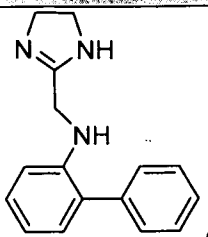
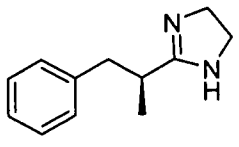
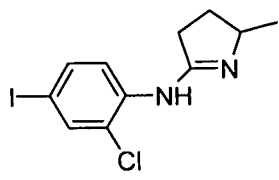
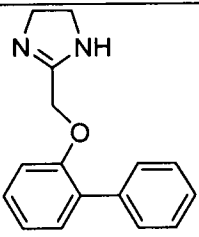
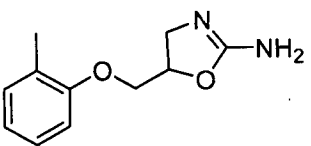
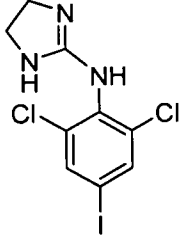
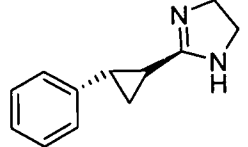
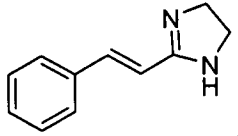
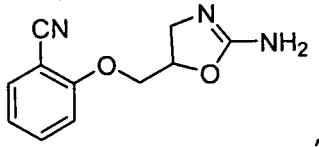
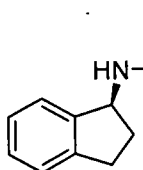
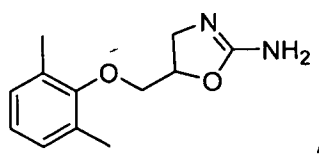
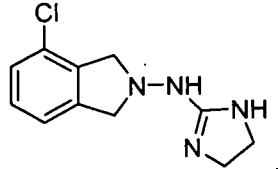
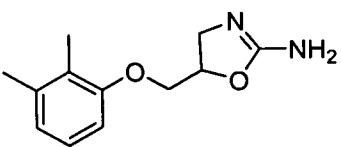
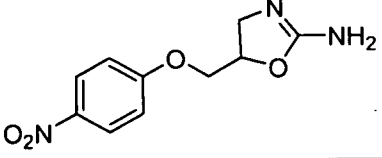
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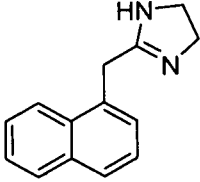
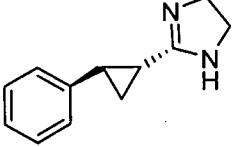
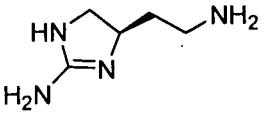
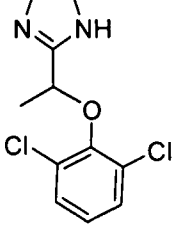
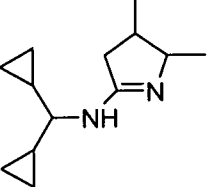
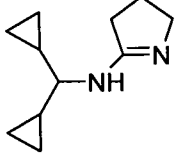
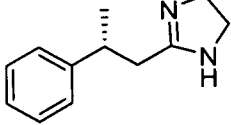
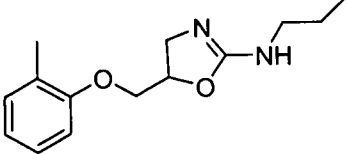
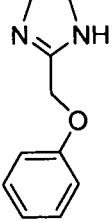

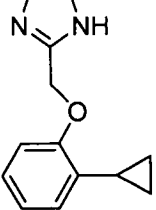
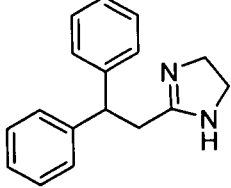
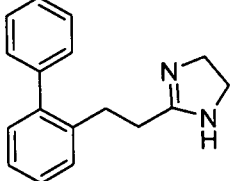
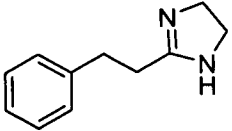
2. A compound for use as an analgesic, the compound having the formula:

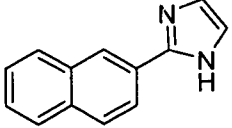
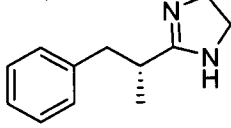
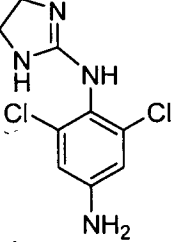
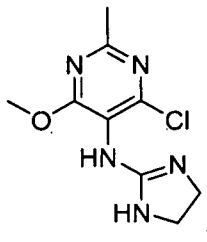
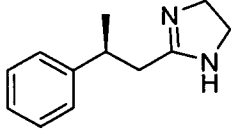
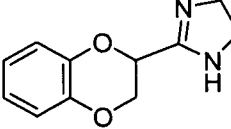
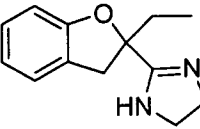
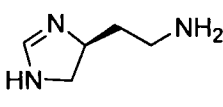
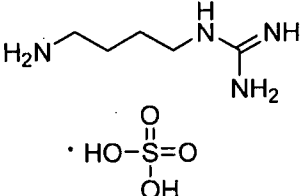
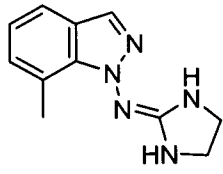
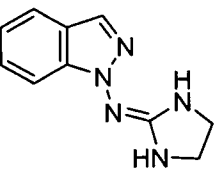
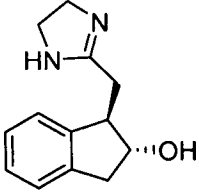
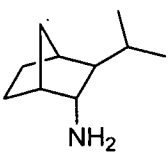
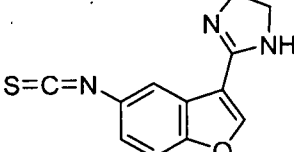
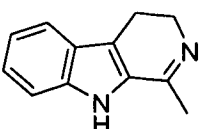
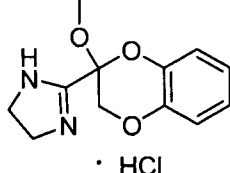
Cpd. ID	Structure	Cpd. ID	Structure
48		52	

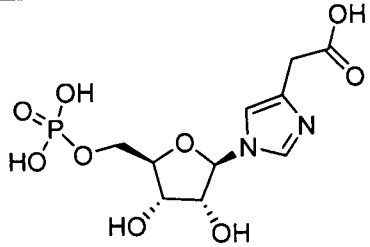
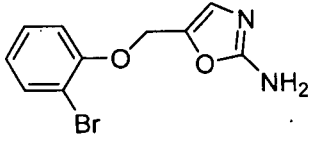
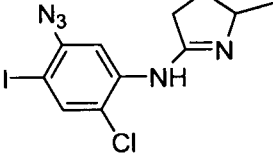
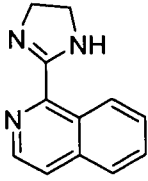
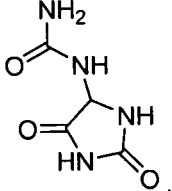
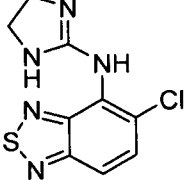
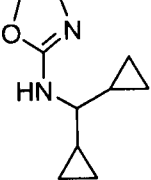
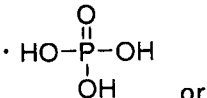
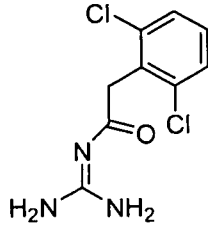
or a mixture thereof, or a pharmaceutically acceptable salt, tautomer, solvate, or prodrug, or a mixture thereof, of any of the foregoing compounds.

3. A pharmaceutical composition comprising as an active ingredient a therapeutically effective amount of a compound having the formula:

Cpd.ID	Structure	Cpd.ID	Structure
1		2	
3		4	
5		6	
7		9	
10		11	
12		13	
14		15	

16		17	
18		19	
20		21	
22		23	
24		25	
27		28	
29		30	

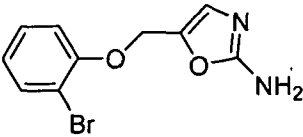
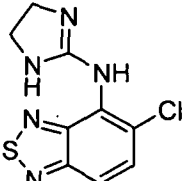
31		32	
33		34	
35		36	
37		38	
39		40	
41		42	
43		44	
45		46	

47		48	
49		50	
51		52	
53	  , or	54	 HCl

or a mixture thereof, or a pharmaceutically acceptable salt, free base form, enantiomer, diastereomer, tautomer, solvate, or prodrug, or a mixture thereof, of any of the foregoing compounds.

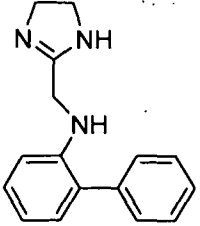
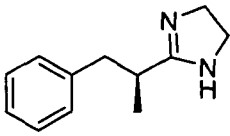
- The pharmaceutical composition of claim 3, further comprising at least one pharmaceutically acceptable excipient, carrier, or diluent.
- Use of the pharmaceutical composition of claim 3 or 4 as an analgesic.
- A pharmaceutical composition comprising as an active ingredient a therapeutically effective amount of a compound having the formula:

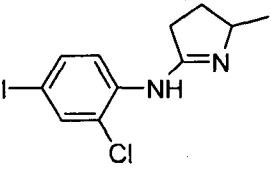
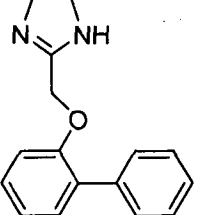
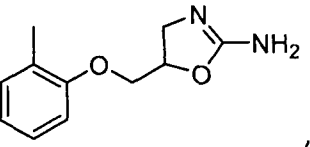
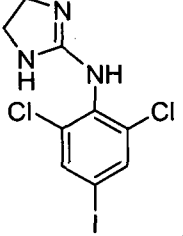
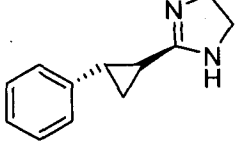
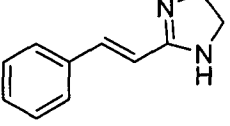
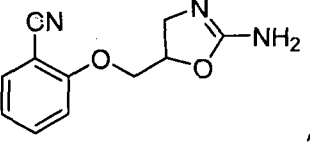
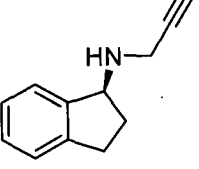
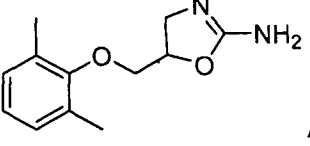
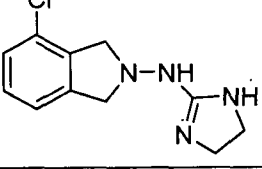
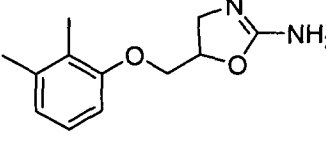
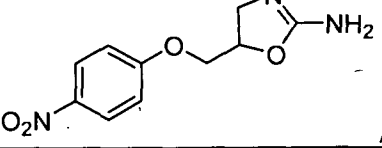
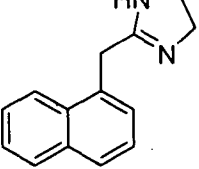
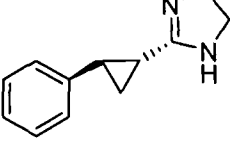
Cpd ID	Structure	Cpd ID	Structure
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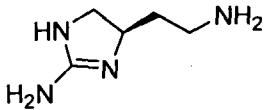
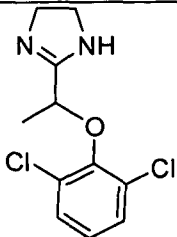
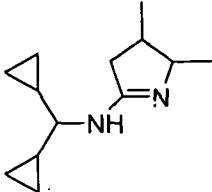
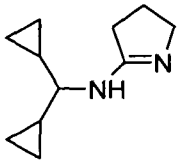
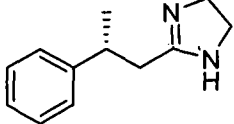
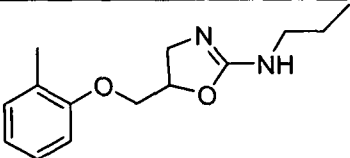
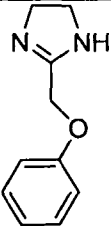
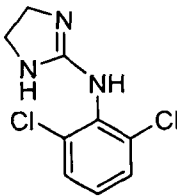
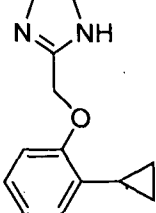
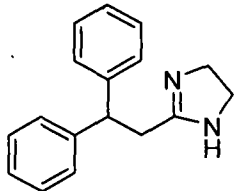
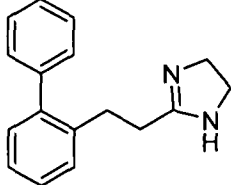
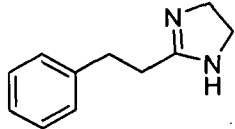
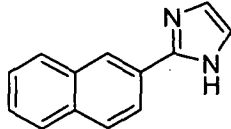
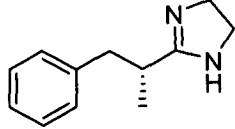
48	 <chem>NC(=O)COc1cccc(Br)c1</chem>	or	 <chem>NC(=O)COc1ccc2c(c1)nc3cc(Cl)ccc3n2</chem>
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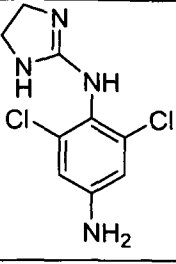
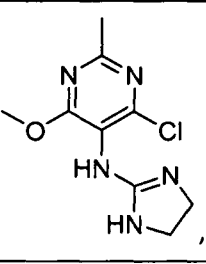
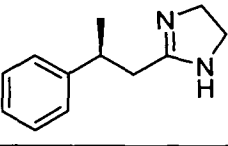
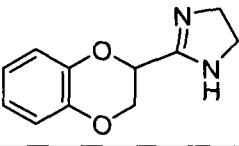
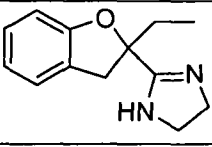
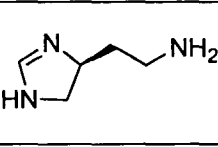
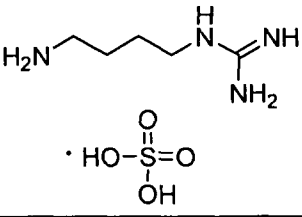
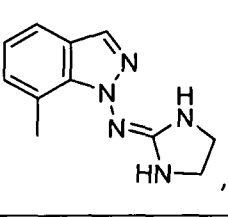
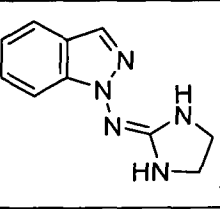
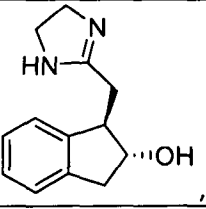
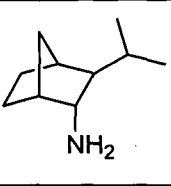
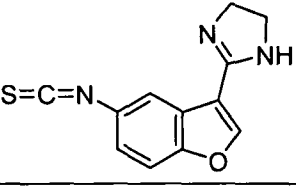
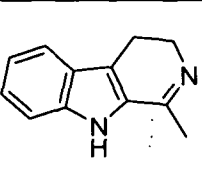
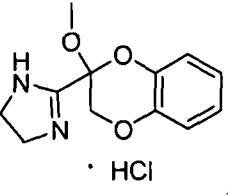
or a mixture thereof, or a pharmaceutically acceptable salt, tautomer, solvate, or prodrug, or a mixture thereof, of any of the foregoing compounds.

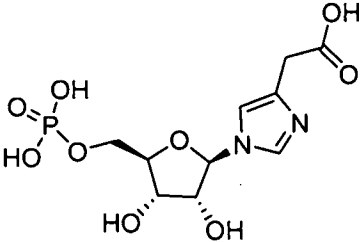
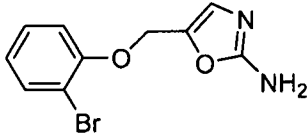
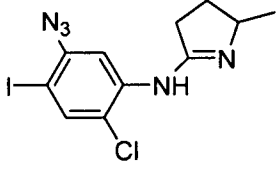
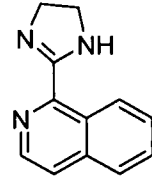
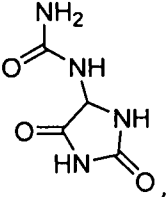
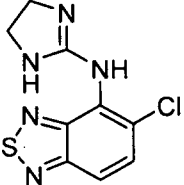
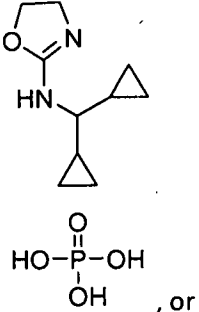
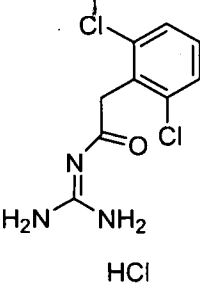
7. The pharmaceutical composition of claim 6, further comprising at least one pharmaceutically acceptable excipient, carrier, or diluent.
8. Use of the pharmaceutical composition of claim 6 or 7 as an analgesic.
9. A method of treating or preventing one or more conditions selected from the group consisting of: pain; psychic pain; psychological pain; psychiatric pain; depression; allodynia; fibromyalgia; fibromyalgia-ness; central sensitization; centralization; regional pain syndrome; temporomandibular joint syndrome (TMJ); lower back pain; interstitial cystitis; Gulf War syndrome; visceral pain; phantom limb pain; kidney stones; gout; neuropathic pain; post-herpetic neuralgia; diabetic neuropathy; sickle cell pain; priapism; nociceptive pain; post-operative pain; orthopedic injury pain; bunionectomy; dental extraction; pain after severed spinal cord injury; osteoarthritis; rheumatoid arthritis; Lyme disease; Parkinson's disease; pain associated with cancer; opioid-induced constipation; an opioid withdrawal symptom; and pain associated with post-traumatic stress disorder (PTSD), in a patient in need thereof, comprising administering to said patient a therapeutically effective amount a compound having the formula:

Cpd ID	Structure	Cpd ID	Structure
1	 <chem>NC(=O)Nc1ccc(cc1)-c2ccccc2NCC3=CN=CN3</chem>	2	 <chem>NC(=O)NCCc1ccc(cc1)NCC2=CN=CN2</chem>

3		4	
5		6	
7		9	
10		11	
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14		15	
16		17	

18		19	
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24		25	
27		28	
29		30	
31		32	

33		34	
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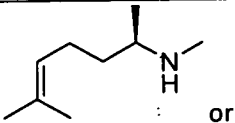
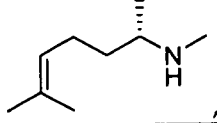
or a mixture thereof, or a pharmaceutically acceptable salt, free base form, enantiomer, diastereomer, tautomer, solvate, or prodrug, or a mixture thereof, of any of the foregoing compounds.

10. The method of claim 9, wherein the condition is allodynia.

11. The method of claim 9, wherein the condition is fibromyalgia.

12. The method of any one of claims 9-11, wherein the compound is administered simultaneously, separately, or sequentially with one or more substances selected from the group consisting of acetaminophen, a non-steroidal anti-inflammatory drug (NSAID), ibuprofen, naprosyn, a cyclooxygenase-2 inhibitor, aspirin, caffeine, dichloralphenazone, a triptan, an antidepressant, a serotonin-norepinephrine reuptake inhibitor (SNRI), and a gabapentinoid.

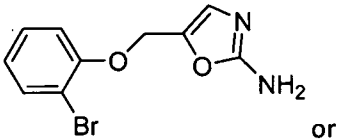
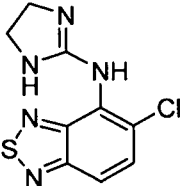
13. The method of any one of claims 9-11, wherein the compound is administered simultaneously, separately, or sequentially with one or more additional therapeutics selected from the group consisting of a chemotherapeutic drug, an antiproliferative agent, an anti-inflammatory agent, a corticosteroid, an anti-asthmatic agent, an anti-allergic agent, an immunosuppressive agent, an immunomodulatory agent, a cardiovascular disease treatment agent, an anti-diabetic agent, a blood disorder treatment agent, a nerve growth factor receptor antagonist, a sodium channel blocker, a CYP2D6 inhibitor, and a TNF-alpha inhibitor.
14. The method of claim 13, wherein the additional therapeutic is a CYP2D6 inhibitor.
15. The method of any one of claims 9-11, wherein the compound is administered simultaneously, separately, or sequentially with one or more opiates.
16. A method of treating or preventing one or more conditions selected from the group consisting of: pain; psychic pain; psychological pain; psychiatric pain; allodynia; fibromyalgia; fibromyalgia-ness; central sensitization; centralization; regional pain syndrome; temporomandibular joint syndrome (TMJ); lower back pain; interstitial cystitis; Gulf War syndrome; visceral pain; phantom limb pain; kidney stones; gout; neuropathic pain; post-herpetic neuralgia; diabetic neuropathy; sickle cell pain; priapism; nociceptive pain; post-operative pain; orthopedic injury pain; bunionectomy; dental extraction; pain after severed spinal cord injury; osteoarthritis; rheumatoid arthritis; Lyme disease; Parkinson's disease; pain associated with cancer; opioid-induced constipation; an opioid withdrawal symptom; and pain associated with post-traumatic stress disorder (PTSD), in a patient in need thereof, comprising administering to said patient a therapeutically effective amount a compound having the formula:

Cpd ID	Structure	Cpd ID	Structure
8	 or	26	

or a mixture thereof, or a pharmaceutically acceptable salt, solvate, or prodrug, or a mixture thereof, of any of the foregoing compounds.

17. The method of claim 16, wherein the condition is allodynia.
18. The method of claim 16, wherein the condition is fibromyalgia.
19. The method of any one of claims 16-18, wherein the compound is administered simultaneously, separately, or sequentially with one or more substances selected from the group consisting of acetaminophen, a non-steroidal anti-inflammatory drug (NSAID), ibuprofen, naprosyn, a cyclooxygenase-2 inhibitor, aspirin, caffeine, dichloralphenazone, a triptan, an antidepressant, a serotonin-norepinephrine reuptake inhibitor (SNRI), and a gabapentinoid.
20. The method of any one of claims 16-18, wherein the compound is administered simultaneously, separately, or sequentially with one or more additional therapeutics selected from the group consisting of a chemotherapeutic drug, an antiproliferative agent, an anti-inflammatory agent, a corticosteroid, an anti-asthmatic agent, an anti-allergic agent, an immunosuppressive agent, an immunomodulatory agent, a cardiovascular disease treatment agent, an anti-diabetic agent, a blood disorder treatment agent, a nerve growth factor receptor antagonist, a sodium channel blocker, a CYP2D6 inhibitor, and a TNF-alpha inhibitor.
21. The method of claim 20, wherein the additional therapeutic is a CYP2D6 inhibitor.
22. The method of any one of claims 16-18, wherein the compound is administered simultaneously, separately, or sequentially with one or more opiates.
23. A method of treating or preventing one or more conditions selected from the group consisting of: pain; psychic pain; psychological pain; psychiatric pain; depression; allodynia; fibromyalgia; fibromyalgia-ness; central sensitization; centralization; regional pain syndrome; temporomandibular joint syndrome (TMJ); lower back pain; interstitial cystitis; Gulf War syndrome; visceral pain; phantom limb pain; kidney stones; gout; neuropathic pain; post-herpetic neuralgia; diabetic neuropathy; sickle cell pain; priapism; nociceptive pain;

post-operative pain; orthopedic injury pain; bunionectomy; dental extraction; pain after severed spinal cord injury; osteoarthritis; rheumatoid arthritis; Lyme disease; Parkinson's disease; pain associated with cancer; opioid-induced constipation; an opioid withdrawal symptom; and pain associated with post-traumatic stress disorder (PTSD), in a patient in need thereof, comprising administering to said patient a therapeutically effective amount a compound having the formula:

Cpd. ID	Structure	Cpd. ID	Structure
48	 or	52	

or a mixture thereof, or a pharmaceutically acceptable salt, tautomer, solvate, or prodrug, or a mixture thereof, of any of the foregoing compounds.

24. The method of claim 23, wherein the condition is allodynia.
25. The method of claim 23, wherein the condition is fibromyalgia.
26. The method of any one of claims 23-25, wherein the compound is administered simultaneously, separately, or sequentially with one or more substances selected from the group consisting of acetaminophen, a non-steroidal anti-inflammatory drug (NSAID), ibuprofen, naprosyn, a cyclooxygenase-2 inhibitor, aspirin, caffeine, dichloralphenazone, a triptan, an antidepressant, a serotonin-norepinephrine reuptake inhibitor (SNRI), and a gabapentinoid.
27. The method of any one of claims 23-25, wherein the compound is administered simultaneously, separately, or sequentially with one or more additional therapeutics selected from the group consisting of a chemotherapeutic drug, an antiproliferative agent, an anti-inflammatory agent, a corticosteroid, an anti-asthmatic agent, an anti-allergic agent, an immunosuppressive agent, an immunomodulatory agent, a cardiovascular disease treatment agent, an anti-diabetic agent, a blood disorder treatment agent, a nerve growth factor receptor antagonist, a sodium channel blocker, a CYP2D6 inhibitor, and a TNF-alpha inhibitor.

28. The method of claim 27, wherein the additional therapeutic is a CYP2D6 inhibitor.
29. The method of any one of claims 23-25, wherein the compound is administered simultaneously, separately, or sequentially with one or more opiates.
30. A method of treating or preventing one or more conditions selected from the group consisting of: pain; psychic pain; psychological pain; psychiatric pain; depression; allodynia; fibromyalgia; fibromyalgia-ness; central sensitization; centralization; regional pain syndrome; temporomandibular joint syndrome (TMJ); lower back pain; interstitial cystitis; Gulf War syndrome; visceral pain; phantom limb pain; kidney stones; gout; neuropathic pain; post-herpetic neuralgia; diabetic neuropathy; sickle cell pain; priapism; nociceptive pain; post-operative pain; orthopedic injury pain; bunionectomy; dental extraction; pain after severed spinal cord injury; osteoarthritis; rheumatoid arthritis; Lyme disease; Parkinson's disease; pain associated with cancer; opioid-induced constipation; an opioid withdrawal symptom; and pain associated with post-traumatic stress disorder (PTSD), in a patient in need thereof, comprising administering to said patient a therapeutically effective amount of the pharmaceutical composition of claim 3.
31. The method of claim 30, wherein the condition is allodynia.
32. The method of claim 30, wherein the condition is fibromyalgia.
33. The method of any one of claims 30-32, wherein the pharmaceutical composition is administered simultaneously, separately, or sequentially with one or more substances selected from the group consisting of acetaminophen, a non-steroidal anti-inflammatory drug (NSAID), ibuprofen, naprosyn, a cyclooxygenase-2 inhibitor, aspirin, caffeine, dichloralphenazone, a triptan, an antidepressant, a serotonin-norepinephrine reuptake inhibitor (SNRI), and a gabapentinoid.
34. The method of any one of claims 30-32, wherein the pharmaceutical composition is administered simultaneously, separately, or sequentially with one or more additional therapeutics selected from the group consisting of a

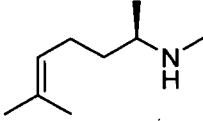
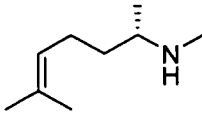
chemotherapeutic drug, an antiproliferative agent, an anti-inflammatory agent, a corticosteroid, an anti-asthmatic agent, an anti-allergic agent, an immunosuppressive agent, an immunomodulatory agent, a cardiovascular disease treatment agent, an anti-diabetic agent, a blood disorder treatment agent, a nerve growth factor receptor antagonist, a sodium channel blocker, a CYP2D6 inhibitor, and a TNF-alpha inhibitor.

35. The method of claim 34, wherein the additional therapeutic is a CYP2D6 inhibitor.
36. The method of any one of claims 30-32, wherein the pharmaceutical composition is administered simultaneously, separately, or sequentially with one or more opiates.
37. A method of treating or preventing one or more conditions selected from the group consisting of: pain; psychic pain; psychological pain; psychiatric pain; allodynia; fibromyalgia; fibromyalgia-ness; central sensitization; centralization; regional pain syndrome; temporomandibular joint syndrome (TMJ); lower back pain; interstitial cystitis; Gulf War syndrome; visceral pain; phantom limb pain; kidney stones; gout; neuropathic pain; post-herpetic neuralgia; diabetic neuropathy; sickle cell pain; priapism; nociceptive pain; post-operative pain; orthopedic injury pain; bunionectomy; dental extraction; pain after severed spinal cord injury; osteoarthritis; rheumatoid arthritis; Lyme disease; Parkinson's disease; pain associated with cancer; opioid-induced constipation; an opioid withdrawal symptom; and pain associated with post-traumatic stress disorder (PTSD), in a patient in need thereof, comprising administering to said patient a therapeutically effective amount of the pharmaceutical composition of claim 6.
38. The method of claim 37, wherein the condition is allodynia.
39. The method of claim 37, wherein the condition is fibromyalgia.
40. The method of any one of claims 37-39, wherein the pharmaceutical composition is administered simultaneously, separately, or sequentially with one or more substances selected from the group consisting of acetaminophen, a

non-steroidal anti-inflammatory drug (NSAID), ibuprofen, naprosyn, a cyclooxygenase-2 inhibitor, aspirin, caffeine, dichloralphenazone, a triptan, an antidepressant, a serotonin–norepinephrine reuptake inhibitor (SNRI), and a gabapentinoid.

41. The method of any one of claims 37-39, wherein the pharmaceutical composition is administered simultaneously, separately, or sequentially with one or more additional therapeutics selected from the group consisting of a chemotherapeutic drug, an antiproliferative agent, an anti-inflammatory agent, a corticosteroid, an anti-asthmatic agent, an anti-allergic agent, an immunosuppressive agent, an immunomodulatory agent, a cardiovascular disease treatment agent, an anti-diabetic agent, a blood disorder treatment agent, a nerve growth factor receptor antagonist, a sodium channel blocker, a CYP2D6 inhibitor, and a TNF-alpha inhibitor.
42. The method of claim 41, wherein the additional therapeutic is a CYP2D6 inhibitor.
43. The method of any one of claims 37-39, wherein the pharmaceutical composition is administered simultaneously, separately, or sequentially with one or more opiates.
44. A method of treating or preventing one or more conditions selected from the group consisting of: pain; psychic pain; psychological pain; psychiatric pain; depression; allodynia; fibromyalgia; fibromyalgia-ness; central sensitization; centralization; regional pain syndrome; temporomandibular joint syndrome (TMJ); lower back pain; interstitial cystitis; Gulf War syndrome; visceral pain; phantom limb pain; kidney stones; gout; neuropathic pain; post-herpetic neuralgia; diabetic neuropathy; sickle cell pain; priapism; nociceptive pain; post-operative pain; orthopedic injury pain; bunionectomy; dental extraction; pain after severed spinal cord injury; osteoarthritis; rheumatoid arthritis; Lyme disease; Parkinson's disease; pain associated with cancer; opioid-induced constipation; an opioid withdrawal symptom; and pain associated with post-traumatic stress disorder (PTSD), in a patient in need thereof, comprising

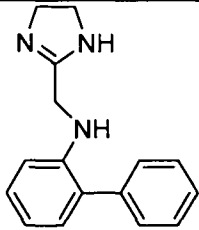
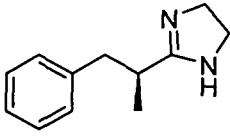
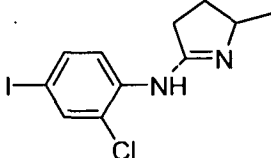
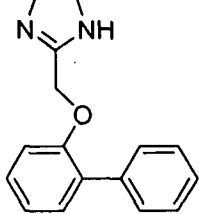
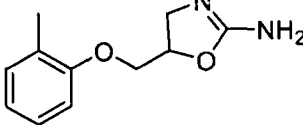
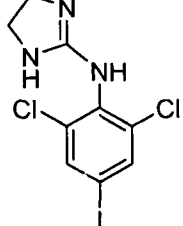
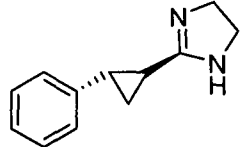
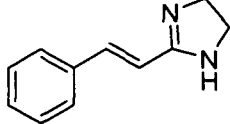
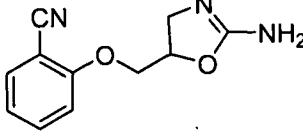
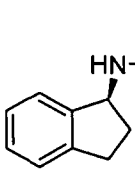
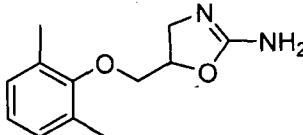
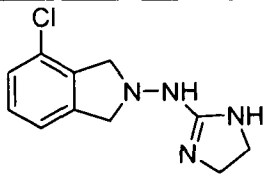
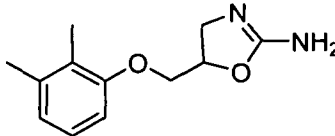
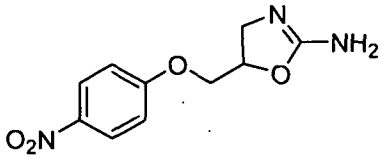
administering to said patient a therapeutically effective amount of the pharmaceutical composition comprising a compound having the formula:

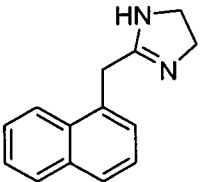
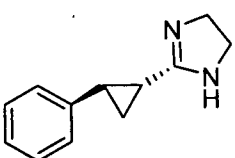
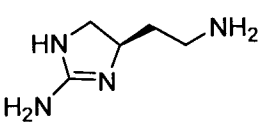
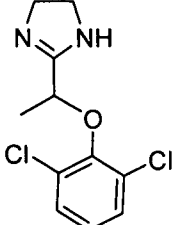
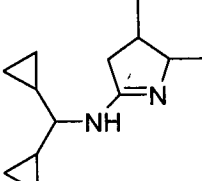
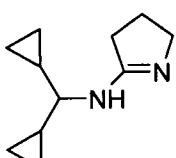
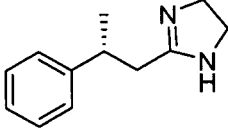
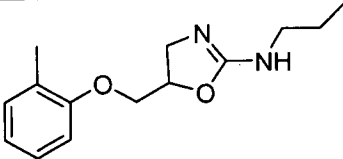
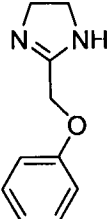
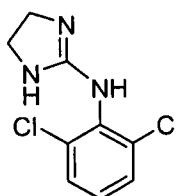
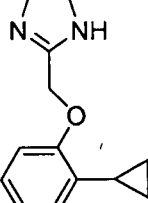
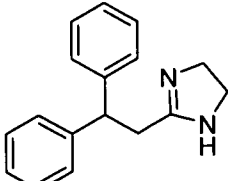
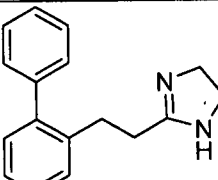
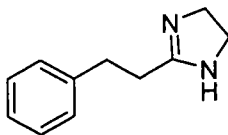
Cpd ID	Structure	Cpd ID	Structure
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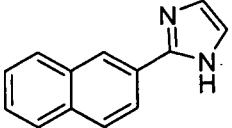
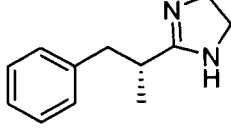
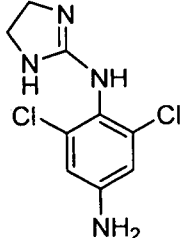
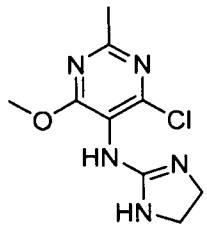
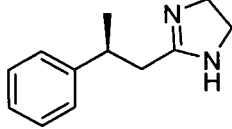
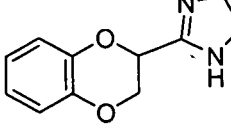
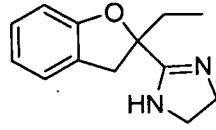
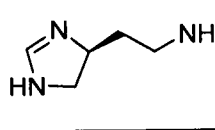
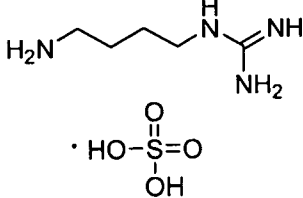
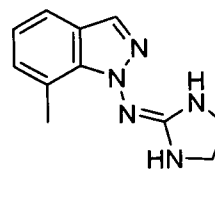
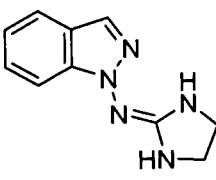
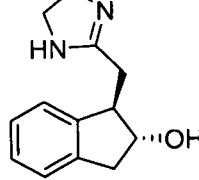
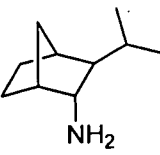
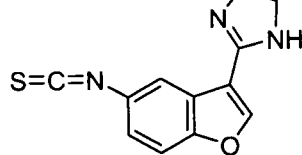
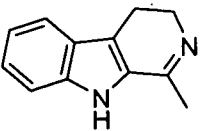
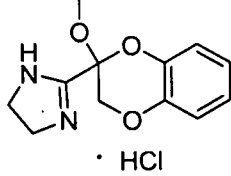
or a mixture thereof, or a pharmaceutically acceptable salt, solvate, or prodrug, or a mixture thereof, of any of the foregoing compounds.

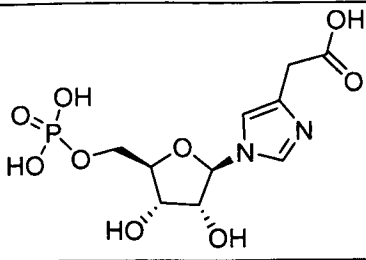
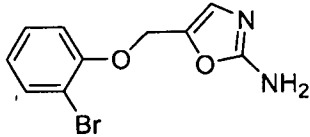
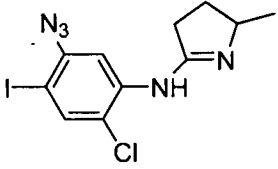
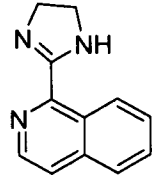
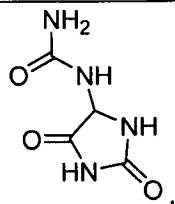
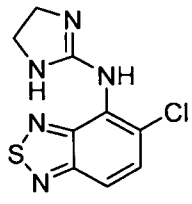
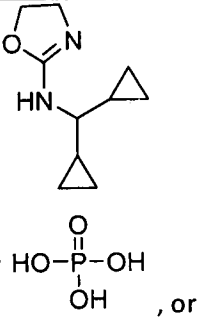
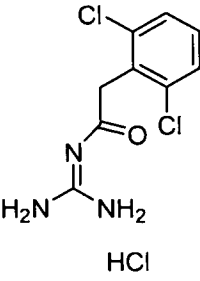
45. The method of claim 44, wherein the condition is allodynia.
46. The method of claim 44, wherein the condition is fibromyalgia.
47. The method of any one of claims 44-46, wherein the pharmaceutical composition is administered simultaneously, separately, or sequentially with one or more substances selected from the group consisting of acetaminophen, a non-steroidal anti-inflammatory drug (NSAID), ibuprofen, naprosyn, a cyclooxygenase-2 inhibitor, aspirin, caffeine, dichloralphenazone, a triptan, an antidepressant, a serotonin-norepinephrine reuptake inhibitor (SNRI), and a gabapentinoid.
48. The method of any one of claims 44-46, wherein the pharmaceutical composition is administered simultaneously, separately, or sequentially with one or more additional therapeutics selected from the group consisting of a chemotherapeutic drug, an antiproliferative agent, an anti-inflammatory agent, a corticosteroid, an anti-asthmatic agent, an anti-allergic agent, an immunosuppressive agent, an immunomodulatory agent, a cardiovascular disease treatment agent, an anti-diabetic agent, a blood disorder treatment agent, a nerve growth factor receptor antagonist, a sodium channel blocker, a CYP2D6 inhibitor, and a TNF-alpha inhibitor.
49. The method of claim 48, wherein the additional therapeutic is a CYP2D6 inhibitor.
50. The method of any one of claims 44-46, wherein the pharmaceutical composition is administered simultaneously, separately, or sequentially with one or more opiates.

51. Use of a compound having the formula:

Cpd ID	Structure	Cpd ID	Structure
1		2	
3		4	
5		6	
7		9	
10		11	
12		13	
14		15	

16		17	
18		19	
20		21	
22		23	
24		25	
27		28	
29		30	

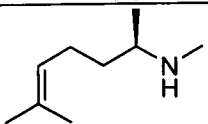
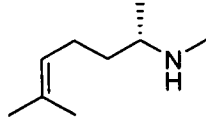
31		32	
33		34	
35		36	
37		38	
39		40	
41		42	
43		44	
45		46	

47		48	
49		50	
51		52	
53		54	

or a mixture thereof, or a pharmaceutically acceptable salt, free base form, enantiomer, diastereomer, tautomer, solvate, or prodrug, or a mixture thereof, of any of the foregoing compounds, for the manufacture of a medicament for treating or preventing one or more conditions selected from the group consisting of: pain; psychic pain; psychological pain; psychiatric pain; depression; allodynia; fibromyalgia; fibromyalgia-ness; central sensitization; centralization; regional pain syndrome; temporomandibular joint syndrome (TMJ); lower back pain; interstitial cystitis; Gulf War syndrome; visceral pain; phantom limb pain; kidney stones; gout; neuropathic pain; post-herpetic neuralgia; diabetic neuropathy; sickle cell pain; priapism; nociceptive pain; post-operative pain; orthopedic injury pain; bunionectomy; dental extraction; pain after severed spinal cord injury; osteoarthritis; rheumatoid arthritis; Lyme

disease; Parkinson's disease; pain associated with cancer; opioid-induced constipation; an opioid withdrawal symptom; and pain associated with post-traumatic stress disorder (PTSD).

52. The use of claim 51, wherein the condition is allodynia.
53. The use of claim 51, wherein the condition is fibromyalgia.
54. The use of any one of claims 51-53, wherein the medicament is administered simultaneously, separately, or sequentially with one or more substances selected from the group consisting of acetaminophen, a non-steroidal anti-inflammatory drug (NSAID), ibuprofen, naprosyn, a cyclooxygenase-2 inhibitor, aspirin, caffeine, dichloralphenazone, a triptan, an antidepressant, a serotonin-norepinephrine reuptake inhibitor (SNRI), and a gabapentinoid.
55. The use of any one of claims 51-53, wherein the medicament is administered simultaneously, separately, or sequentially with one or more additional therapeutics selected from the group consisting of a chemotherapeutic drug, an antiproliferative agent, an anti-inflammatory agent, a corticosteroid, an anti-asthmatic agent, an anti-allergic agent, an immunosuppressive agent, an immunomodulatory agent, a cardiovascular disease treatment agent, an anti-diabetic agent, a blood disorder treatment agent, a nerve growth factor receptor antagonist, a sodium channel blocker, a CYP2D6 inhibitor, and a TNF-alpha inhibitor.
56. The use of claim 55, wherein the additional therapeutic is a CYP2D6 inhibitor.
57. The use of any one of claims 51-53, wherein the medicament is administered simultaneously, separately, or sequentially with one or more opiates.
58. Use of a compound having the formula:

Cpd ID	Structure	Cpd ID	Structure
8		26	

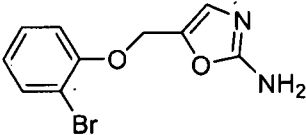
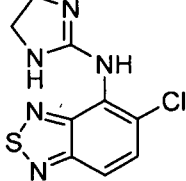
or a mixture thereof, or a pharmaceutically acceptable salt, solvate, or prodrug, or a mixture thereof, of any of the foregoing compounds, for the manufacture of a medicament for treating or preventing one or more conditions selected

from the group consisting of: pain; psychic pain; psychological pain; psychiatric pain; allodynia; fibromyalgia; fibromyalgia-ness; central sensitization; centralization; regional pain syndrome; temporomandibular joint syndrome (TMJ); lower back pain; interstitial cystitis; Gulf War syndrome; visceral pain; phantom limb pain; kidney stones; gout; neuropathic pain; post-herpetic neuralgia; diabetic neuropathy; sickle cell pain; priapism; nociceptive pain; post-operative pain; orthopedic injury pain; bunionectomy; dental extraction; pain after severed spinal cord injury; osteoarthritis; rheumatoid arthritis; Lyme disease; Parkinson's disease; pain associated with cancer; opioid-induced constipation; an opioid withdrawal symptom; and pain associated with post-traumatic stress disorder (PTSD).

59. The use of claim 58, wherein the condition is allodynia.
60. The use of claim 58, wherein the condition is fibromyalgia.
61. The use of any one of claims 58-60, wherein the medicament is administered simultaneously, separately, or sequentially with one or more substances selected from the group consisting of acetaminophen, a non-steroidal anti-inflammatory drug (NSAID), ibuprofen, naprosyn, a cyclooxygenase-2 inhibitor, aspirin, caffeine, dichloralphenazone, a triptan, an antidepressant, a serotonin-norepinephrine reuptake inhibitor (SNRI), and a gabapentinoid.
62. The use of any one of claims 58-60, wherein the medicament is administered simultaneously, separately, or sequentially with one or more additional therapeutics selected from the group consisting of a chemotherapeutic drug, an antiproliferative agent, an anti-inflammatory agent, a corticosteroid, an anti-asthmatic agent, an anti-allergic agent, an immunosuppressive agent, an immunomodulatory agent, a cardiovascular disease treatment agent, an anti-diabetic agent, a blood disorder treatment agent, a nerve growth factor receptor antagonist, a sodium channel blocker, a CYP2D6 inhibitor, and a TNF-alpha inhibitor.
63. The use of claim 62, wherein the additional therapeutic is a CYP2D6 inhibitor.

64. The use of any one of claims 58-60, wherein the medicament is administered simultaneously, separately, or sequentially with one or more opiates.

65. Use of a compound having the formula:

Cpd ID	Structure	Cpd ID	Structure
48	 or	52	

or a mixture thereof, or a pharmaceutically acceptable salt, tautomer, solvate, or prodrug, or a mixture thereof, of any of the foregoing compounds, for the manufacture of a medicament for treating or preventing one or more conditions selected from the group consisting of: pain; psychic pain; psychological pain; psychiatric pain; depression; allodynia; fibromyalgia; fibromyalgia-ness; central sensitization; centralization; regional pain syndrome; temporomandibular joint syndrome (TMJ); lower back pain; interstitial cystitis; Gulf War syndrome; visceral pain; phantom limb pain; kidney stones; gout; neuropathic pain; post-herpetic neuralgia; diabetic neuropathy; sickle cell pain; priapism; nociceptive pain; post-operative pain; orthopedic injury pain; bunionectomy; dental extraction; pain after severed spinal cord injury; osteoarthritis; rheumatoid arthritis; Lyme disease; Parkinson's disease; pain associated with cancer; opioid-induced constipation; an opioid withdrawal symptom; and pain associated with post-traumatic stress disorder (PTSD).

66. The use of claim 65, wherein the condition is allodynia.

67. The use of claim 65, wherein the condition is fibromyalgia.

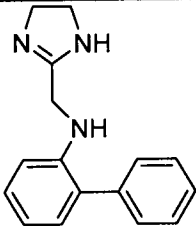
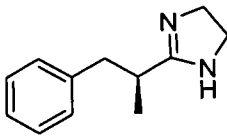
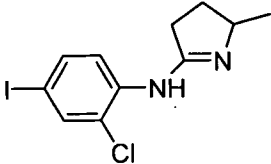
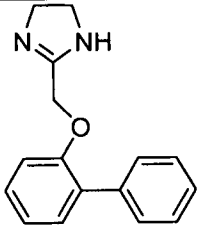
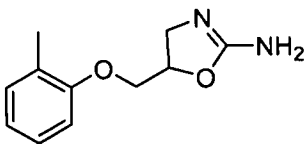

68. The use of any one of claims 65-67, wherein the medicament is administered simultaneously, separately, or sequentially with one or more substances selected from the group consisting of acetaminophen, a non-steroidal anti-inflammatory drug (NSAID), ibuprofen, naprosyn, a cyclooxygenase-2 inhibitor, aspirin, caffeine, dichloralphenazone, a triptan, an antidepressant, a serotonin-norepinephrine reuptake inhibitor (SNRI), and a gabapentinoid.

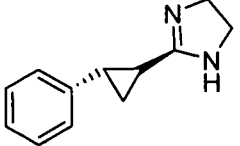
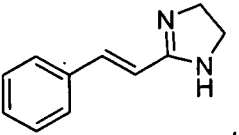
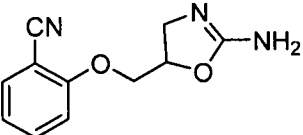
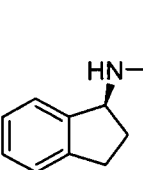
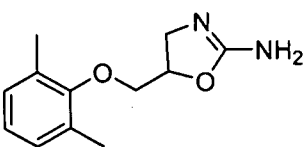
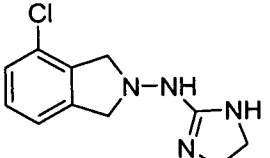
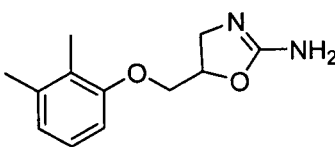
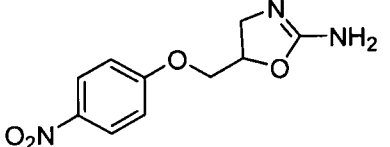
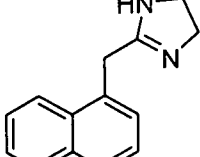
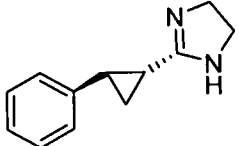
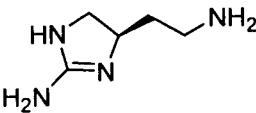
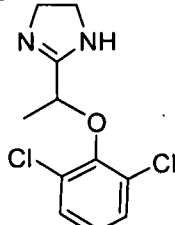
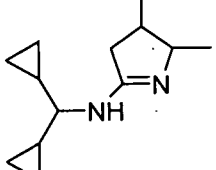
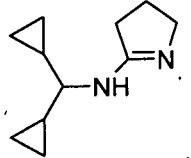
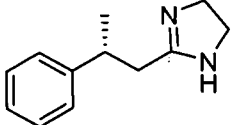
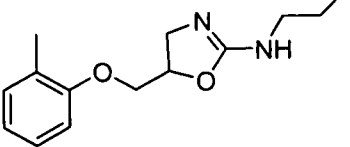
69. The use of any one of claims 65-67, wherein the medicament is administered simultaneously, separately, or sequentially with one or more additional therapeutics selected from the group consisting of a chemotherapeutic drug, an antiproliferative agent, an anti-inflammatory agent, a corticosteroid, an anti-asthmatic agent, an anti-allergic agent, an immunosuppressive agent, an immunomodulatory agent, a cardiovascular disease treatment agent, an anti-diabetic agent, a blood disorder treatment agent, a nerve growth factor receptor antagonist, a sodium channel blocker, a CYP2D6 inhibitor, and a TNF-alpha inhibitor.

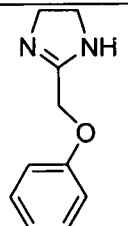
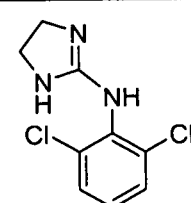
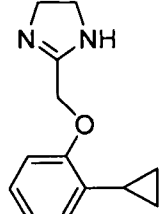
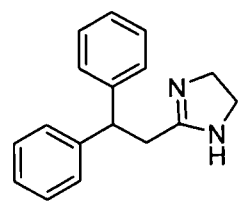
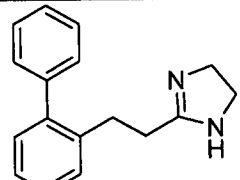
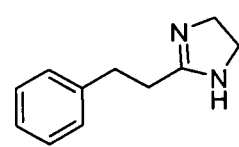
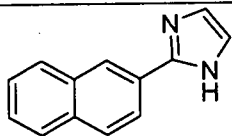
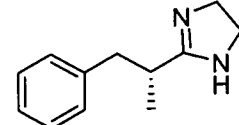
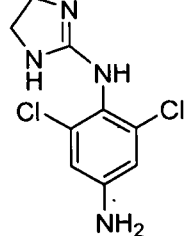
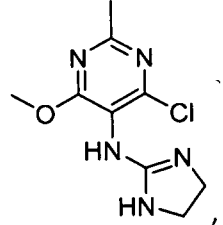
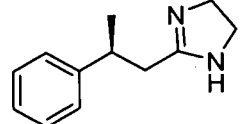
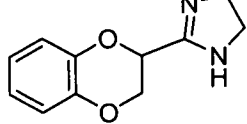
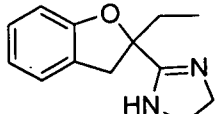
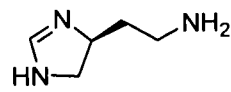
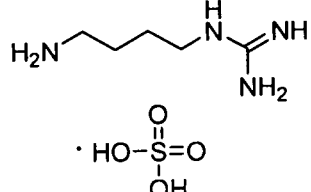
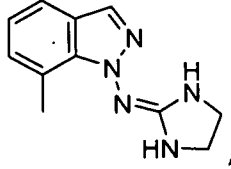
70. The use of claim 69, wherein the additional therapeutic is a CYP2D6 inhibitor.

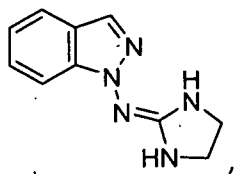
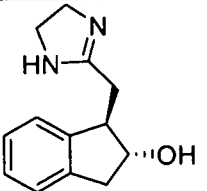
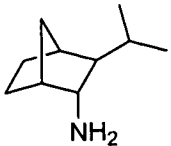
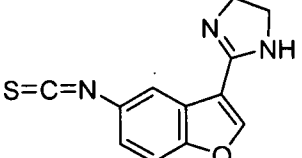
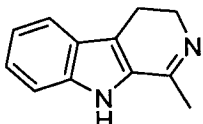
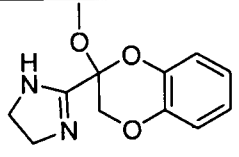
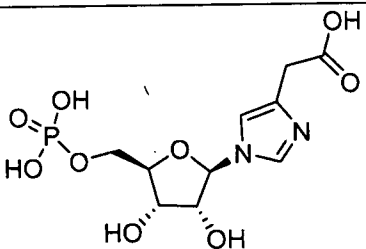
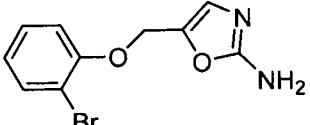
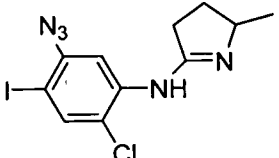
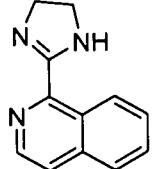
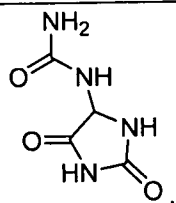
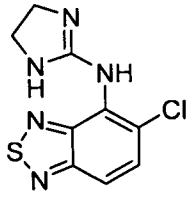
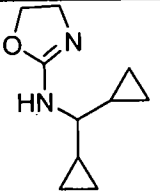
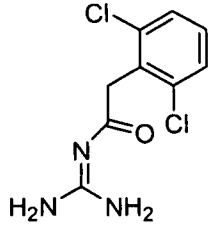
71. The use of any one of claims 65-67, wherein the medicament is administered simultaneously, separately, or sequentially with one or more opiates.

72. A compound having the formula:

Cpd ID	Structure	Cpd ID	Structure
1		2	
3		4	
5		6	

7		9	
10		11	
12		13	
14		15	
16		17	
18		19	
20		21	
22		23	

24		25	
27		28	
29		30	
31		32	
33		34	
35		36	
37		38	
39		40	

41		42	
43		44	
45		46	 <p>HCl</p>
47		48	
49		50	
51		52	
53	 <p>· HO-P(=O)(OH)₂ , or</p>	54	 <p>HCl</p>

or a mixture thereof, or a pharmaceutically acceptable salt, free base form, enantiomer, diastereomer, tautomer, solvate, or prodrug, or a mixture thereof, of any of the foregoing compounds, for use in treating or preventing one or more conditions selected from the group consisting of: pain; psychic pain; psychological pain; psychiatric pain; depression; allodynia; fibromyalgia; fibromyalgia-ness; central sensitization; centralization; regional pain syndrome; temporomandibular joint syndrome (TMJ); lower back pain; interstitial cystitis; Gulf War syndrome; visceral pain; phantom limb pain; kidney stones; gout; neuropathic pain; post-herpetic neuralgia; diabetic neuropathy; sickle cell pain; priapism; nociceptive pain; post-operative pain; orthopedic injury pain; bunionectomy; dental extraction; pain after severed spinal cord injury; osteoarthritis; rheumatoid arthritis; Lyme disease; Parkinson's disease; pain associated with cancer; opioid-induced constipation; an opioid withdrawal symptom; and pain associated with post-traumatic stress disorder (PTSD).

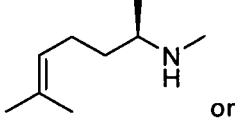
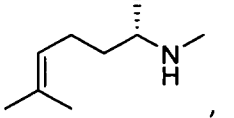
73. The compound of claim 72, wherein the condition is allodynia.
74. The compound of claim 72, wherein the condition is fibromyalgia.
75. The compound of any one of claims 72-74, wherein the compound is used simultaneously, separately, or sequentially with one or more substances selected from the group consisting of acetaminophen, a non-steroidal anti-inflammatory drug (NSAID), ibuprofen, naprosyn, a cyclooxygenase-2 inhibitor, aspirin, caffeine, dichloralphenazone, a triptan, an antidepressant, a serotonin-norepinephrine reuptake inhibitor (SNRI), and a gabapentinoid.
76. The compound of any one of claims 72-74, wherein the compound is used simultaneously, separately, or sequentially with one or more additional therapeutics selected from the group consisting of a chemotherapeutic drug, an antiproliferative agent, an anti-inflammatory agent, a corticosteroid, an anti-asthmatic agent, an anti-allergic agent, an immunosuppressive agent, an immunomodulatory agent, a cardiovascular disease treatment agent, an anti-diabetic agent, a blood disorder treatment agent, a nerve growth factor receptor

antagonist, a sodium channel blocker, a CYP2D6 inhibitor, and a TNF-alpha inhibitor.

77. The compound of claim 76, wherein the additional therapeutic is a CYP2D6 inhibitor.

78. The compound of any one of claims 72-74, wherein the compound is used simultaneously, separately, or sequentially with one or more opiates.

79. A compound having the formula:

Cpd ID	Structure	Cpd ID	Structure
8		26	

or a mixture thereof, or a pharmaceutically acceptable salt, solvate, or prodrug, or a mixture thereof, of any of the foregoing compounds, for use in treating or preventing one or more conditions selected from the group consisting of: pain; psychic pain; psychological pain; psychiatric pain; allodynia; fibromyalgia; fibromyalgia-ness; central sensitization; centralization; regional pain syndrome; temporomandibular joint syndrome (TMJ); lower back pain; interstitial cystitis; Gulf War syndrome; visceral pain; phantom limb pain; kidney stones; gout; neuropathic pain; post-herpetic neuralgia; diabetic neuropathy; sickle cell pain; priapism; nociceptive pain; post-operative pain; orthopedic injury pain; bunionectomy; dental extraction; pain after severed spinal cord injury; osteoarthritis; rheumatoid arthritis; Lyme disease; Parkinson's disease; pain associated with cancer; opioid-induced constipation; an opioid withdrawal symptom; and pain associated with post-traumatic stress disorder (PTSD).

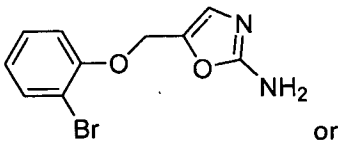
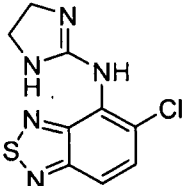
80. The compound of claim 79, wherein the condition is allodynia.

81. The compound of claim 79, wherein the condition is fibromyalgia.

82. The compound of any one of claims 79-81, wherein the compound is used simultaneously, separately, or sequentially with one or more substances selected from the group consisting of acetaminophen, a non-steroidal anti-inflammatory drug (NSAID), ibuprofen, naprosyn, a cyclooxygenase-2

inhibitor, aspirin, caffeine, dichloralphenazone, a triptan, an antidepressant, a serotonin–norepinephrine reuptake inhibitor (SNRI), and a gabapentinoid.

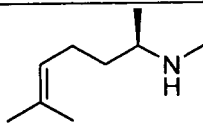
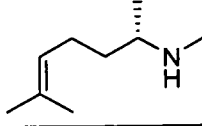
83. The compound of any one of claims 79-81, wherein the compound is used simultaneously, separately, or sequentially with one or more additional therapeutics selected from the group consisting of a chemotherapeutic drug, an antiproliferative agent, an anti-inflammatory agent, a corticosteroid, an anti-asthmatic agent, an anti-allergic agent, an immunosuppressive agent, an immunomodulatory agent, a cardiovascular disease treatment agent, an anti-diabetic agent, a blood disorder treatment agent, a nerve growth factor receptor antagonist, a sodium channel blocker, a CYP2D6 inhibitor, and a TNF-alpha inhibitor.
84. The compound of claim 83, wherein the additional therapeutic is a CYP2D6 inhibitor.
85. The compound of any one of claims 79-81, wherein the compound is used simultaneously, separately, or sequentially with one or more opiates.
86. A compound having the formula:

Cpd ID	Structure	Cpd ID	Structure
48	 or	52	

or a mixture thereof, or a pharmaceutically acceptable salt, tautomer, solvate, or prodrug, or a mixture thereof, of any of the foregoing compounds, for use in treating or preventing one or more conditions selected from the group consisting of: pain; psychic pain; psychological pain; psychiatric pain; depression; allodynia; fibromyalgia; fibromyalgia-ness; central sensitization; centralization; regional pain syndrome; temporomandibular joint syndrome (TMJ); lower back pain; interstitial cystitis; Gulf War syndrome; visceral pain; phantom limb pain; kidney stones; gout; neuropathic pain; post-herpetic neuralgia; diabetic neuropathy; sickle cell pain; priapism; nociceptive pain; post-operative pain; orthopedic injury pain; bunionectomy; dental extraction;

pain after severed spinal cord injury; osteoarthritis; rheumatoid arthritis; Lyme disease; Parkinson's disease; pain associated with cancer; opioid-induced constipation; an opioid withdrawal symptom; and pain associated with post-traumatic stress disorder (PTSD).

87. The compound of claim 86, wherein the condition is allodynia.
88. The compound of claim 86, wherein the condition is fibromyalgia.
89. The compound of any one of claims 86-88, wherein the compound is used simultaneously, separately, or sequentially with one or more substances selected from the group consisting of acetaminophen, a non-steroidal anti-inflammatory drug (NSAID), ibuprofen, naprosyn, a cyclooxygenase-2 inhibitor, aspirin, caffeine, dichloralphenazone, a triptan, an antidepressant, a serotonin-norepinephrine reuptake inhibitor (SNRI), and a gabapentinoid.
90. The compound of any one of claims 86-88, wherein the compound is used simultaneously, separately, or sequentially with one or more additional therapeutics selected from the group consisting of a chemotherapeutic drug, an antiproliferative agent, an anti-inflammatory agent, a corticosteroid, an anti-asthmatic agent, an anti-allergic agent, an immunosuppressive agent, an immunomodulatory agent, a cardiovascular disease treatment agent, an anti-diabetic agent, a blood disorder treatment agent, a nerve growth factor receptor antagonist, a sodium channel blocker, a CYP2D6 inhibitor, and a TNF-alpha inhibitor.
91. The compound of claim 90, wherein the additional therapeutic is a CYP2D6 inhibitor.
92. The compound of any one of claims 86-88, wherein the compound is used simultaneously, separately, or sequentially with one or more opiates.
93. Use of the pharmaceutical composition of claim 3 or 6, or a pharmaceutical composition comprising a compound having the formula:

Cpd ID	Structure	Cpd ID	Structure
8	 or	26	

or a mixture thereof, or a pharmaceutically acceptable salt, solvate, or prodrug, or a mixture thereof, of any of the foregoing compounds, for the manufacture of a medicament for treating or preventing one or more conditions selected from the group consisting of: pain; psychic pain; psychological pain; psychiatric pain; allodynia; fibromyalgia; fibromyalgia-ness; central sensitization; centralization; regional pain syndrome; temporomandibular joint syndrome (TMJ); lower back pain; interstitial cystitis; Gulf War syndrome; visceral pain; phantom limb pain; kidney stones; gout; neuropathic pain; post-herpetic neuralgia; diabetic neuropathy; sickle cell pain; priapism; nociceptive pain; post-operative pain; orthopedic injury pain; bunionectomy; dental extraction; pain after severed spinal cord injury; osteoarthritis; rheumatoid arthritis; Lyme disease; Parkinson's disease; pain associated with cancer; opioid-induced constipation; an opioid withdrawal symptom; and pain associated with post-traumatic stress disorder (PTSD).

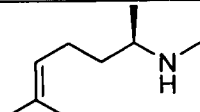
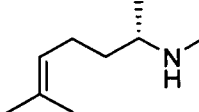
94. The use of claim 93, wherein the condition is allodynia.
95. The use of claim 93, wherein the condition is fibromyalgia.
96. The use of any one of claims 93-95, wherein the medicament is administered simultaneously, separately, or sequentially with one or more substances selected from the group consisting of acetaminophen, a non-steroidal anti-inflammatory drug (NSAID), ibuprofen, naprosyn, a cyclooxygenase-2 inhibitor, aspirin, caffeine, dichloralphenazone, a triptan, an antidepressant, a serotonin-norepinephrine reuptake inhibitor (SNRI), and a gabapentinoid.
97. The use of any one of claims 93-95, wherein the medicament is administered simultaneously, separately, or sequentially with one or more additional therapeutics selected from the group consisting of a chemotherapeutic drug, an antiproliferative agent, an anti-inflammatory agent, a corticosteroid, an anti-asthmatic agent, an anti-allergic agent, an immunosuppressive agent, an immunomodulatory agent, a cardiovascular disease treatment agent, an anti-diabetic agent, a blood disorder treatment agent, a nerve growth factor receptor

antagonist, a sodium channel blocker, a CYP2D6 inhibitor, and a TNF-alpha inhibitor.

98. The use of claim 97, wherein the additional therapeutic is a CYP2D6 inhibitor.

99. The use of any one of claims 93-95, wherein the medicament is administered simultaneously, separately, or sequentially with one or more opiates.

100. The pharmaceutical composition of claim 3 or 6, or a pharmaceutical composition comprising a compound having the formula:

Cpd ID	Structure	Cpd ID	Structure
8	 or	26	

or a mixture thereof, or a pharmaceutically acceptable salt, solvate, or prodrug, or a mixture thereof, of any of the foregoing compounds, for use in treating or preventing one or more conditions selected from the group consisting of: pain; psychic pain; psychological pain; psychiatric pain; allodynia; fibromyalgia; fibromyalgia-ness; central sensitization; centralization; regional pain syndrome; temporomandibular joint syndrome (TMJ); lower back pain; interstitial cystitis; Gulf War syndrome; visceral pain; phantom limb pain; kidney stones; gout; neuropathic pain; post-herpetic neuralgia; diabetic neuropathy; sickle cell pain; priapism; nociceptive pain; post-operative pain; orthopedic injury pain; bunionectomy; dental extraction; pain after severed spinal cord injury; osteoarthritis; rheumatoid arthritis; Lyme disease; Parkinson's disease; pain associated with cancer; opioid-induced constipation; an opioid withdrawal symptom; opioid-induced constipation; an opioid withdrawal symptom; and pain associated with post-traumatic stress disorder (PTSD).

101. The pharmaceutical composition of claim 100, wherein the condition is allodynia.

102. The pharmaceutical composition of claim 100, wherein the condition is fibromyalgia.

103. The pharmaceutical composition of any one of claims **100-102**, wherein the pharmaceutical composition is used simultaneously, separately, or sequentially with one or more substances selected from the group consisting of acetaminophen, a non-steroidal anti-inflammatory drug (NSAID), ibuprofen, naprosyn, a cyclooxygenase-2 inhibitor, aspirin, caffeine, dichloralphenazone, a triptan, an antidepressant, a serotonin–norepinephrine reuptake inhibitor (SNRI), and a gabapentinoid.
104. The pharmaceutical composition of any one of claims **100-102**, wherein the pharmaceutical composition is used simultaneously, separately, or sequentially with one or more additional therapeutics selected from the group consisting of a chemotherapeutic drug, an antiproliferative agent, an anti-inflammatory agent, a corticosteroid, an anti-asthmatic agent, an anti-allergic agent, an immunosuppressive agent, an immunomodulatory agent, a cardiovascular disease treatment agent, an anti-diabetic agent, a blood disorder treatment agent, a nerve growth factor receptor antagonist, a sodium channel blocker, a CYP2D6 inhibitor, and a TNF-alpha inhibitor.
105. The pharmaceutical composition of claim **104**, wherein the additional therapeutic is a CYP2D6 inhibitor.
106. The pharmaceutical composition of any one of claims **100-102**, wherein the pharmaceutical composition is used simultaneously, separately, or sequentially with one or more opiates.

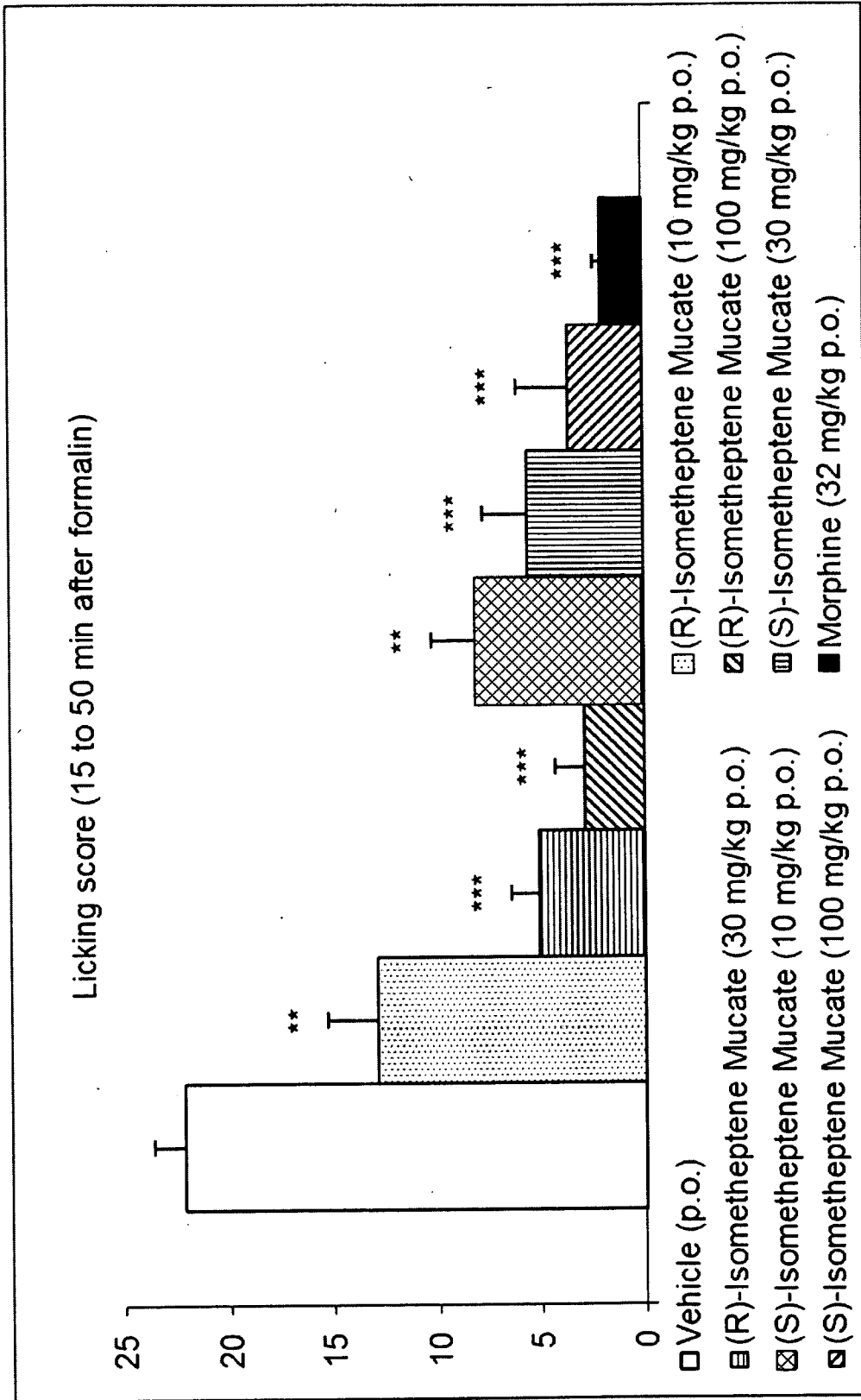


FIG. 1

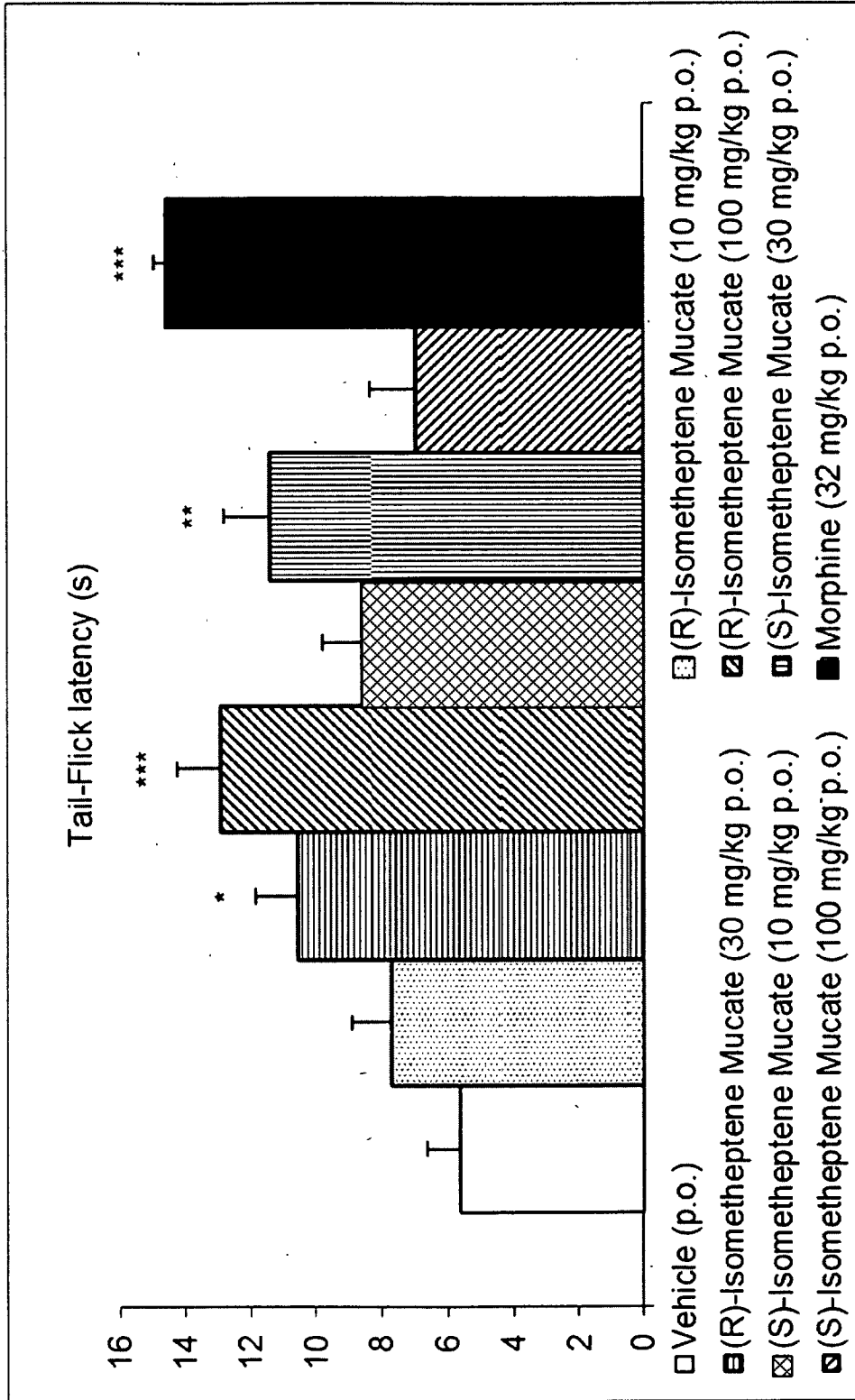


FIG. 2

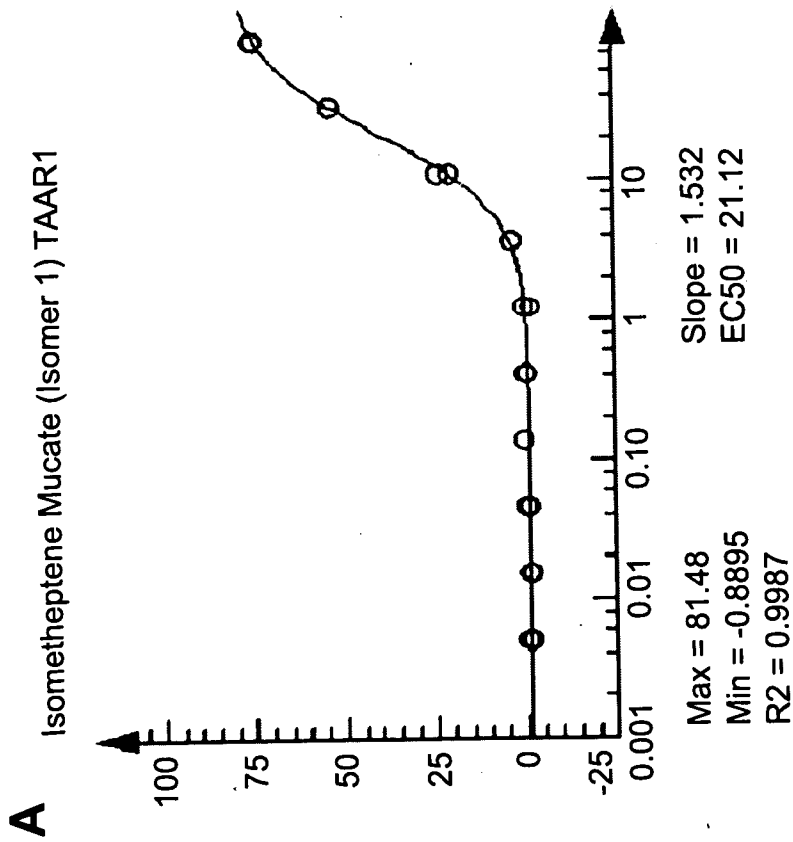
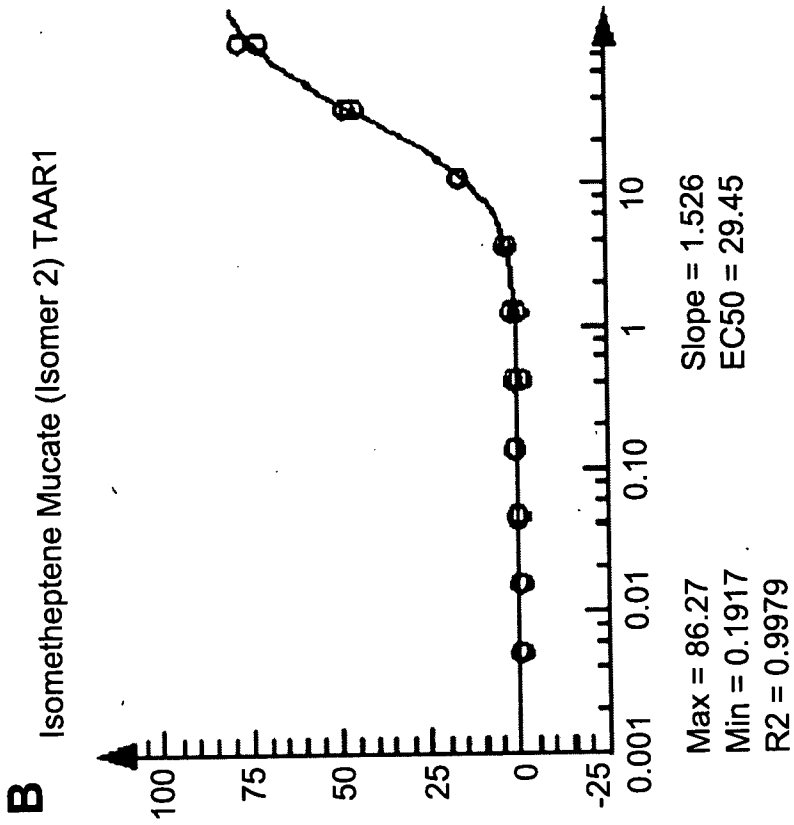


FIG. 3

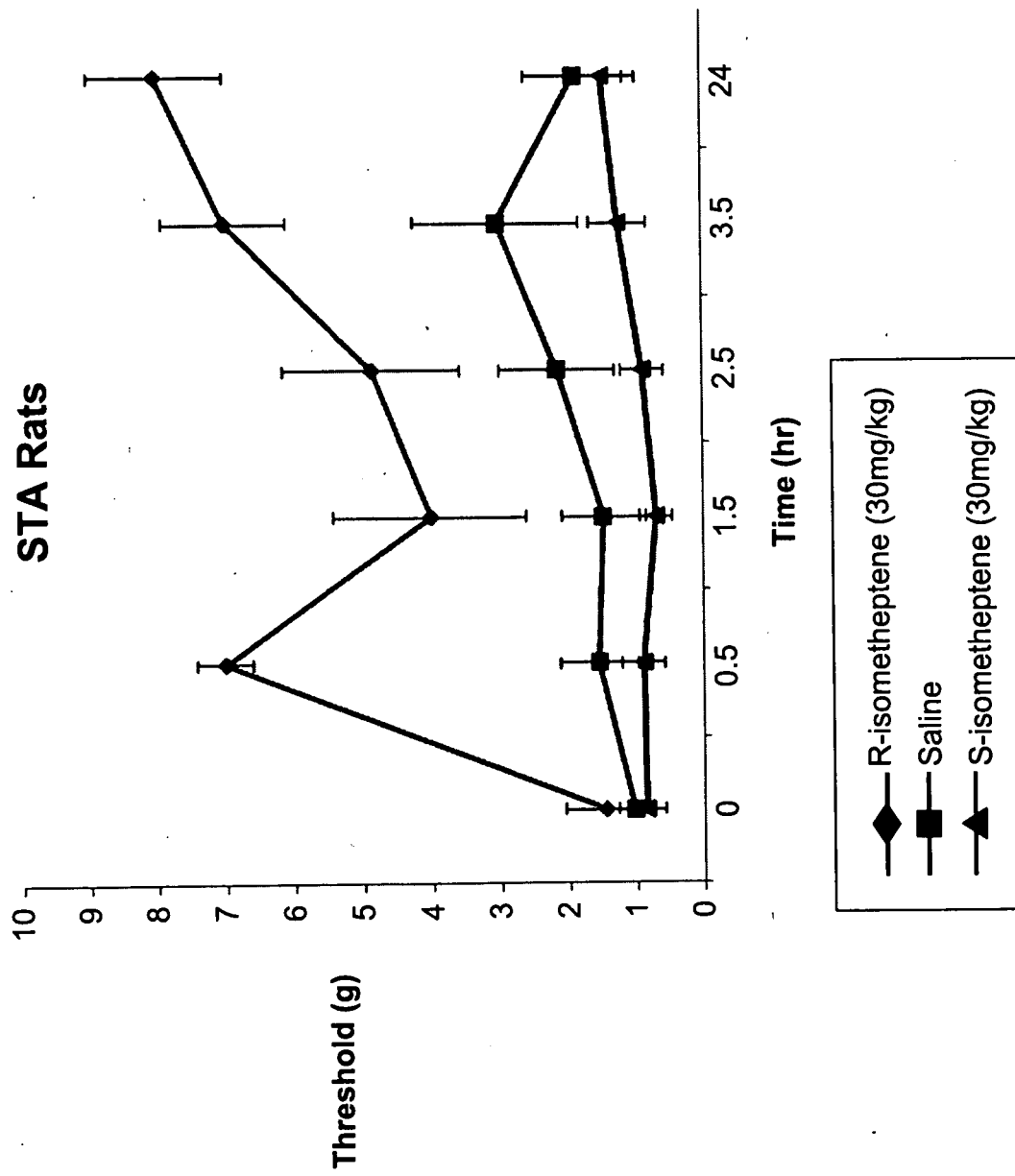


FIG. 4

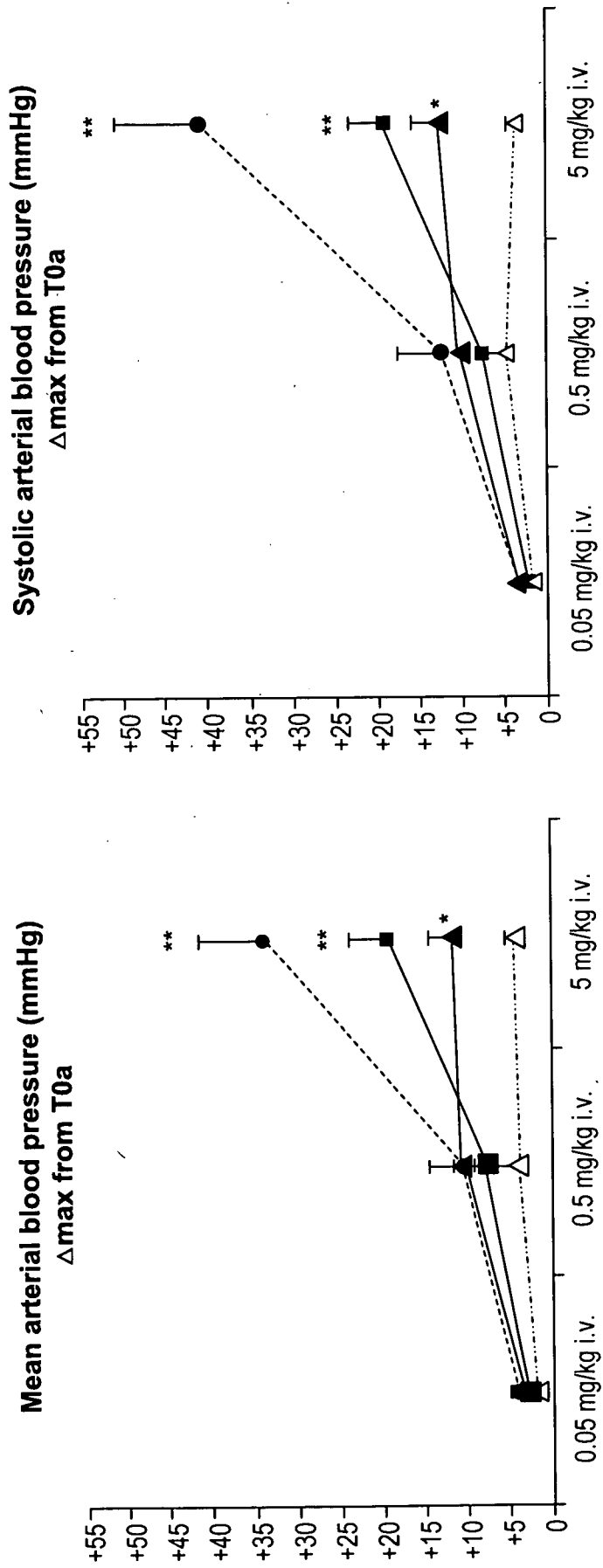
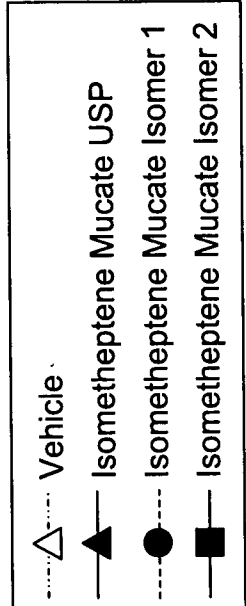


FIG. 5A

FIG. 5B



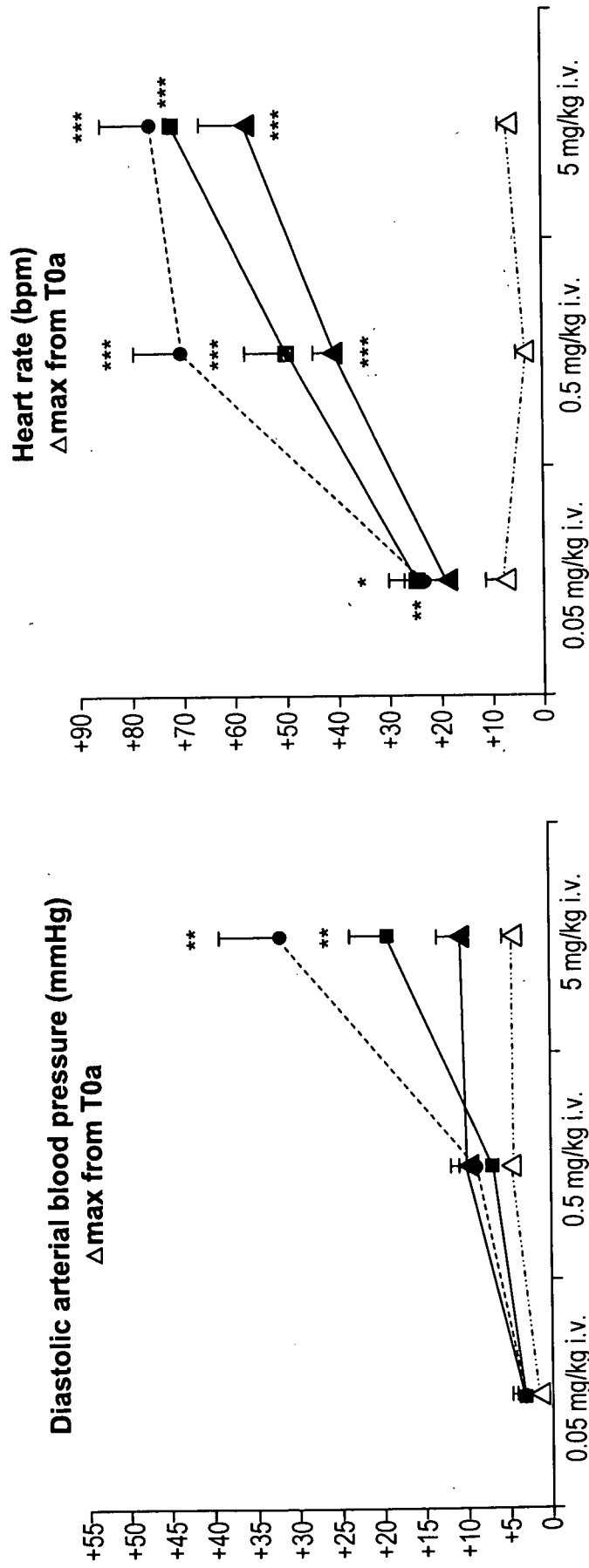
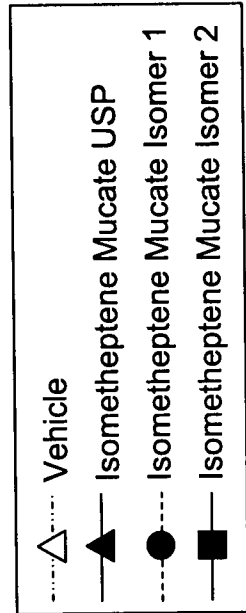
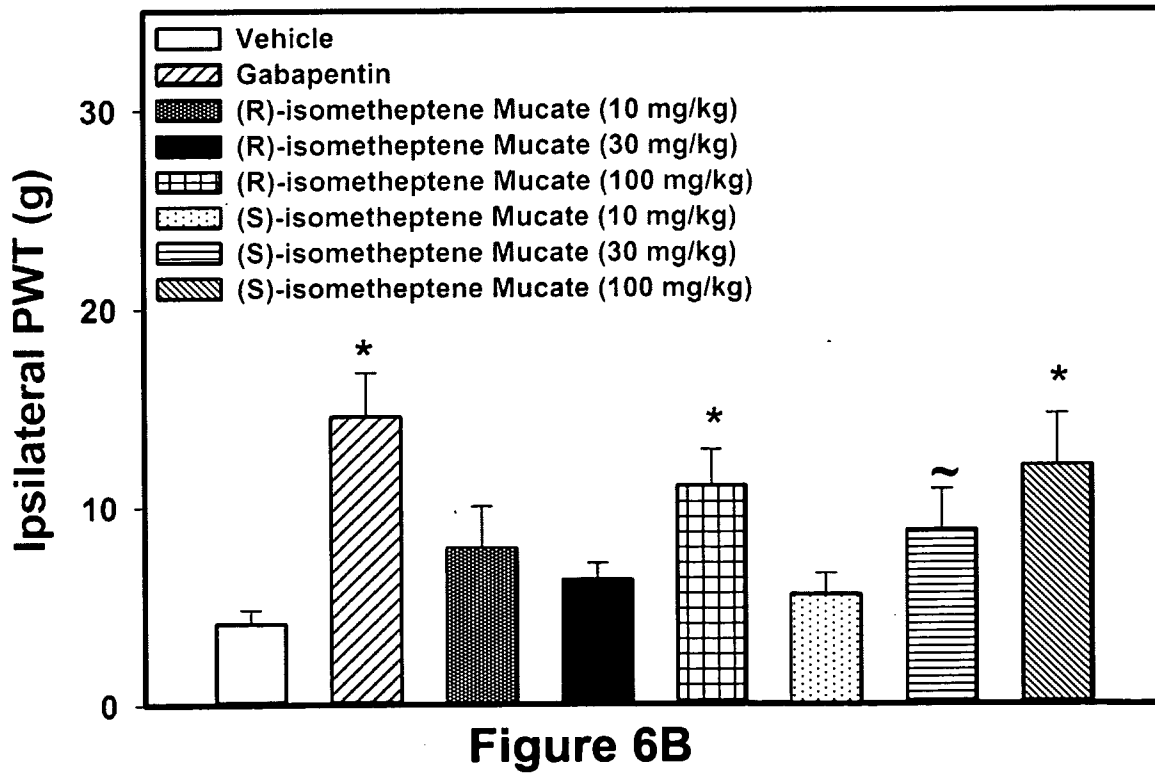
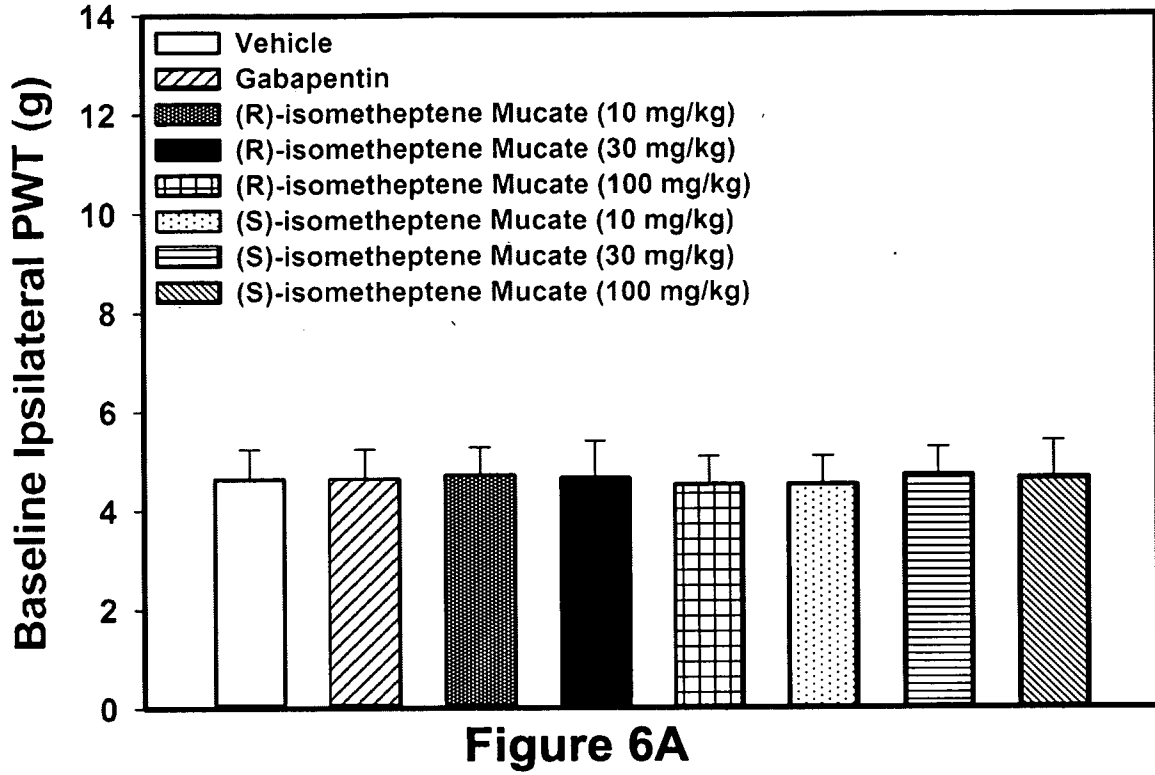


FIG. 5D

FIG. 5C





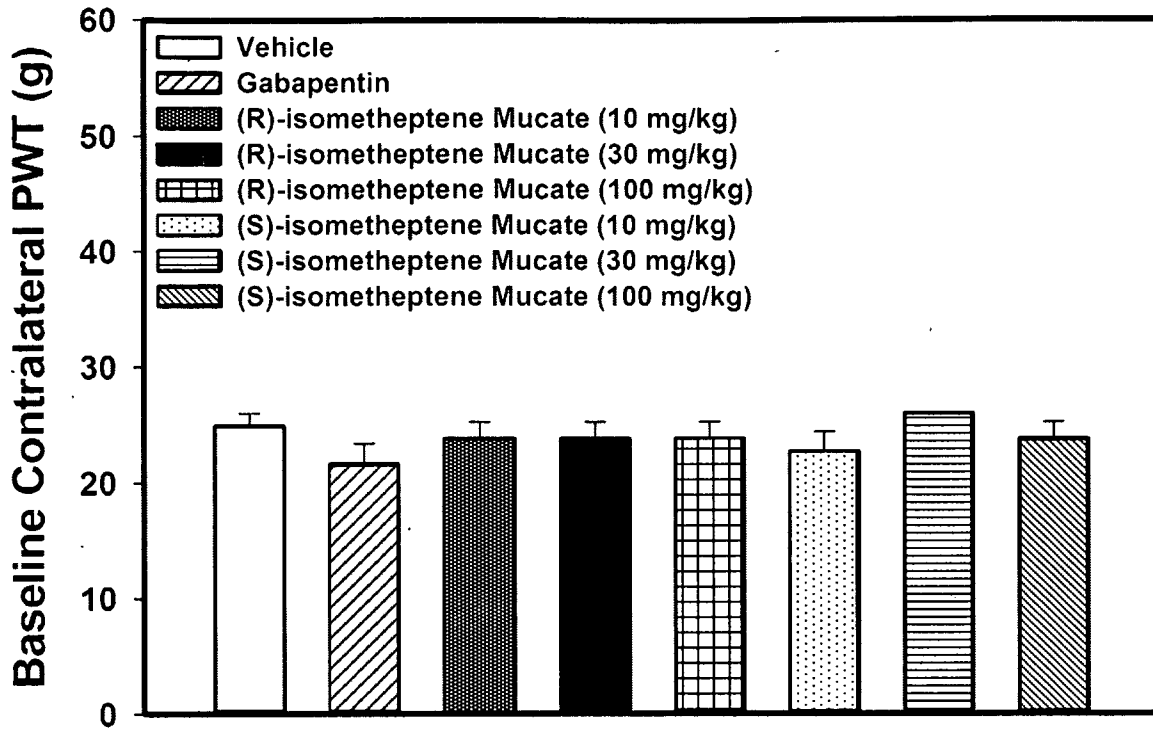


Figure 6C

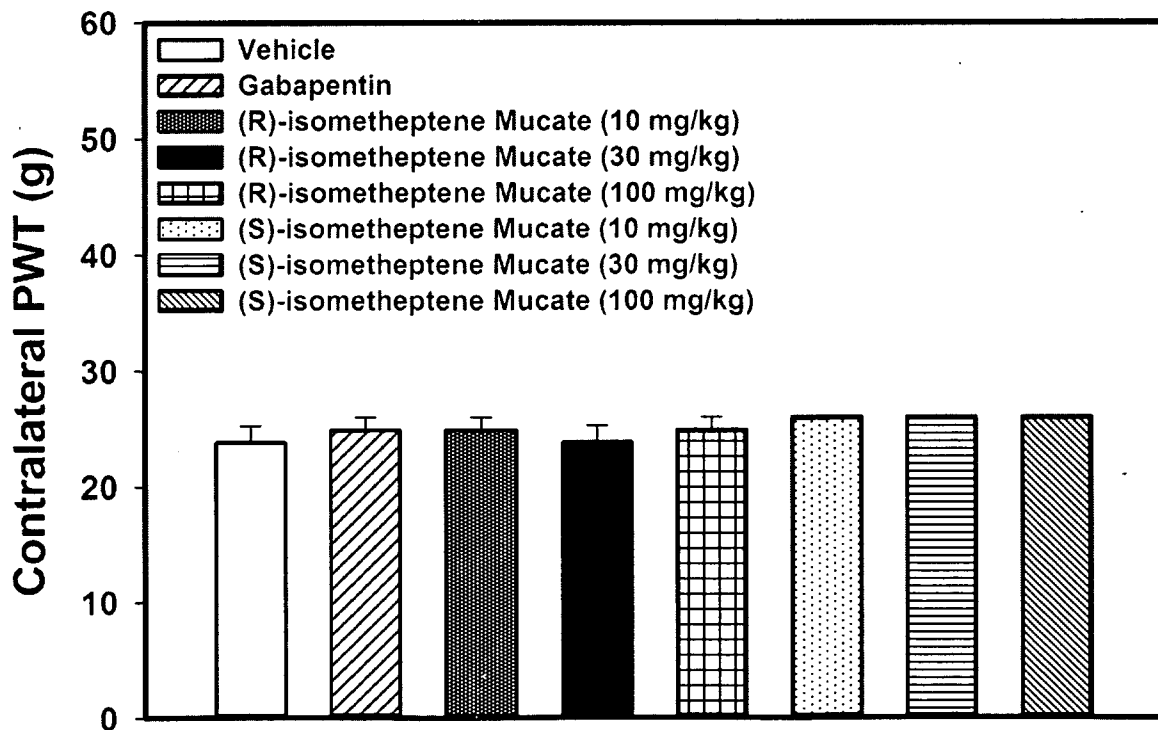


Figure 6D

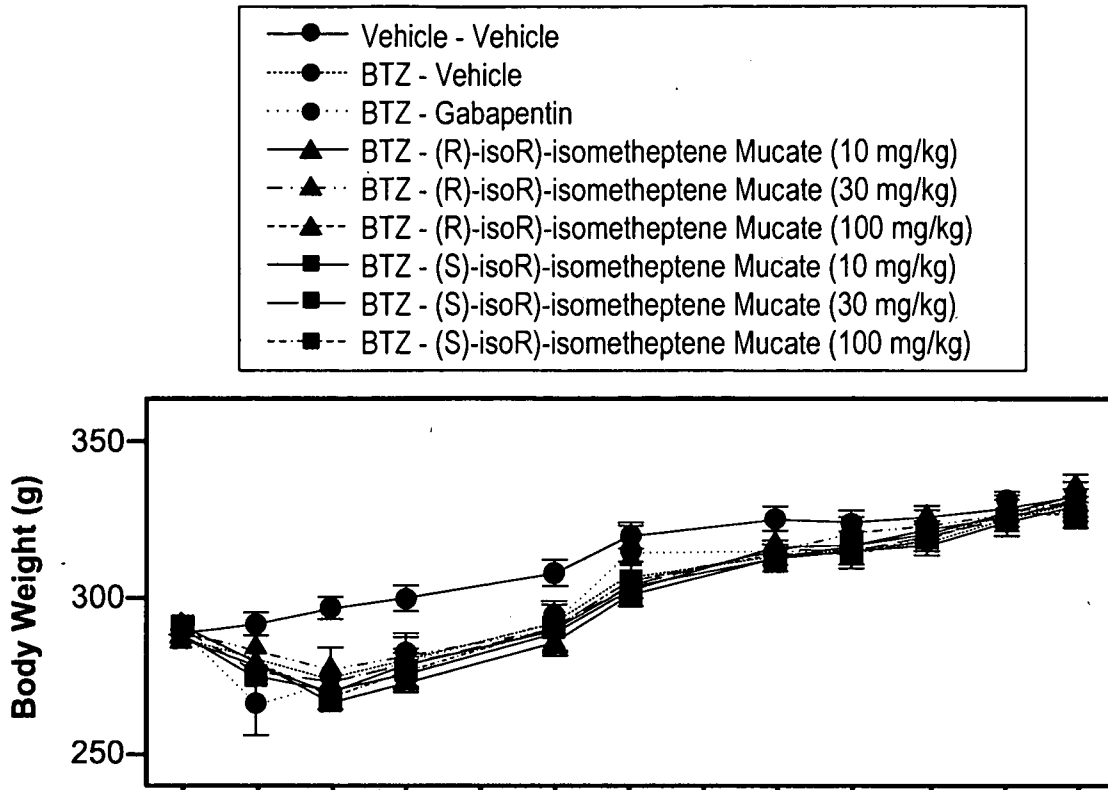


Figure 7A

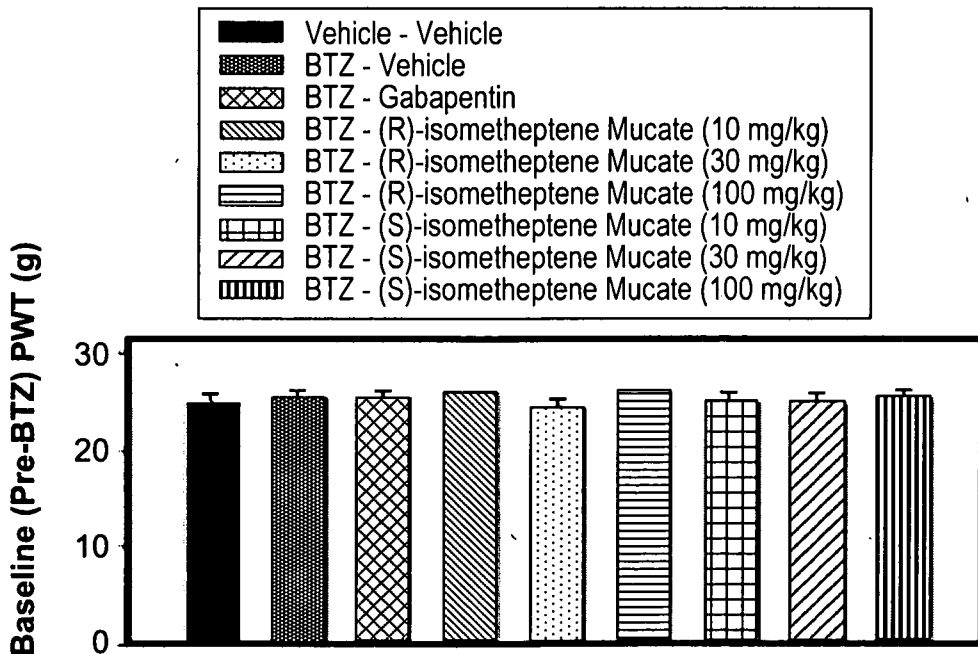
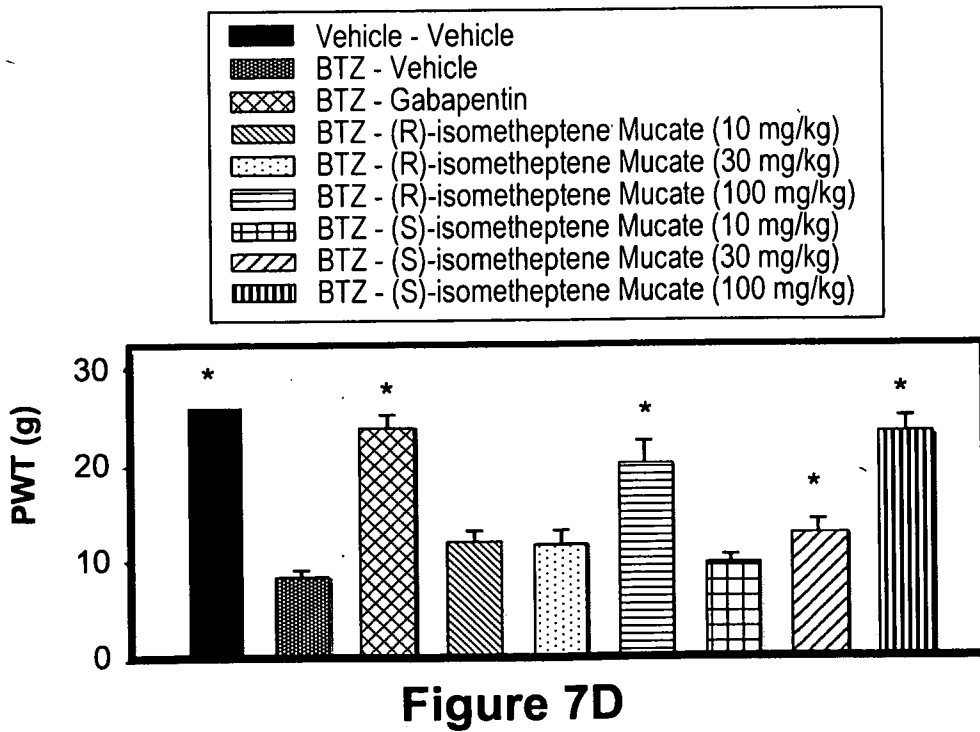
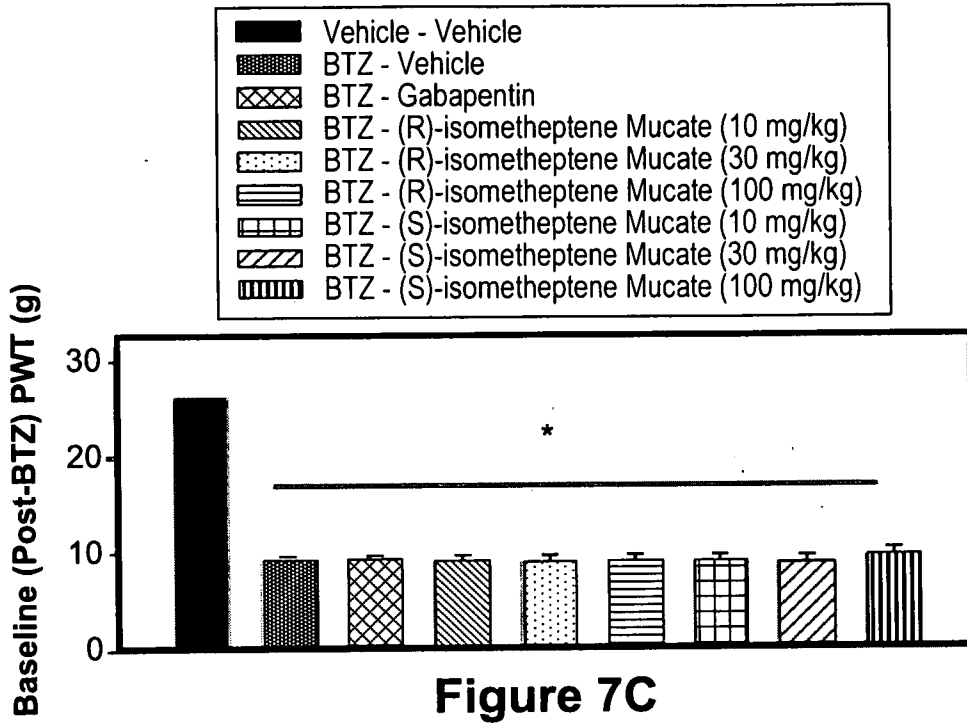


Figure 7B



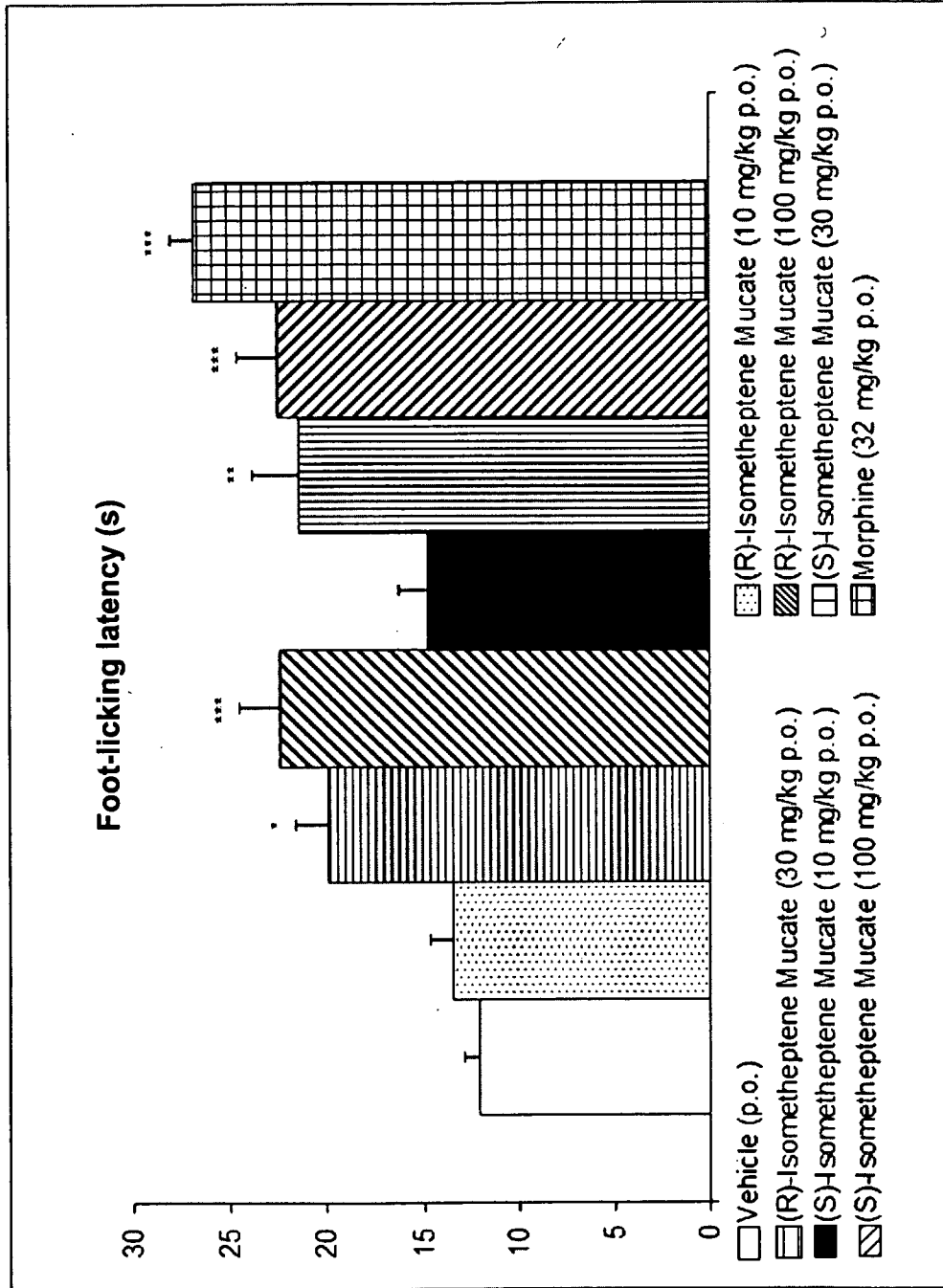
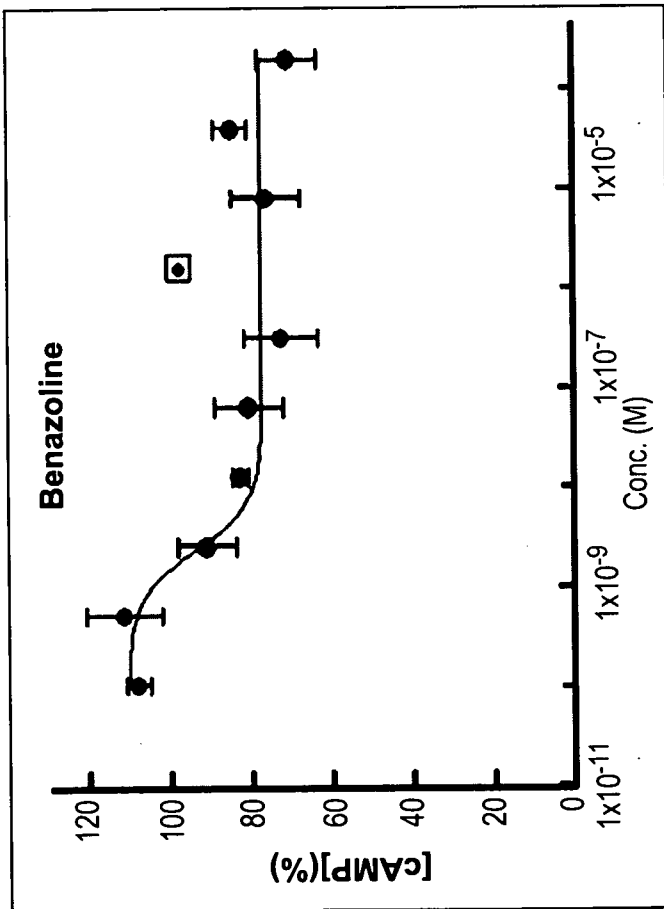
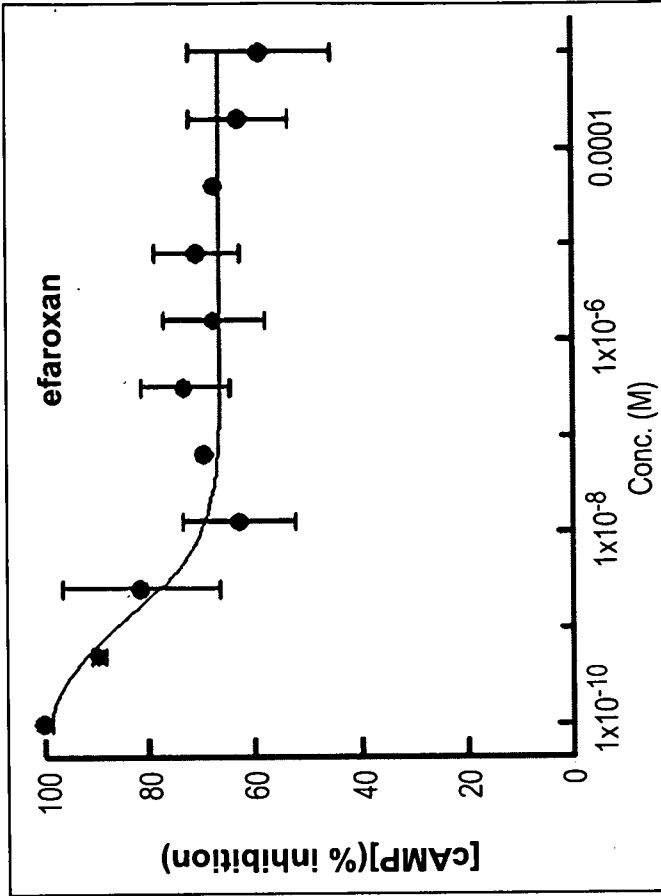


Figure 8



compounds	benazolin			efaroxan		
	run1	run 2	run 3	run1	run 2	run 3
assay date	(06/19)	(06/27)	(07/23)	(07/10)	(07/18)	(07/25)
IC50 (nM)	2.3	1.2	7.2	1.3	1.3	0.8
IC50 (nM) in literature	2.2			0.4		

Figure 10A

Effects of efaroxan or benazoline on forskolin-stimulated cAMP level in CHO/I1R cells

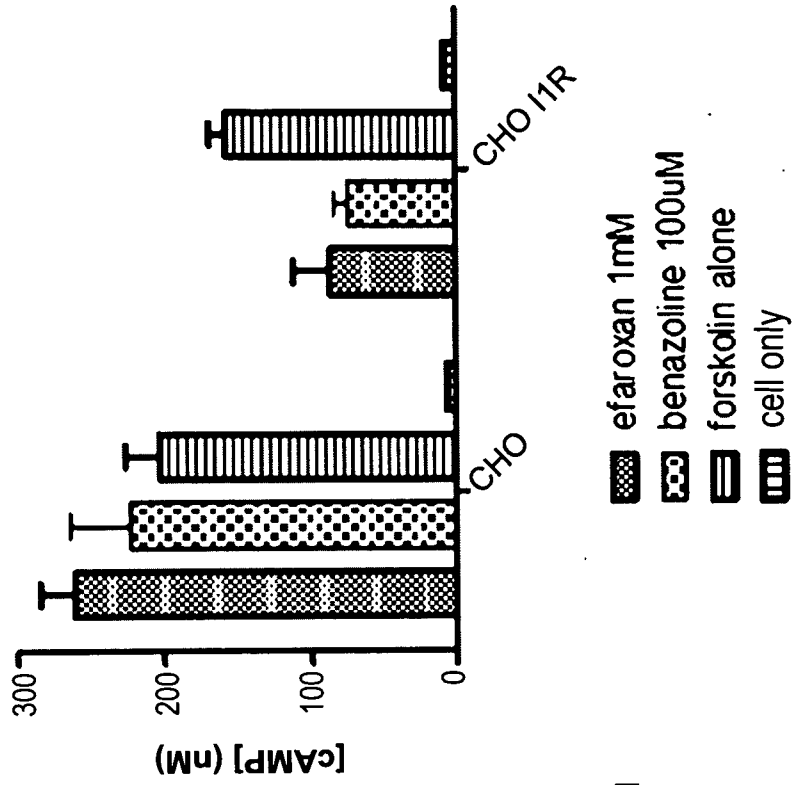


Figure 10C

Effects of compounds on forskolin-stimulated cAMP level in PC12 cells

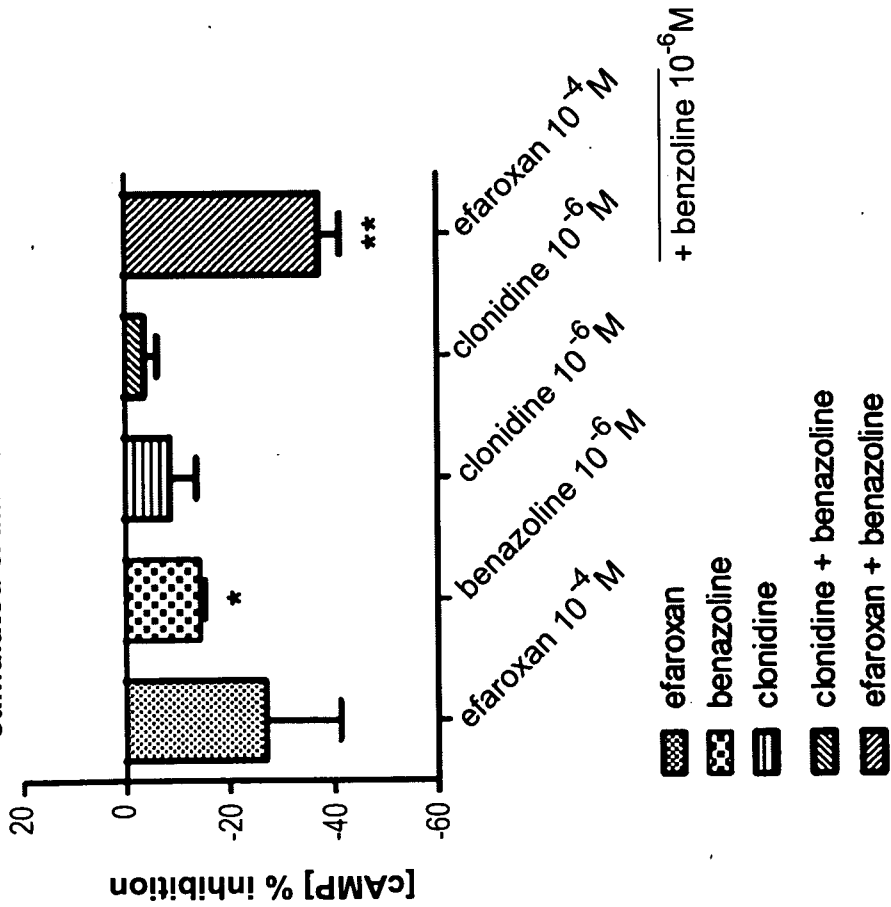


Figure 10B

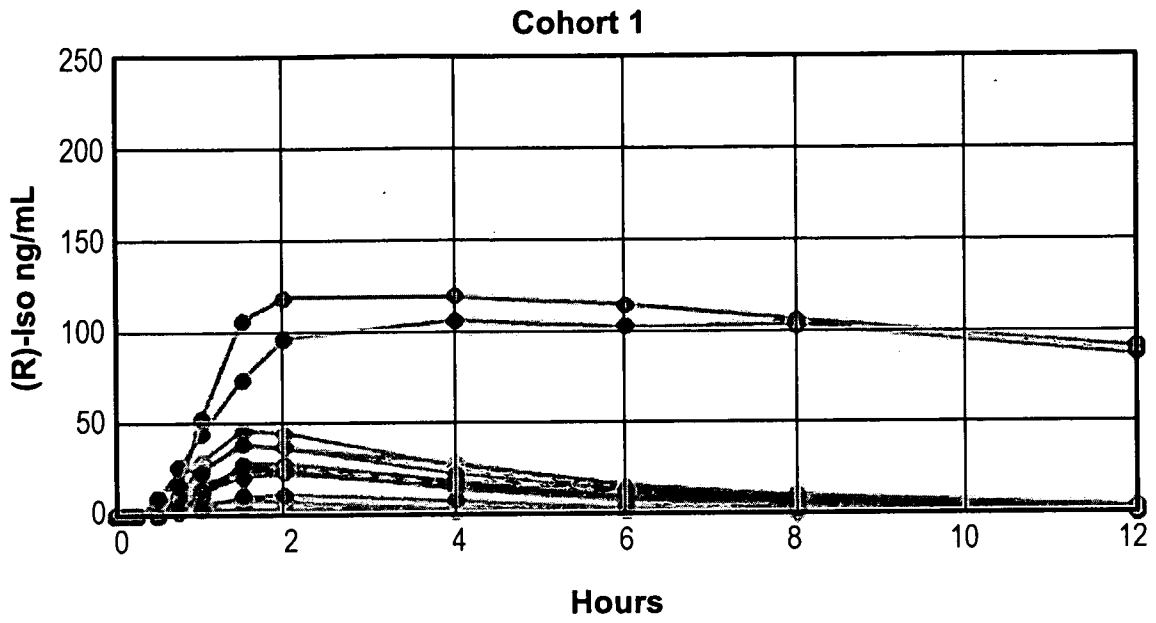


Figure 11A

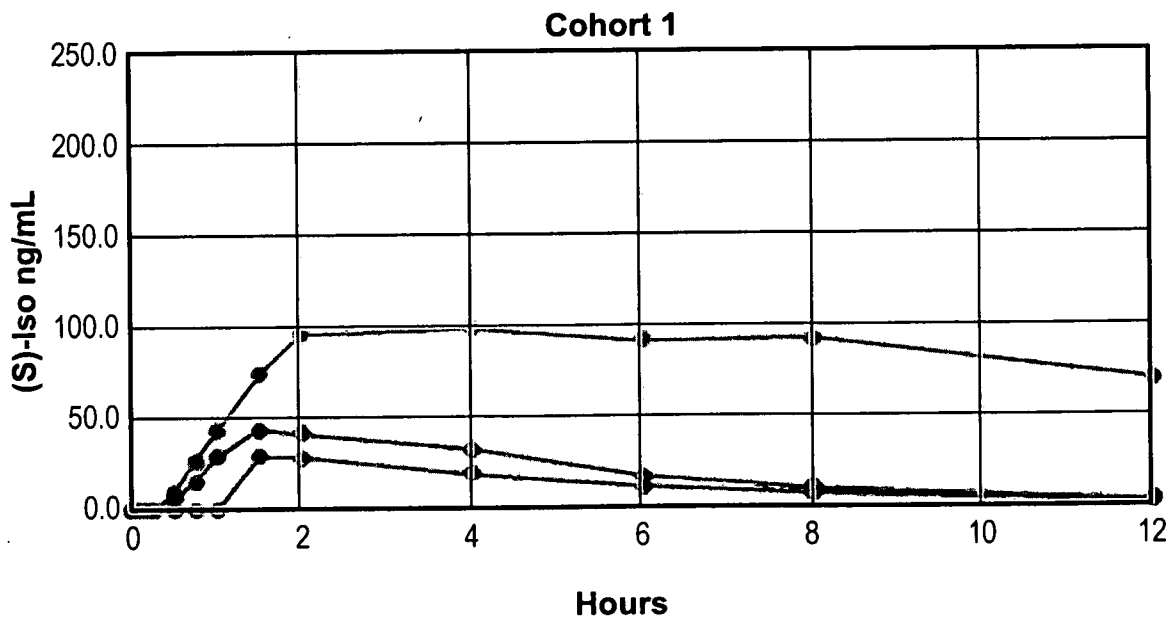


Figure 11B

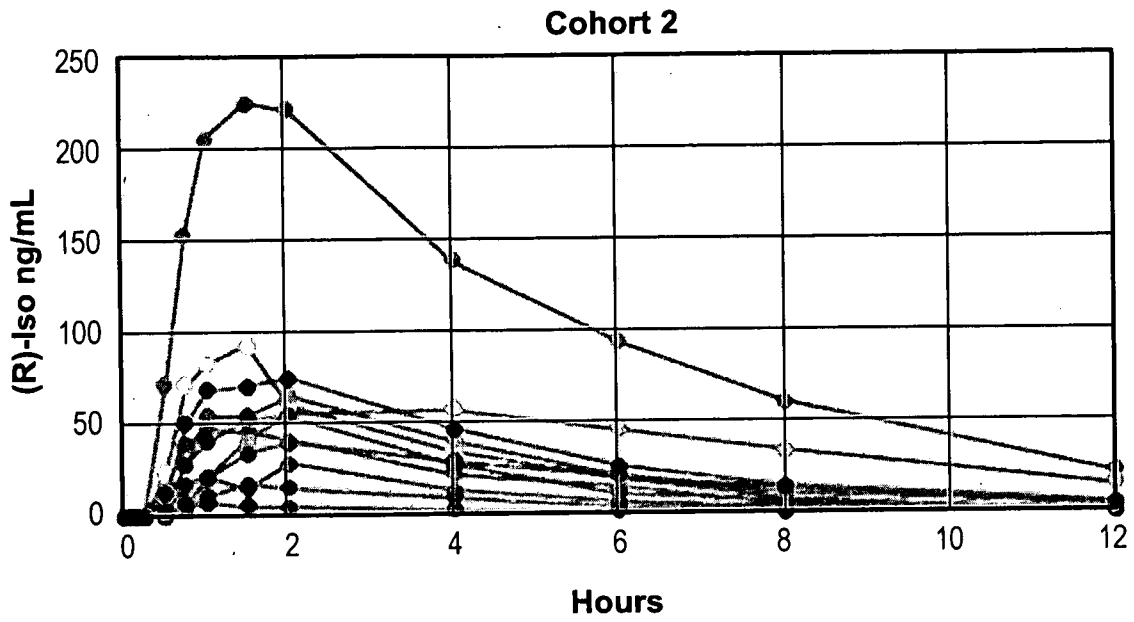


Figure 11C

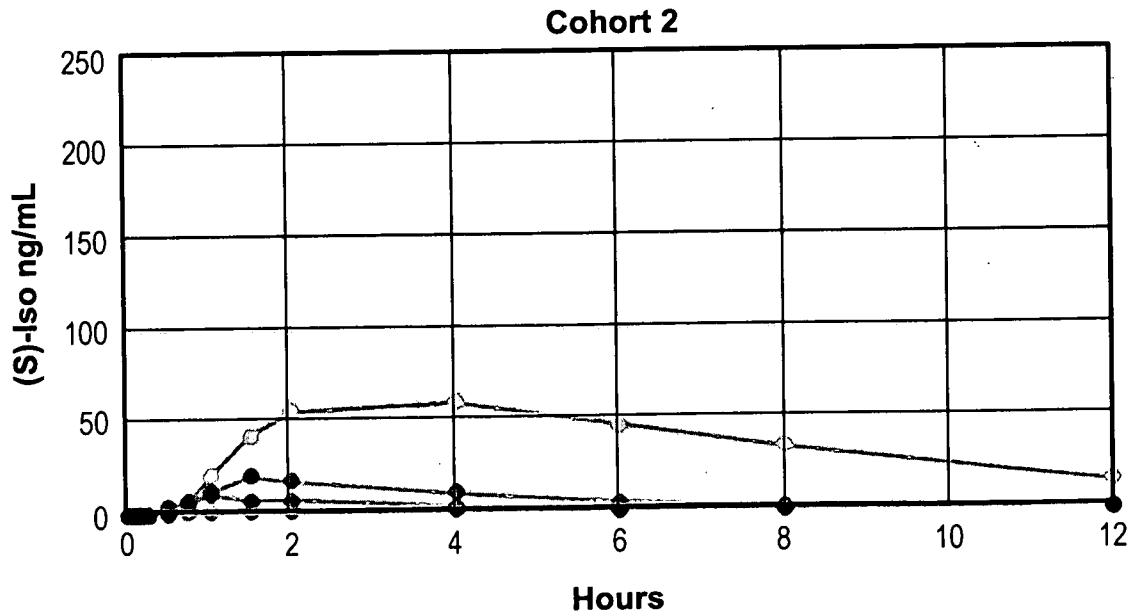


Figure 11D

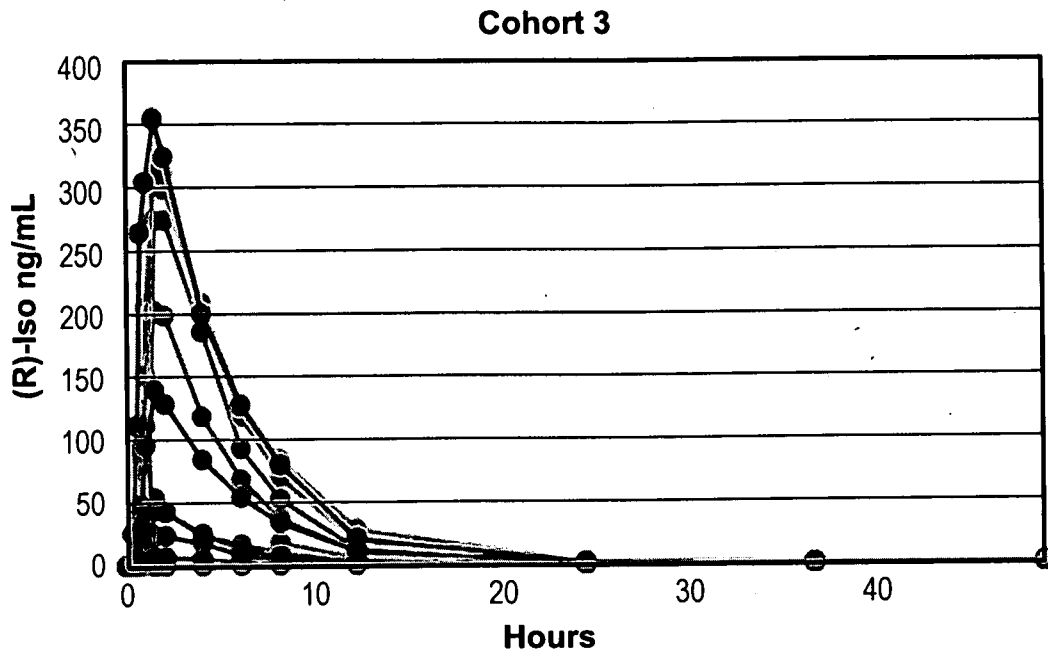


Figure 12A

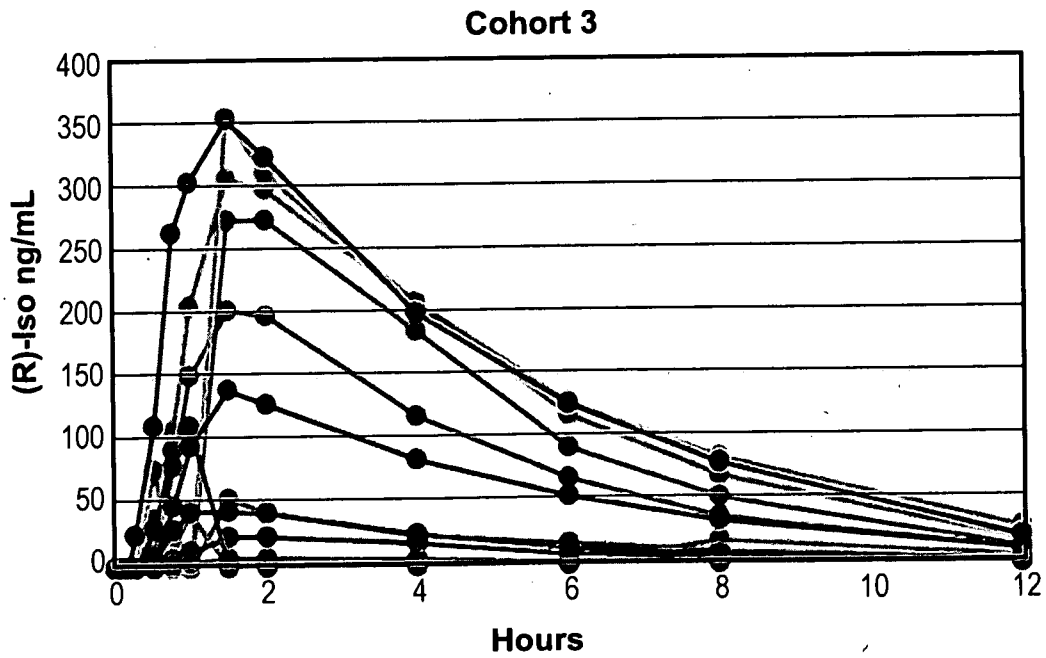


Figure 12B

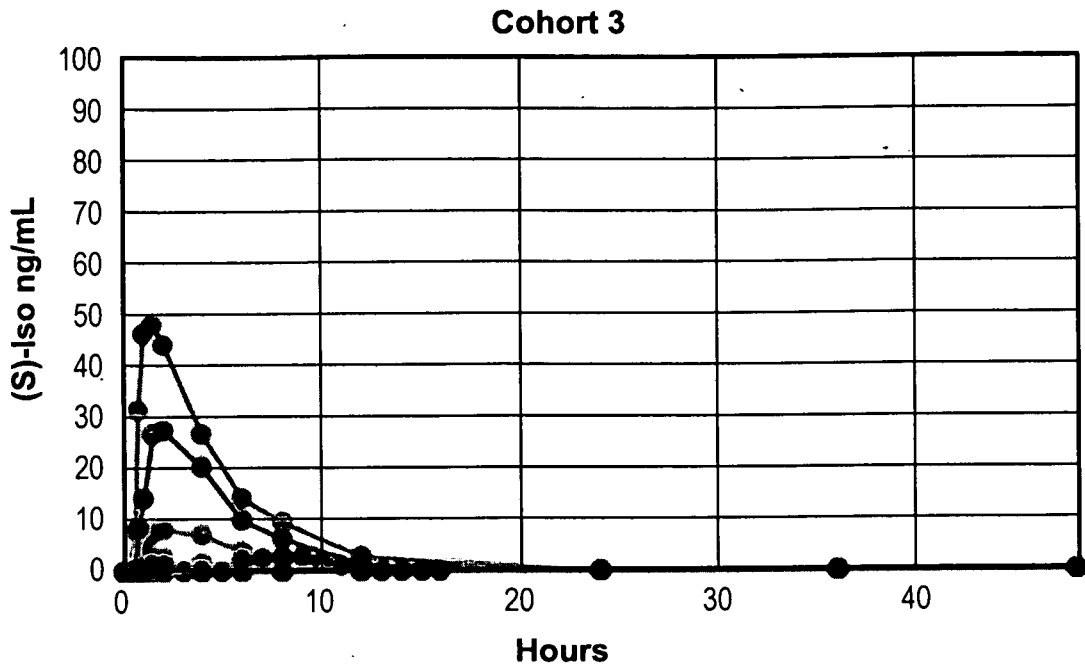


Figure 12C

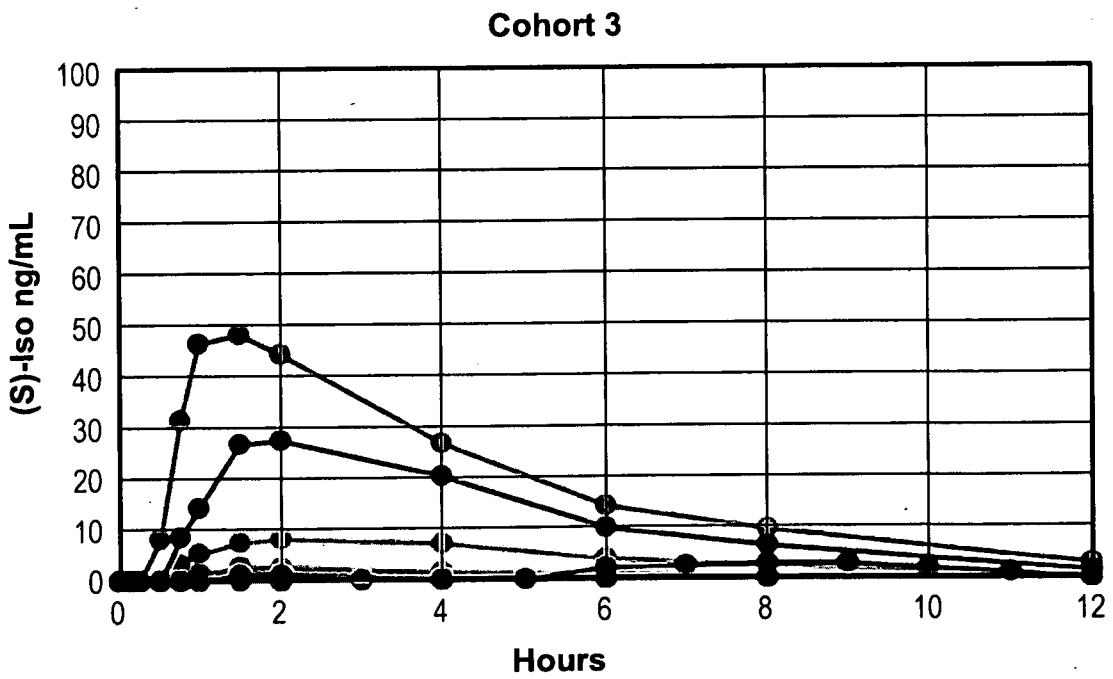


Figure 12D

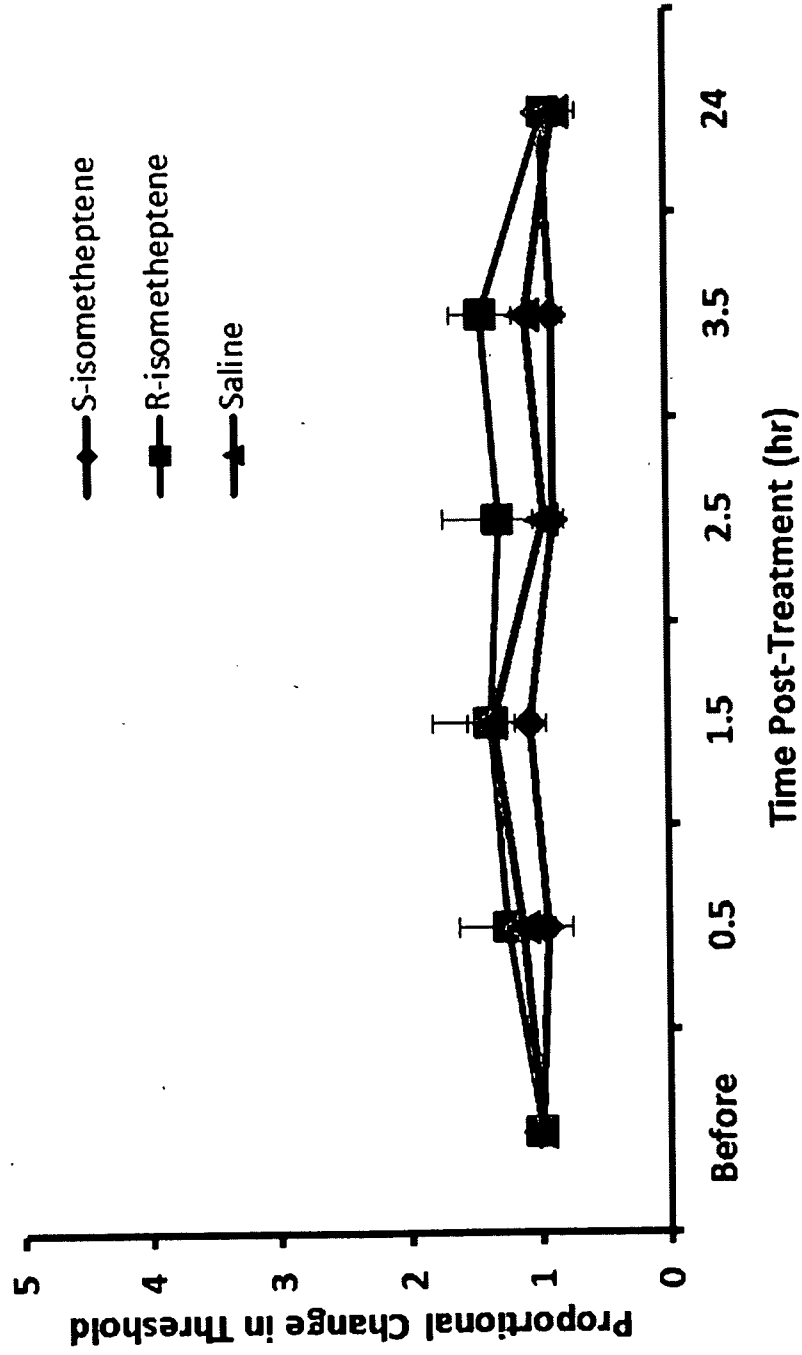


Figure 13

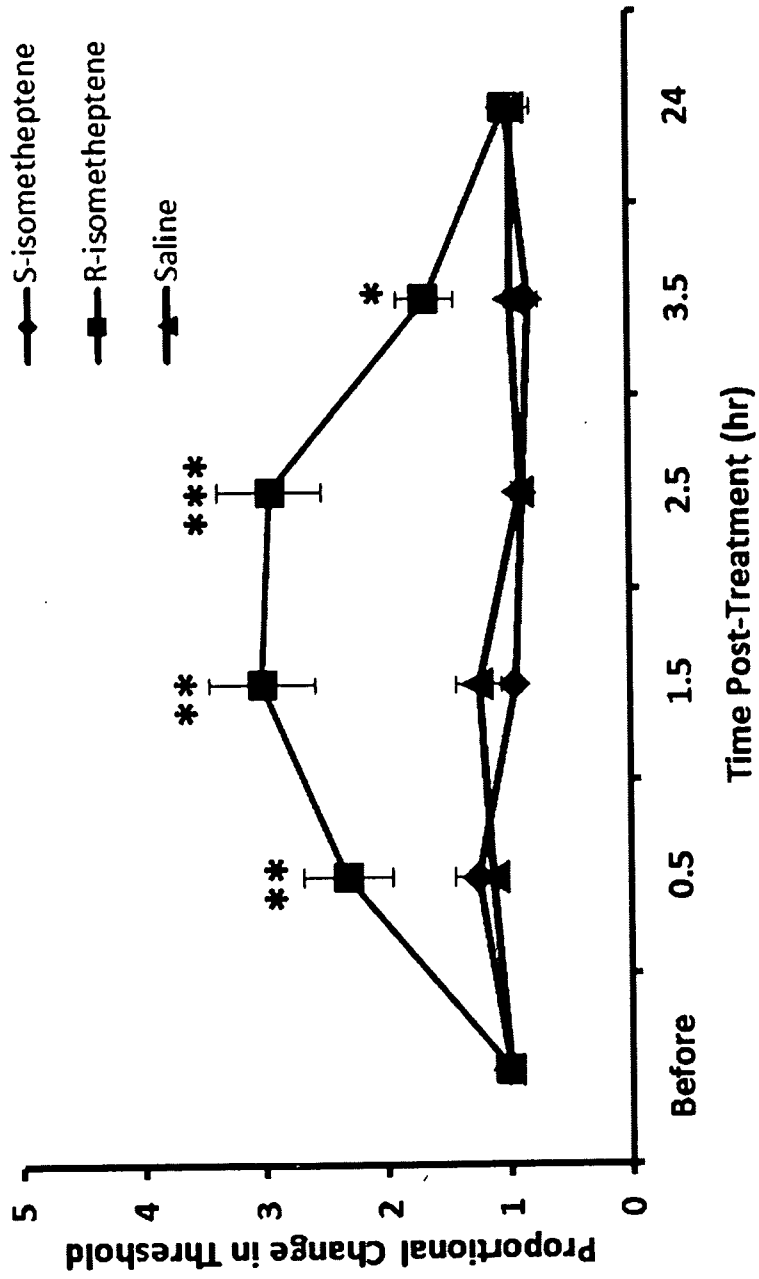


Figure 14

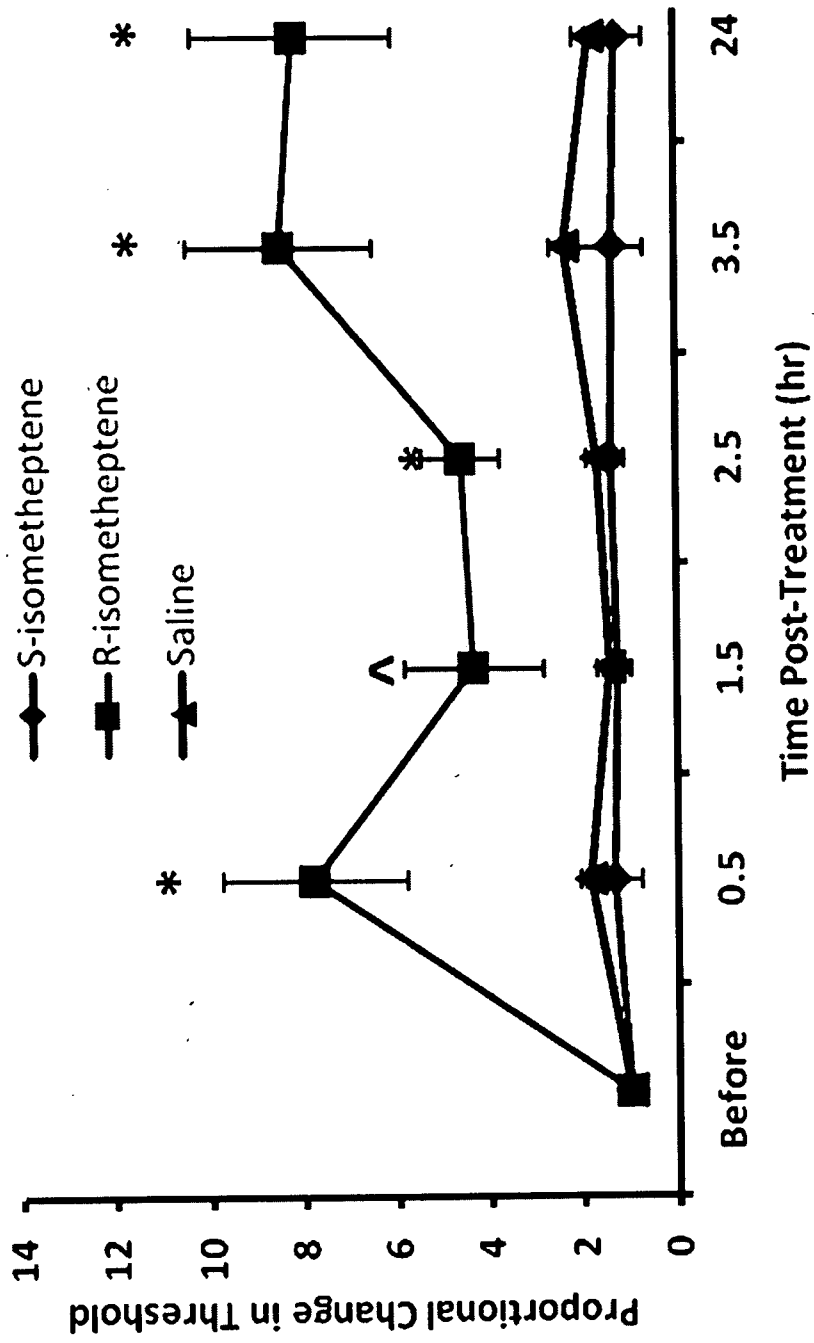


Figure 15

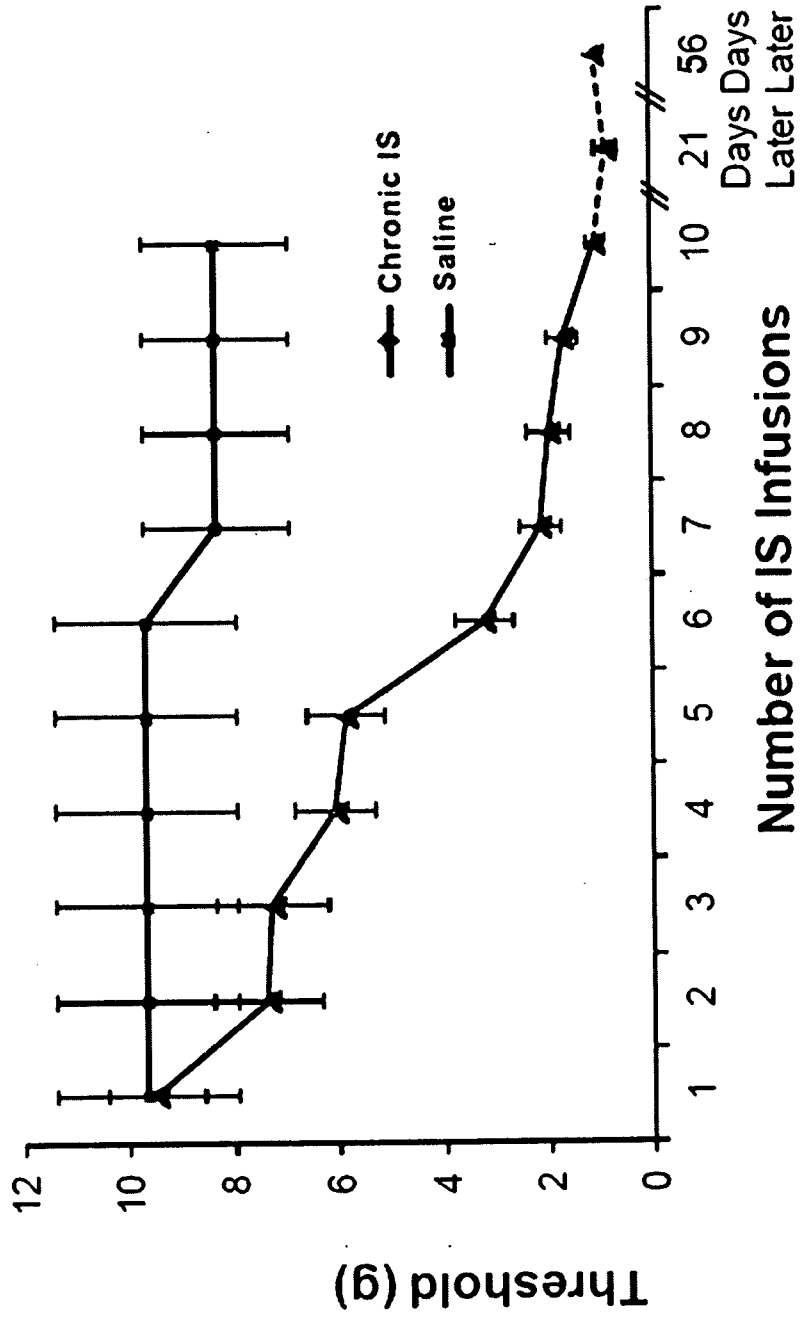


Figure 16

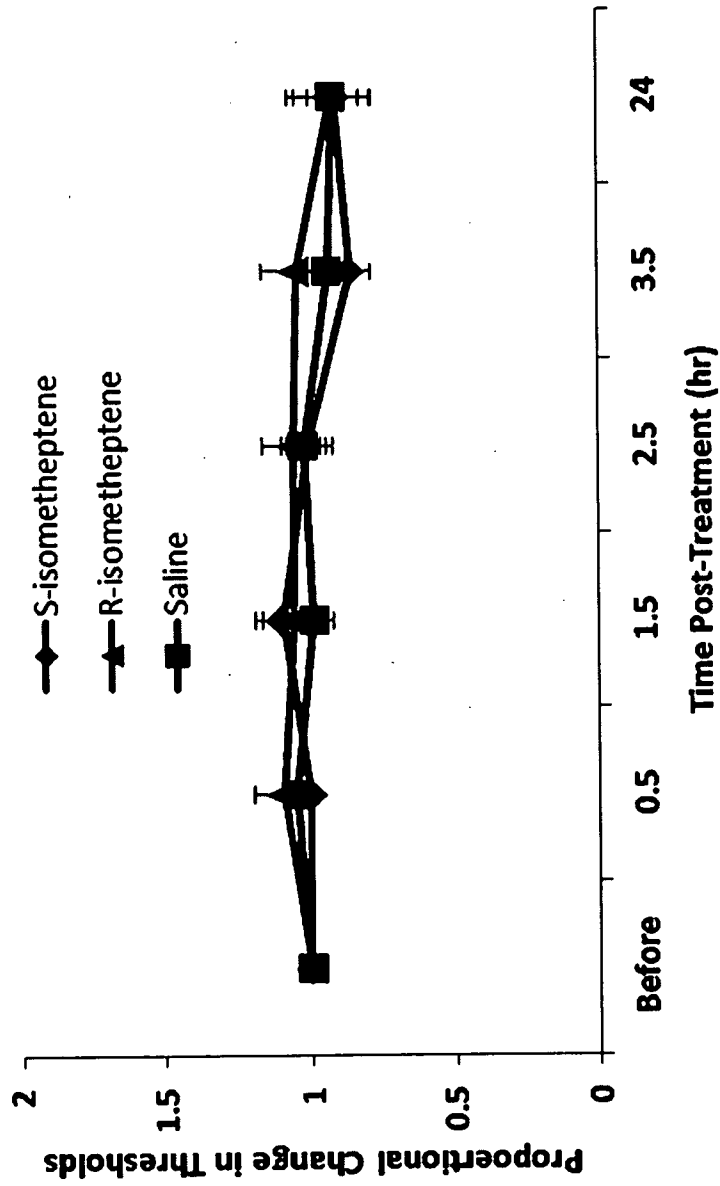


Figure 17

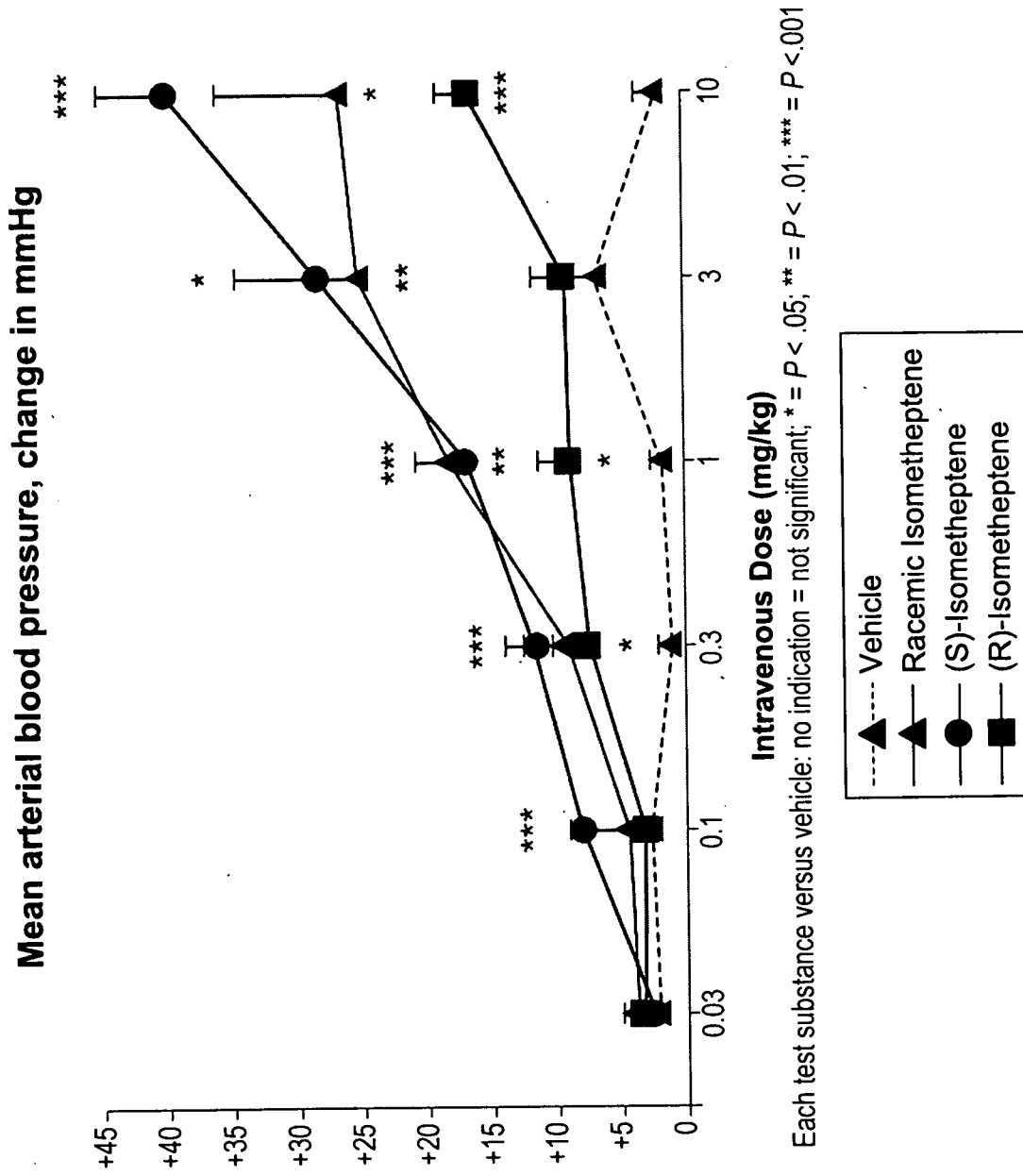


Figure 18

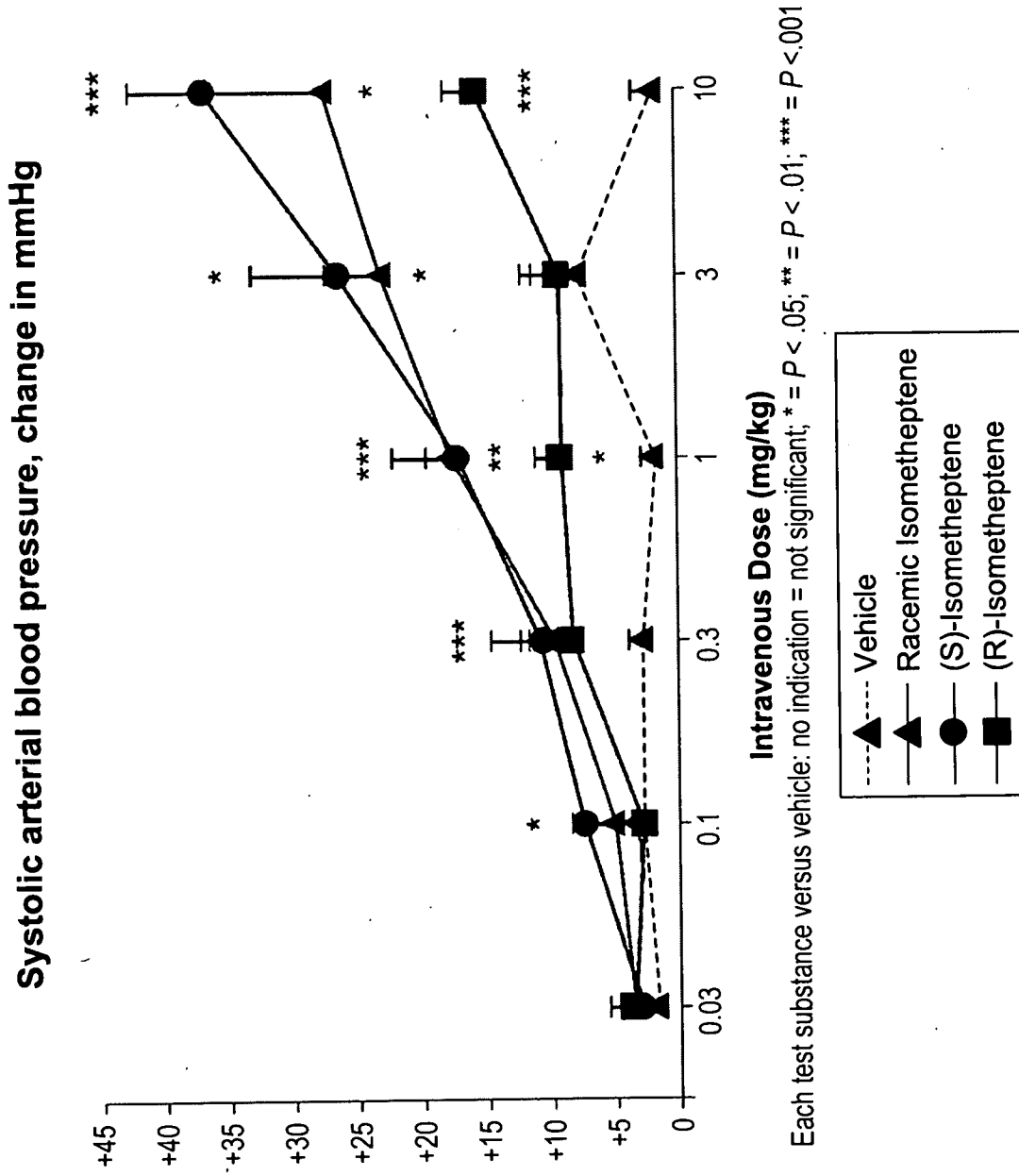


Figure 19

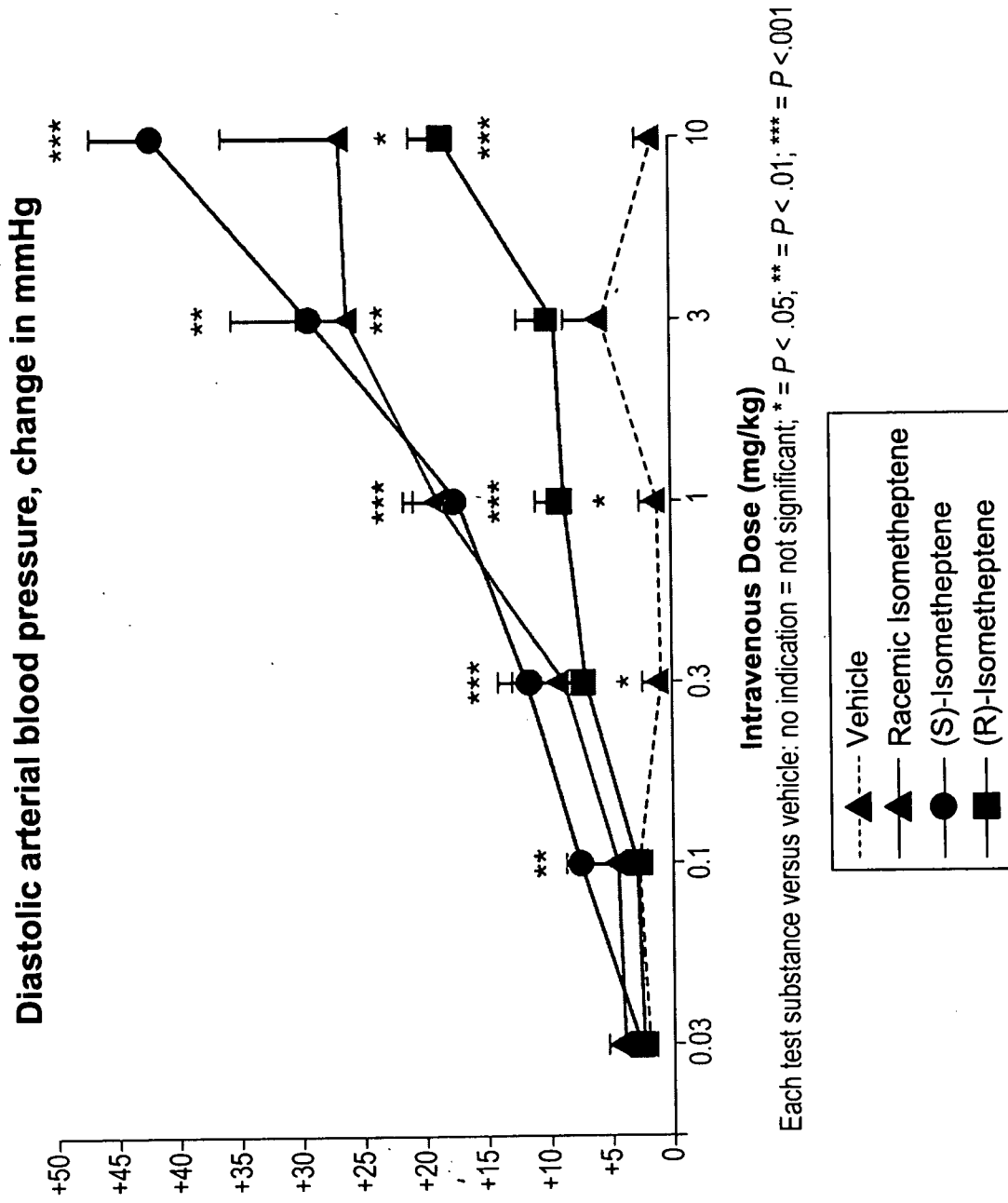
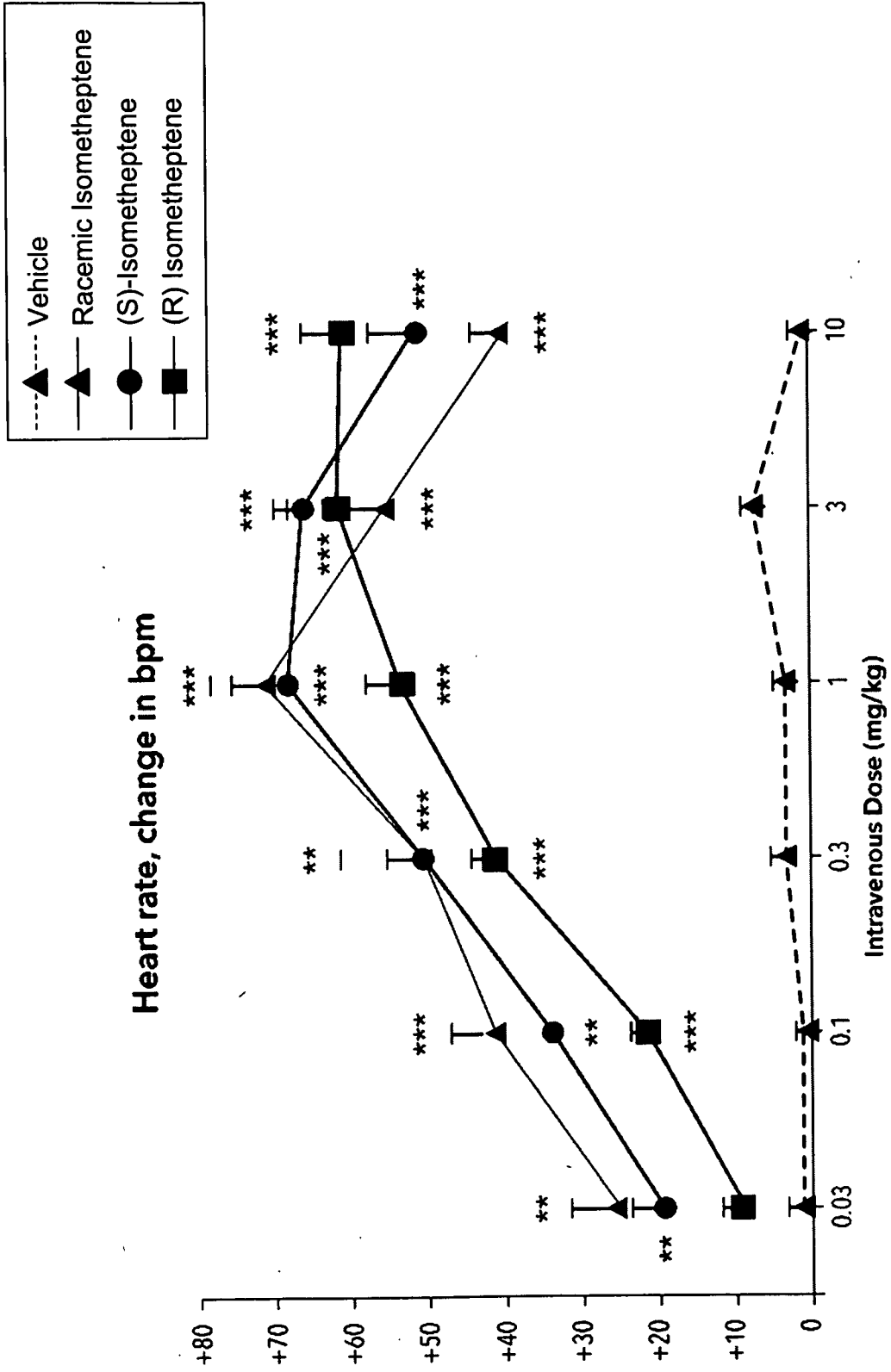


Figure 20



Each test substance versus vehicle: no indication = not significant; * = $P < .05$; ** = $P < .01$; *** = $P < .001$

Figure 21

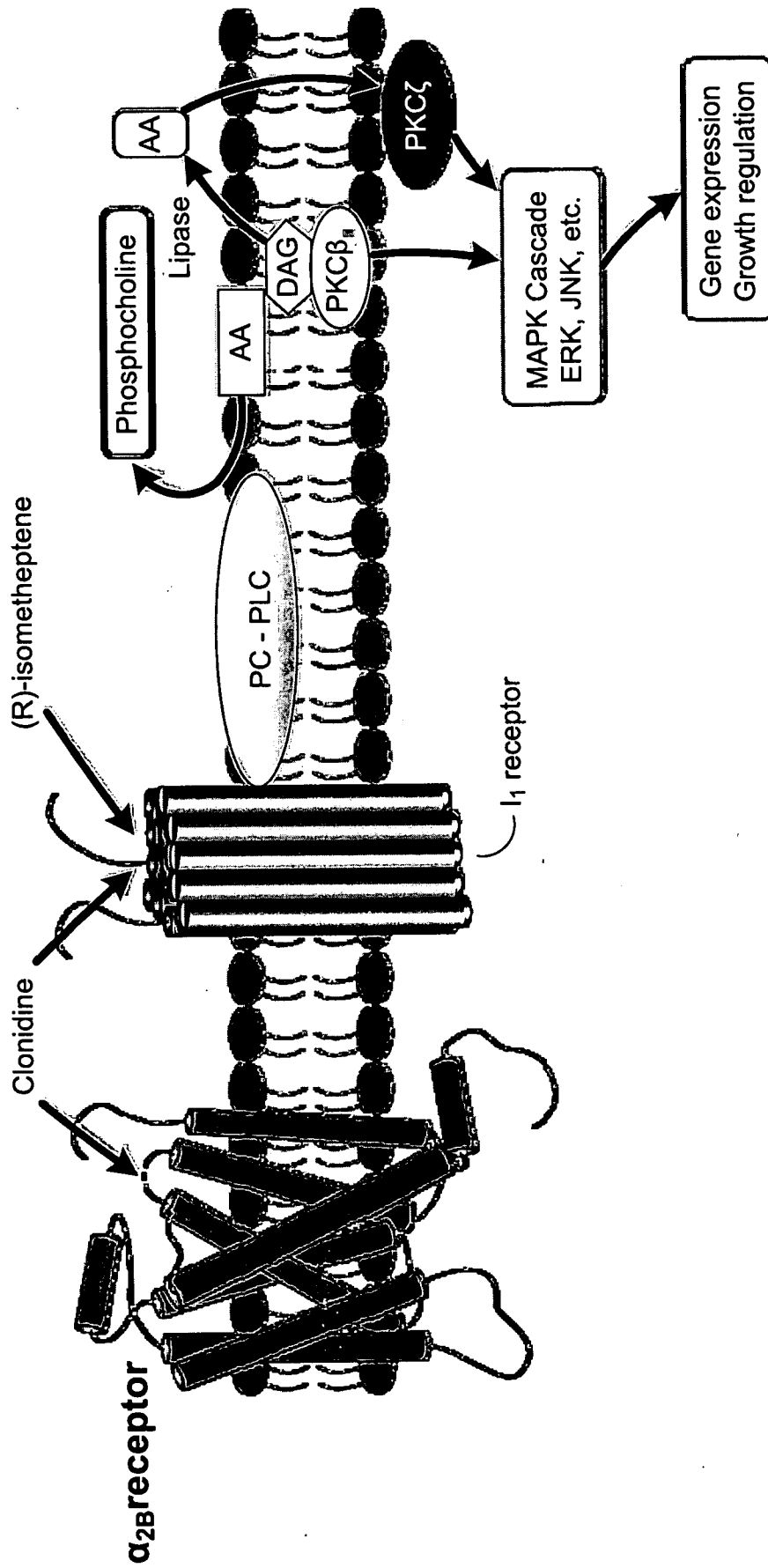


Figure 22

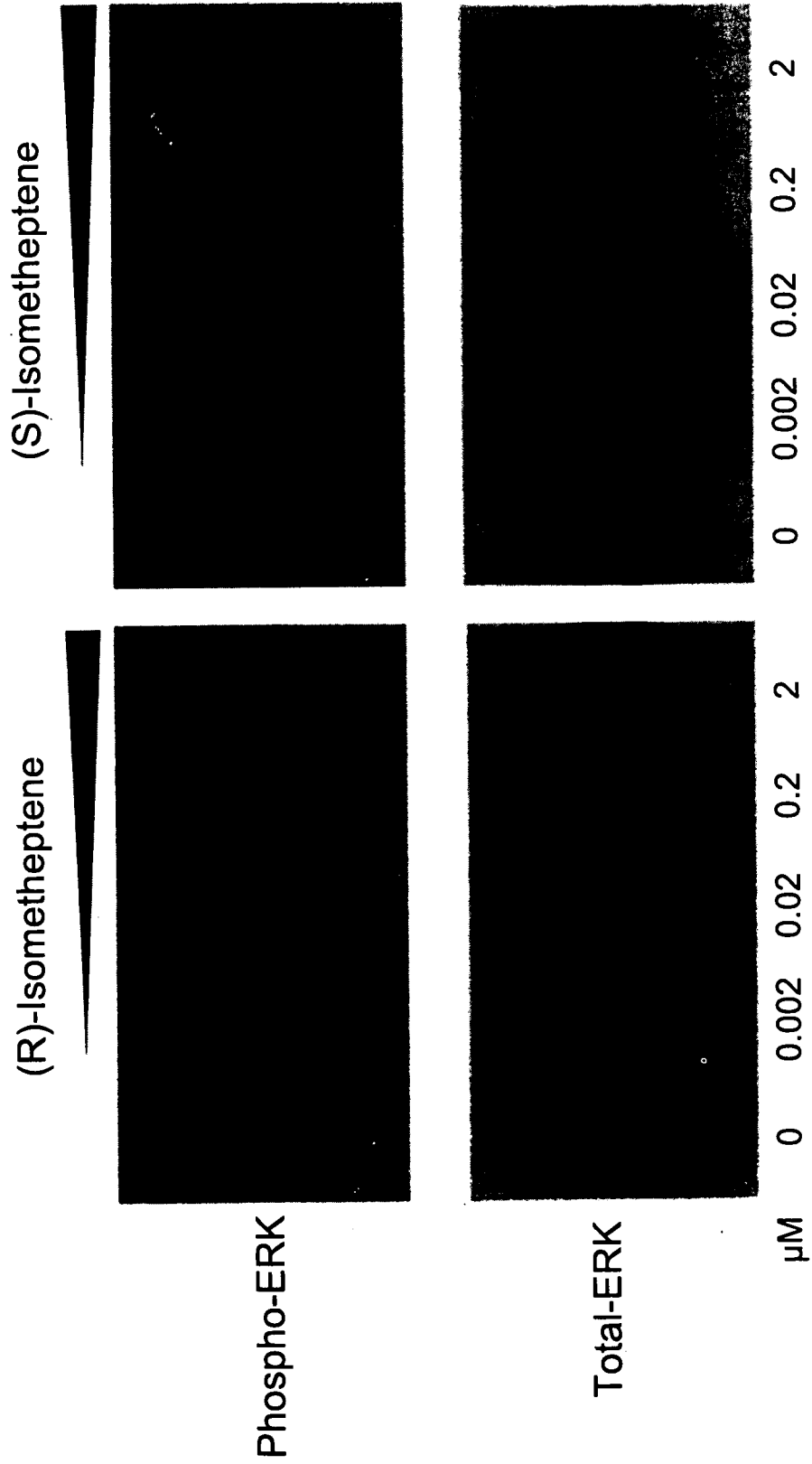


Figure 23

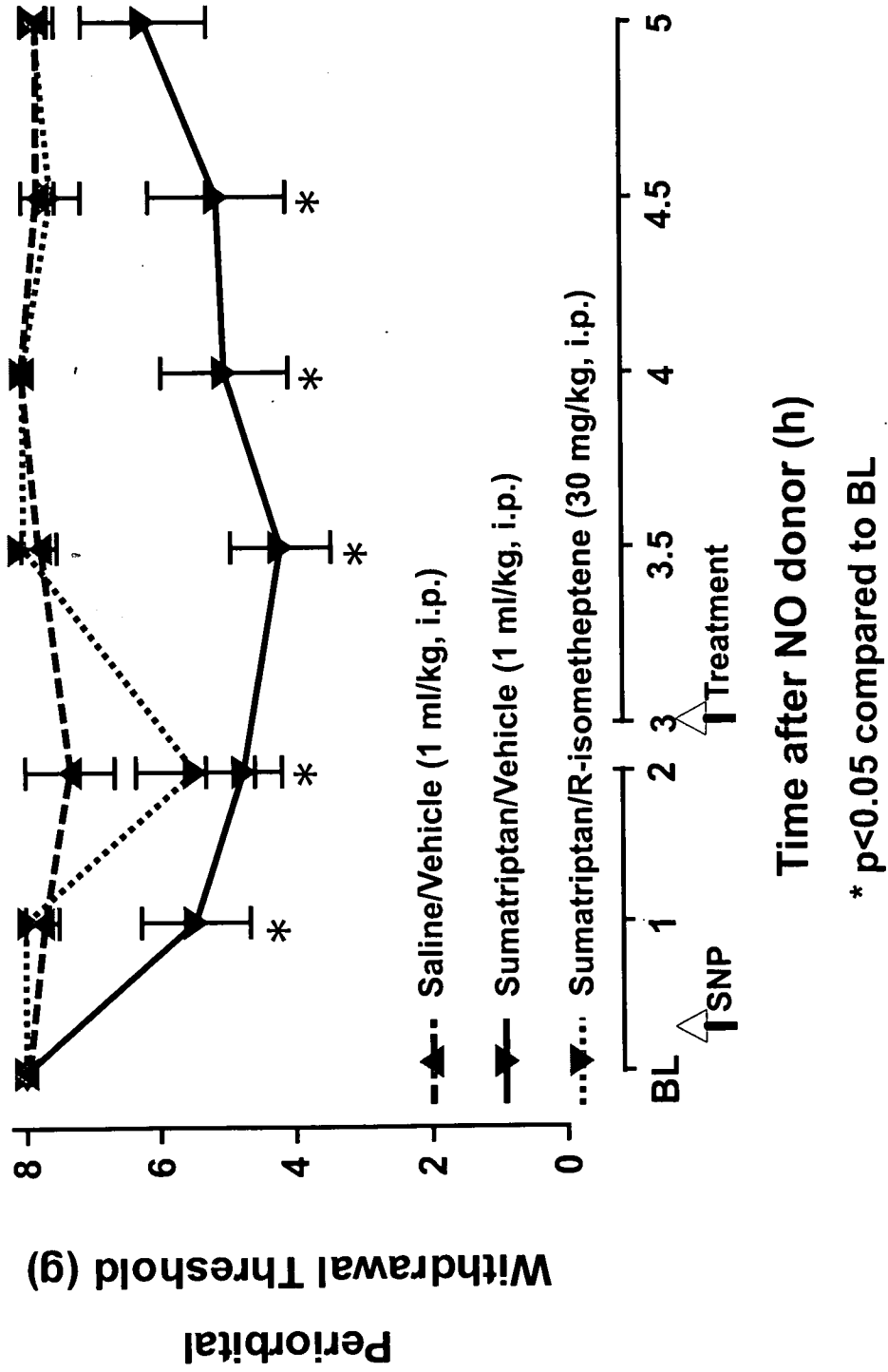


Figure 24

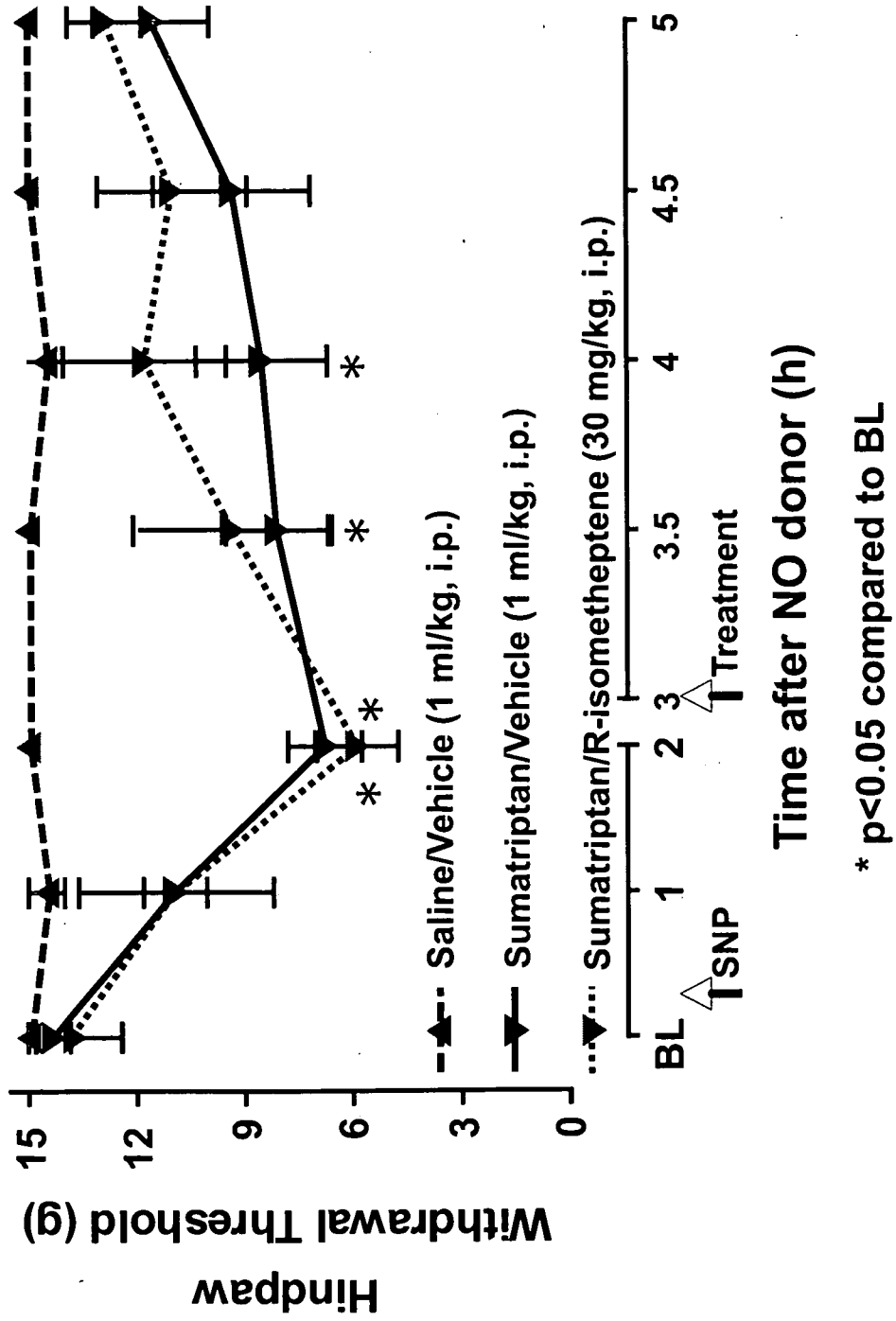
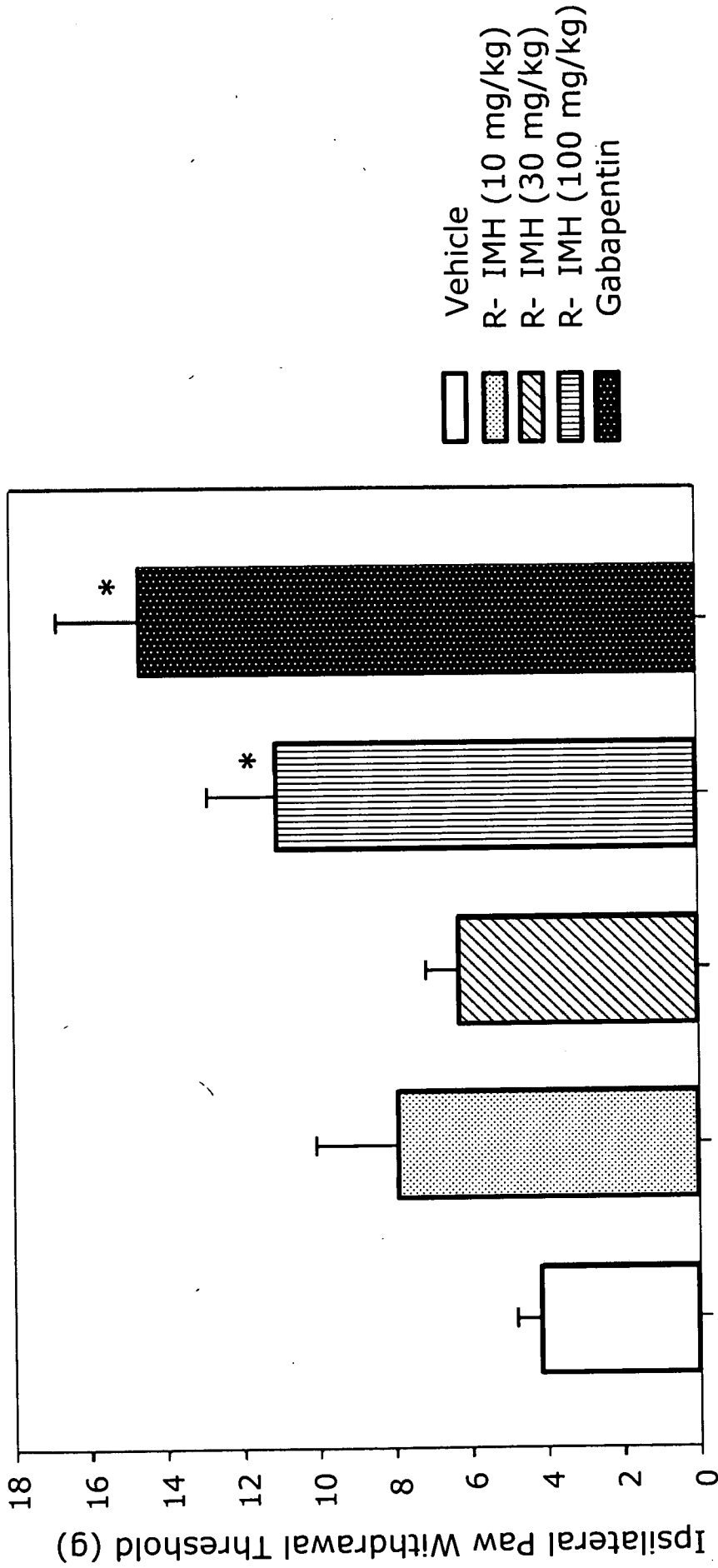


Figure 25



Data presented as mean SEM. * = p<0.05 compared to the Vehicle

Figure 26

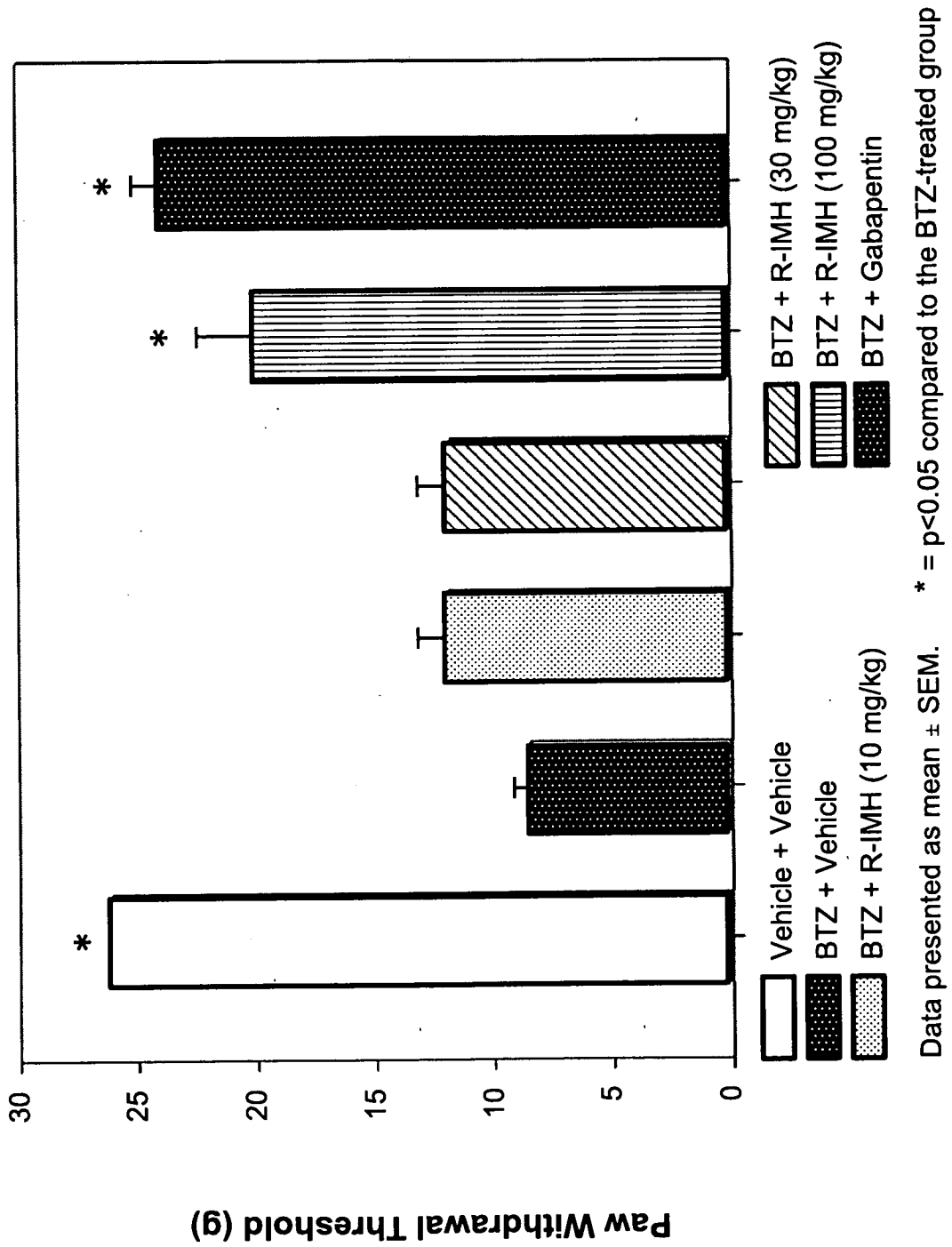


Figure 27

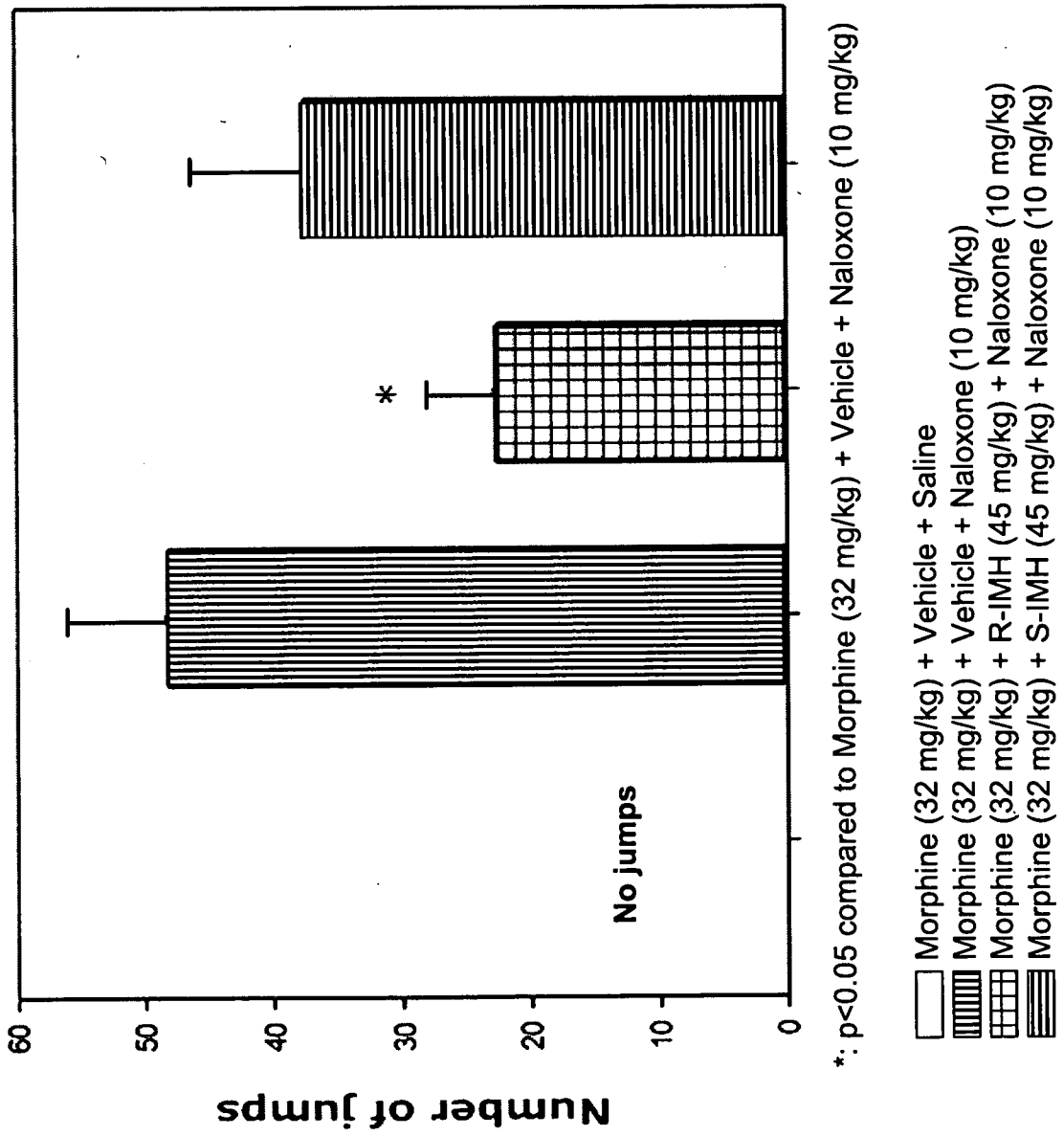


Figure 28

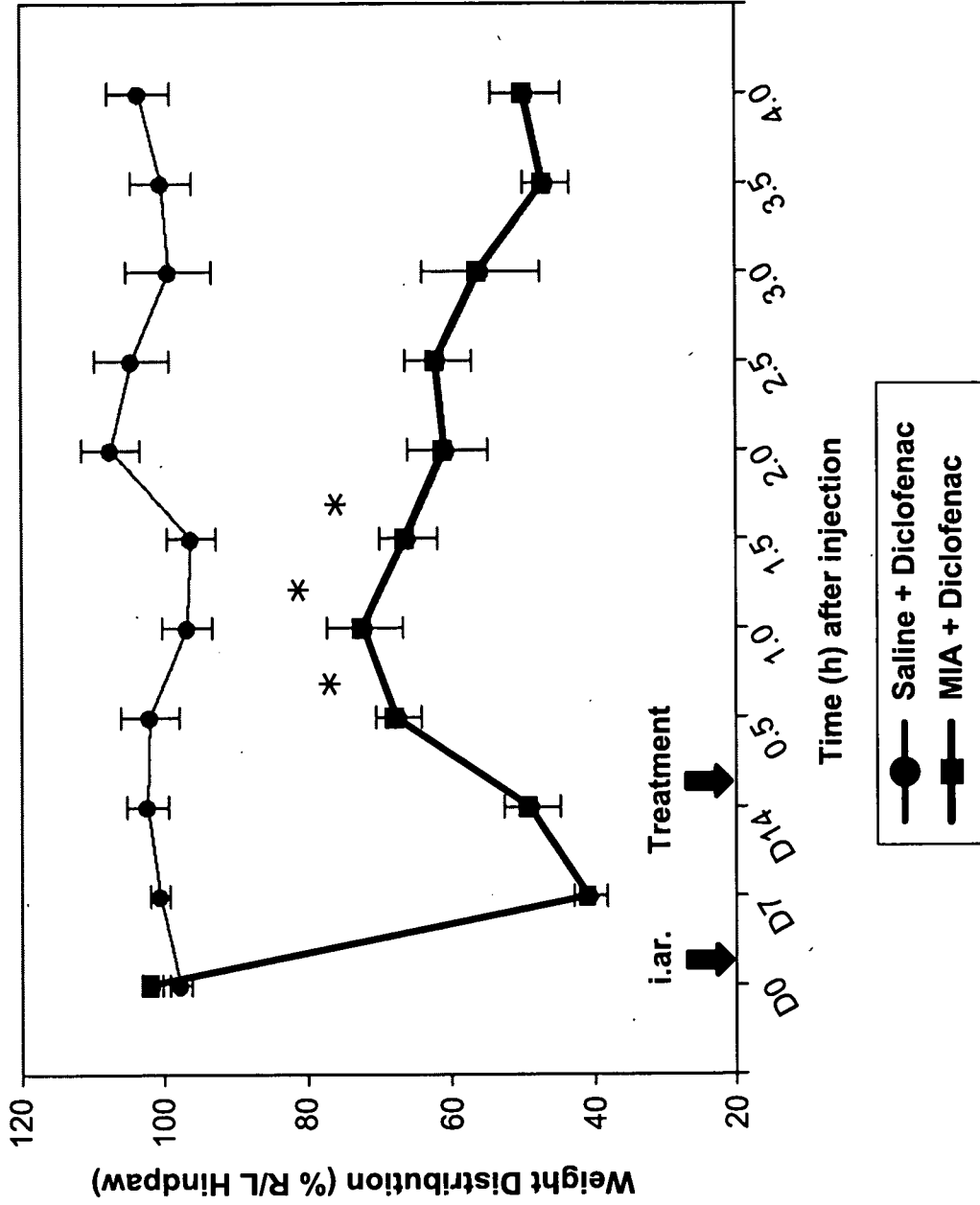


Figure 29

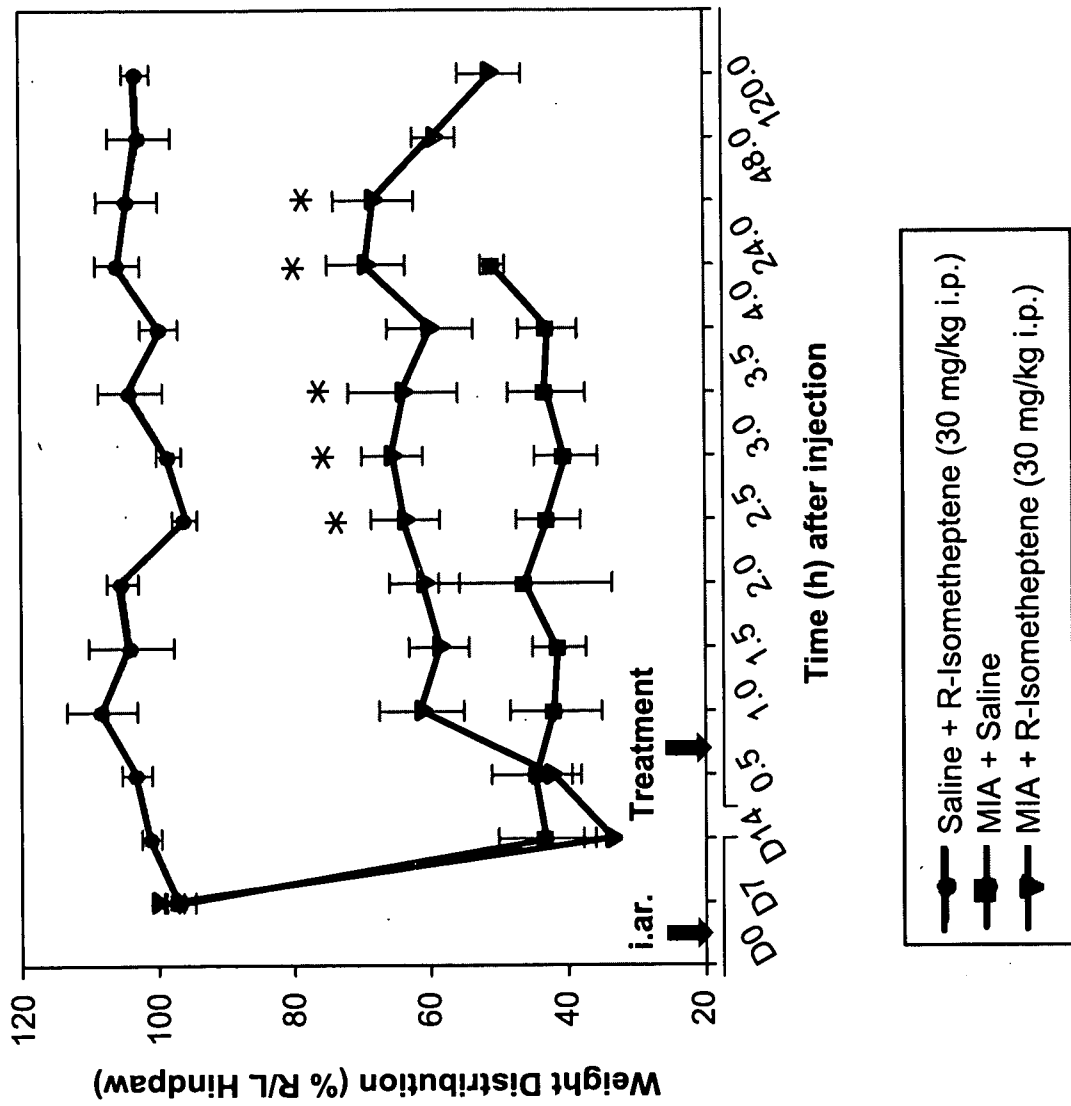


Figure 30

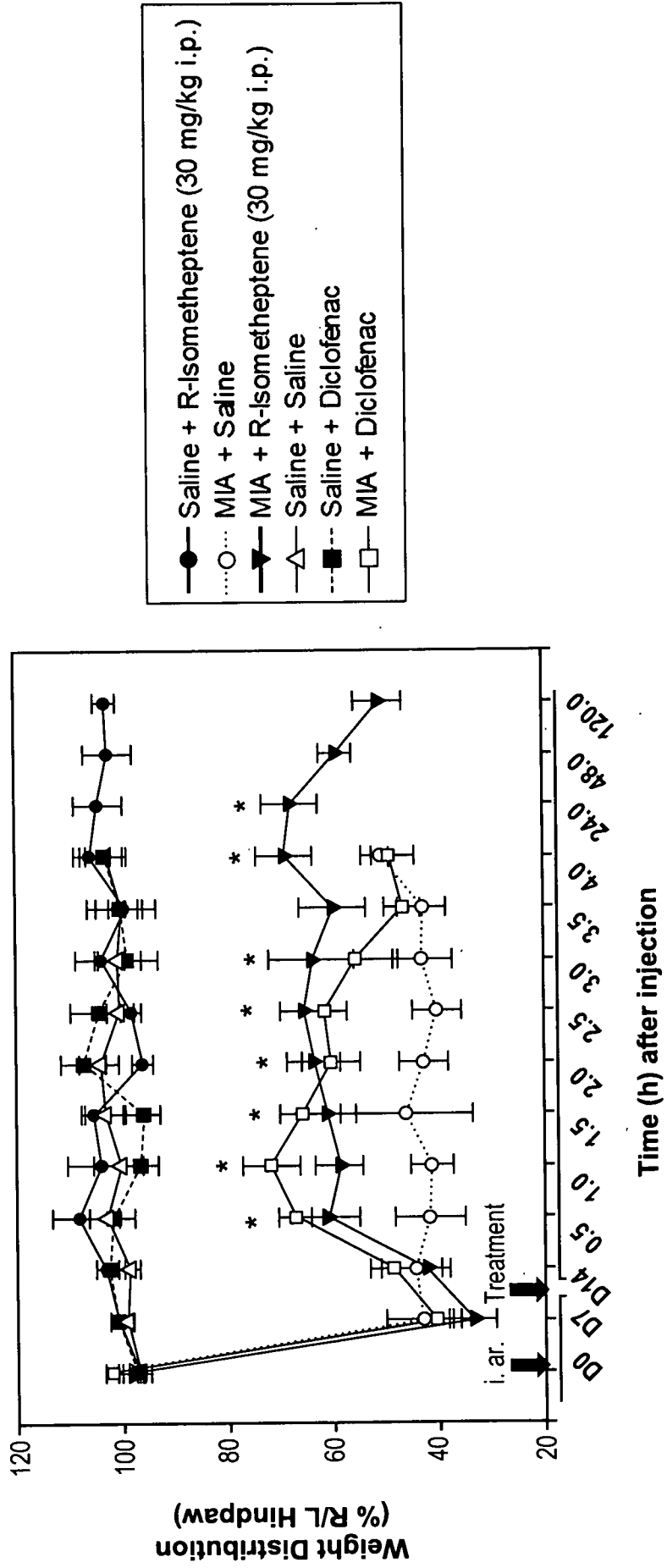


Figure 31

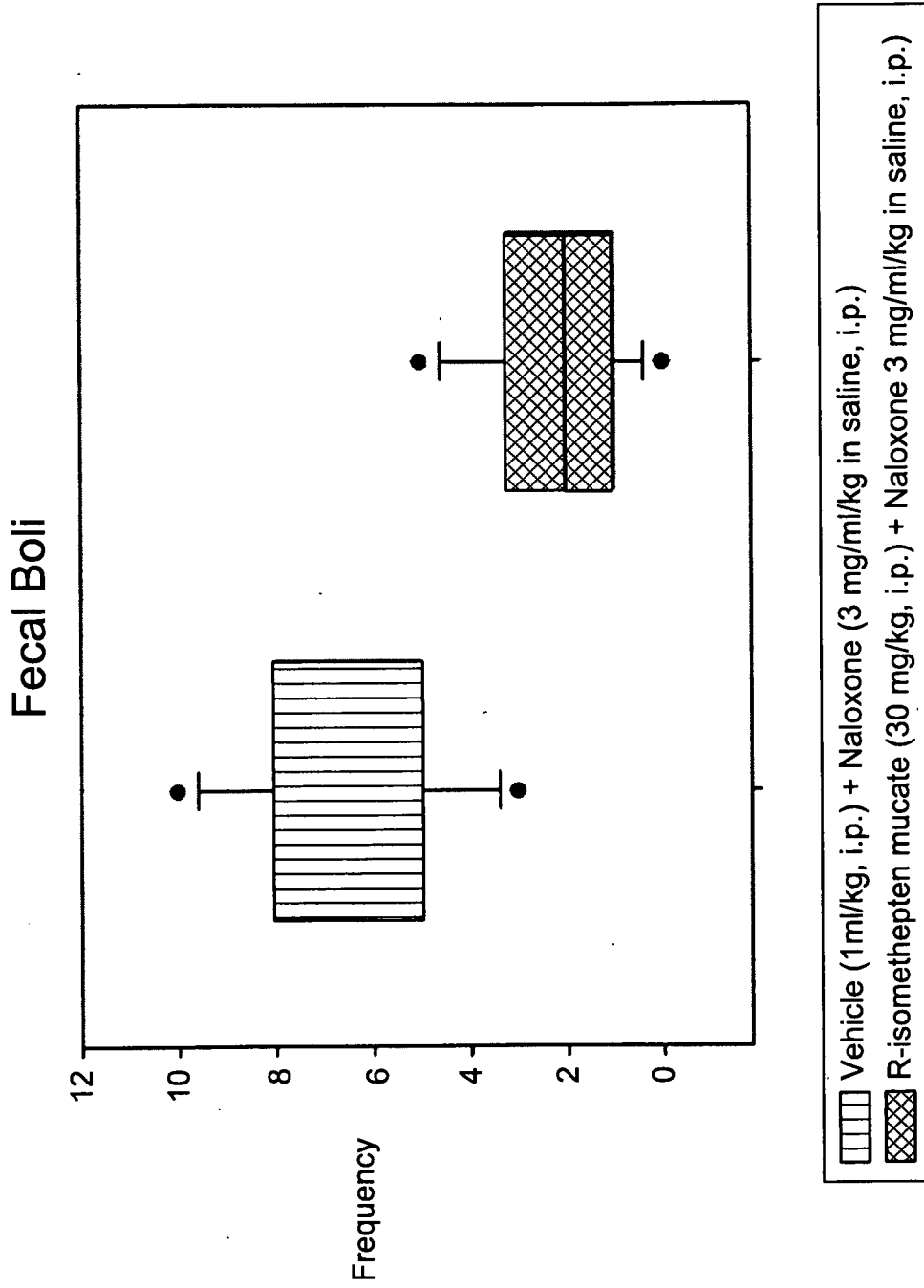


Figure 32

Diarrhea

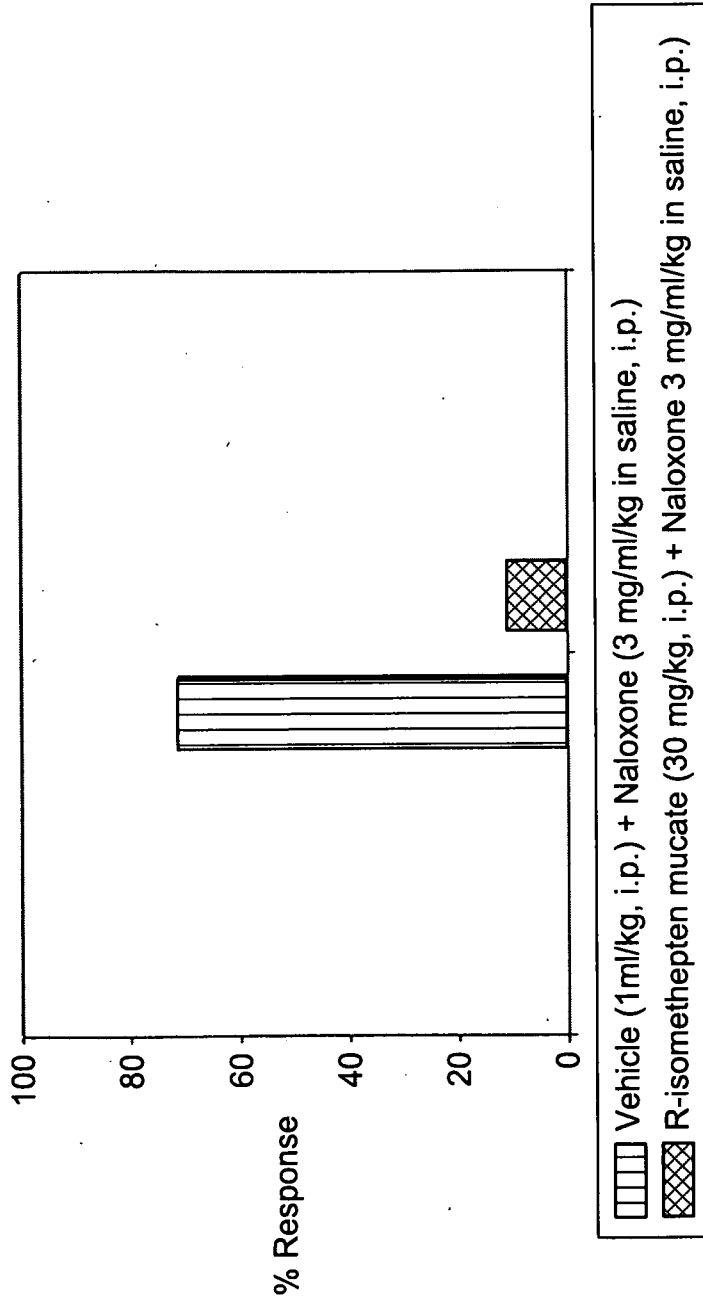


Figure 33

Saivation

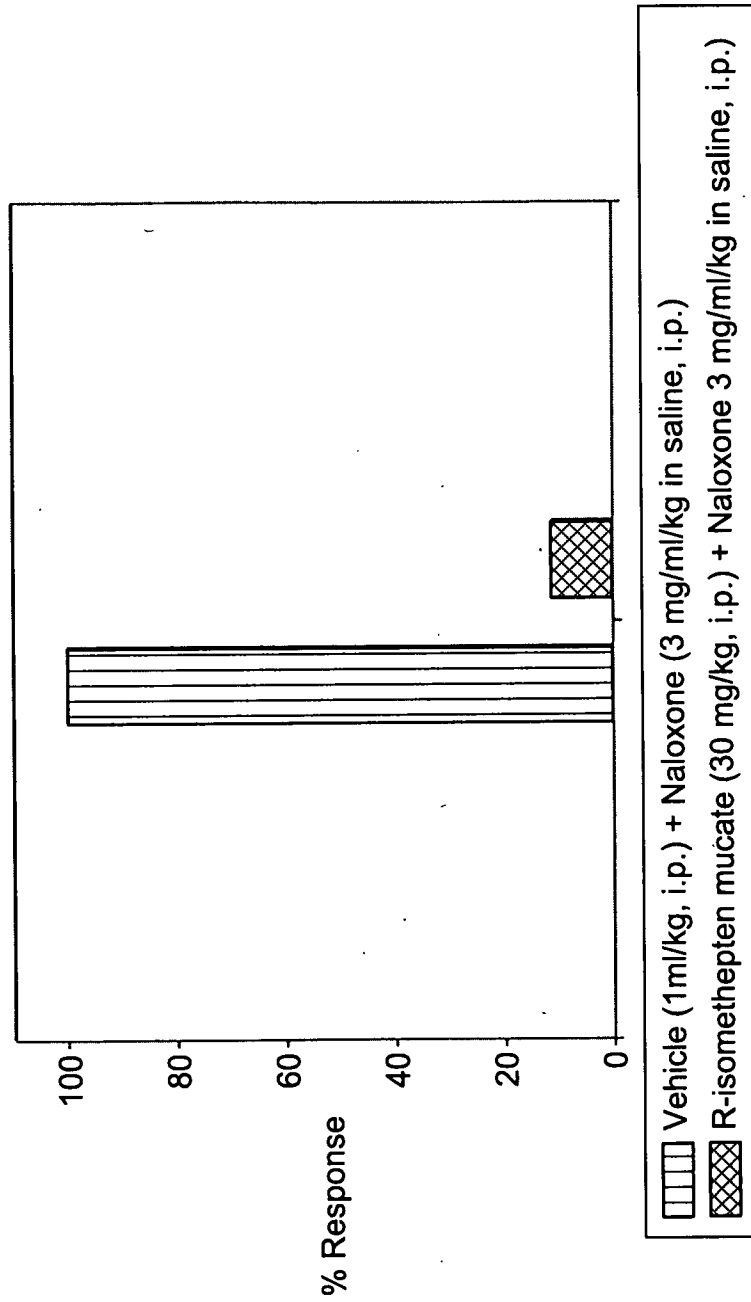


Figure 34

Teeth Chattering

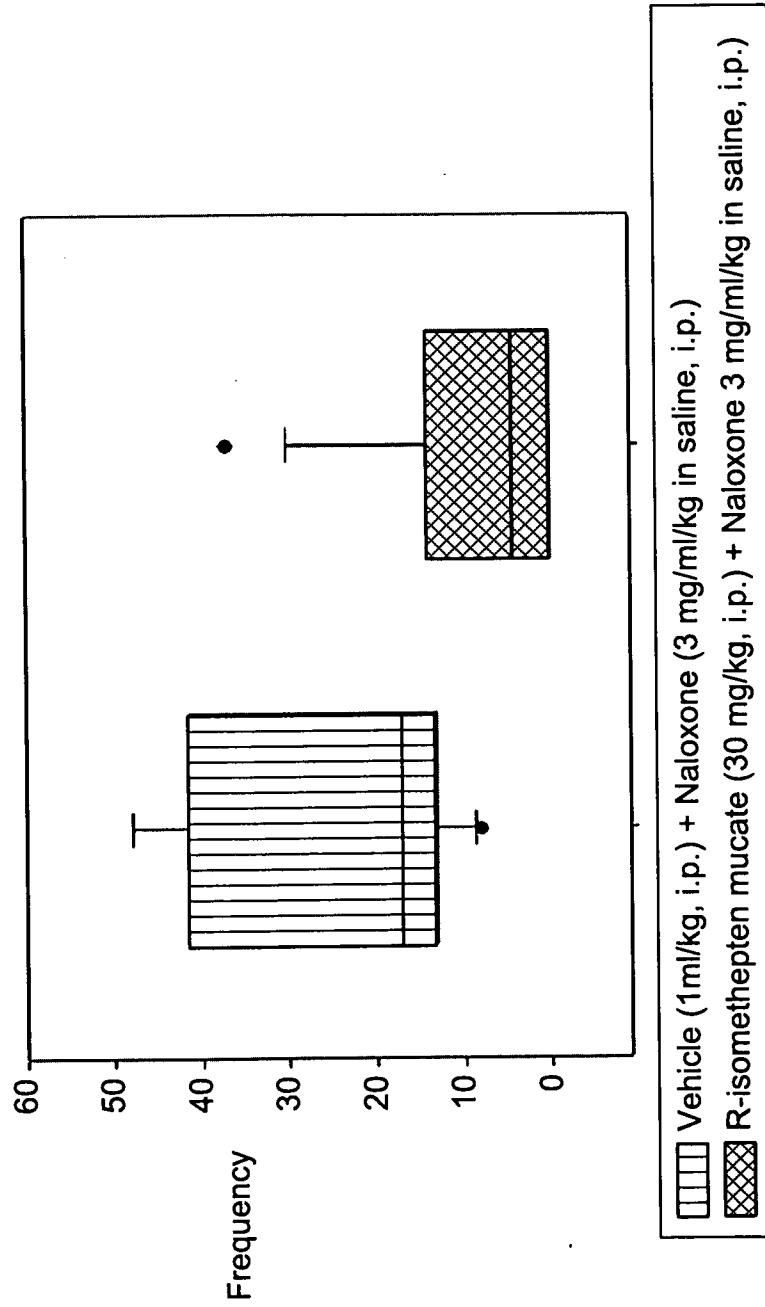


Figure 35

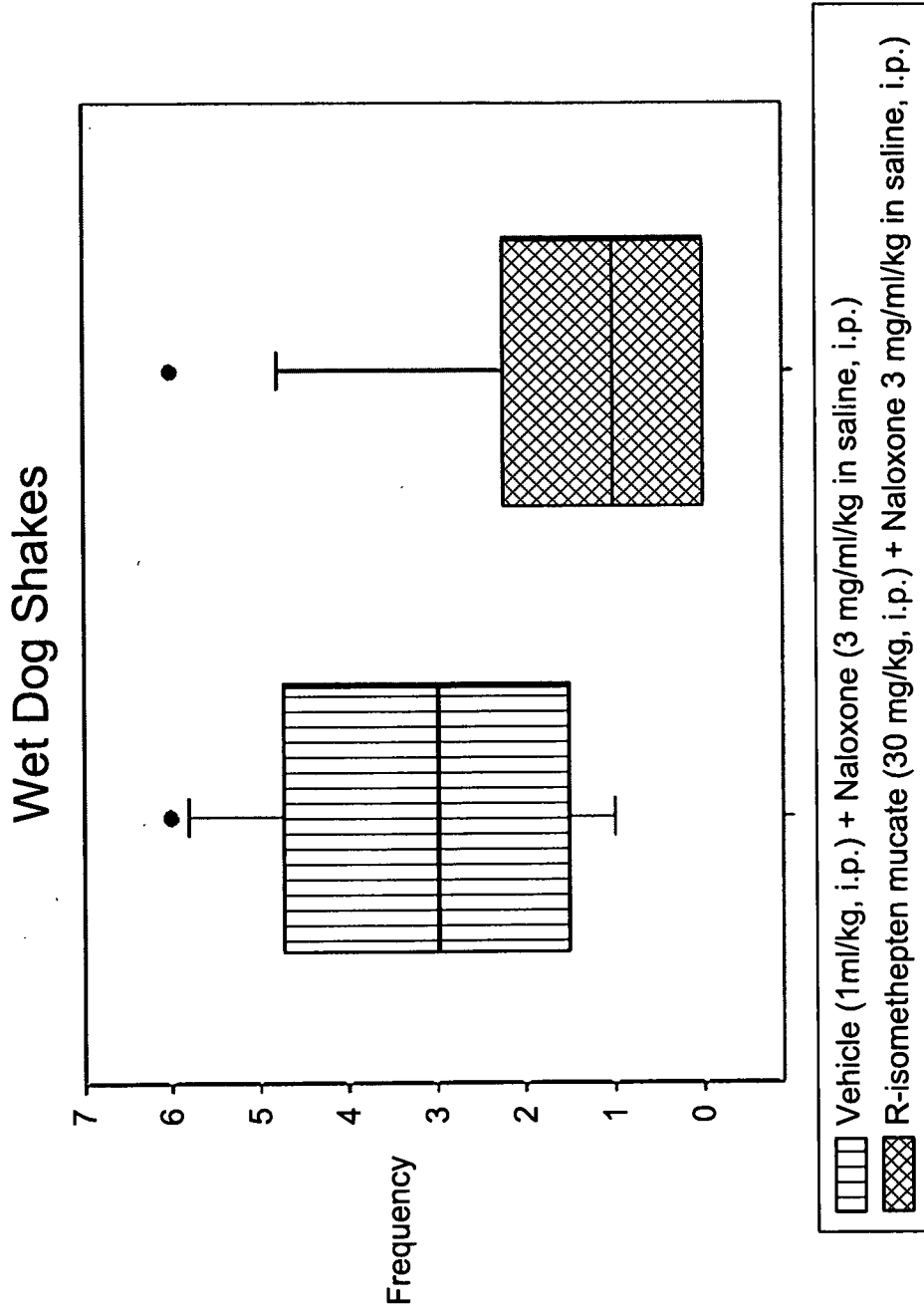


Figure 36

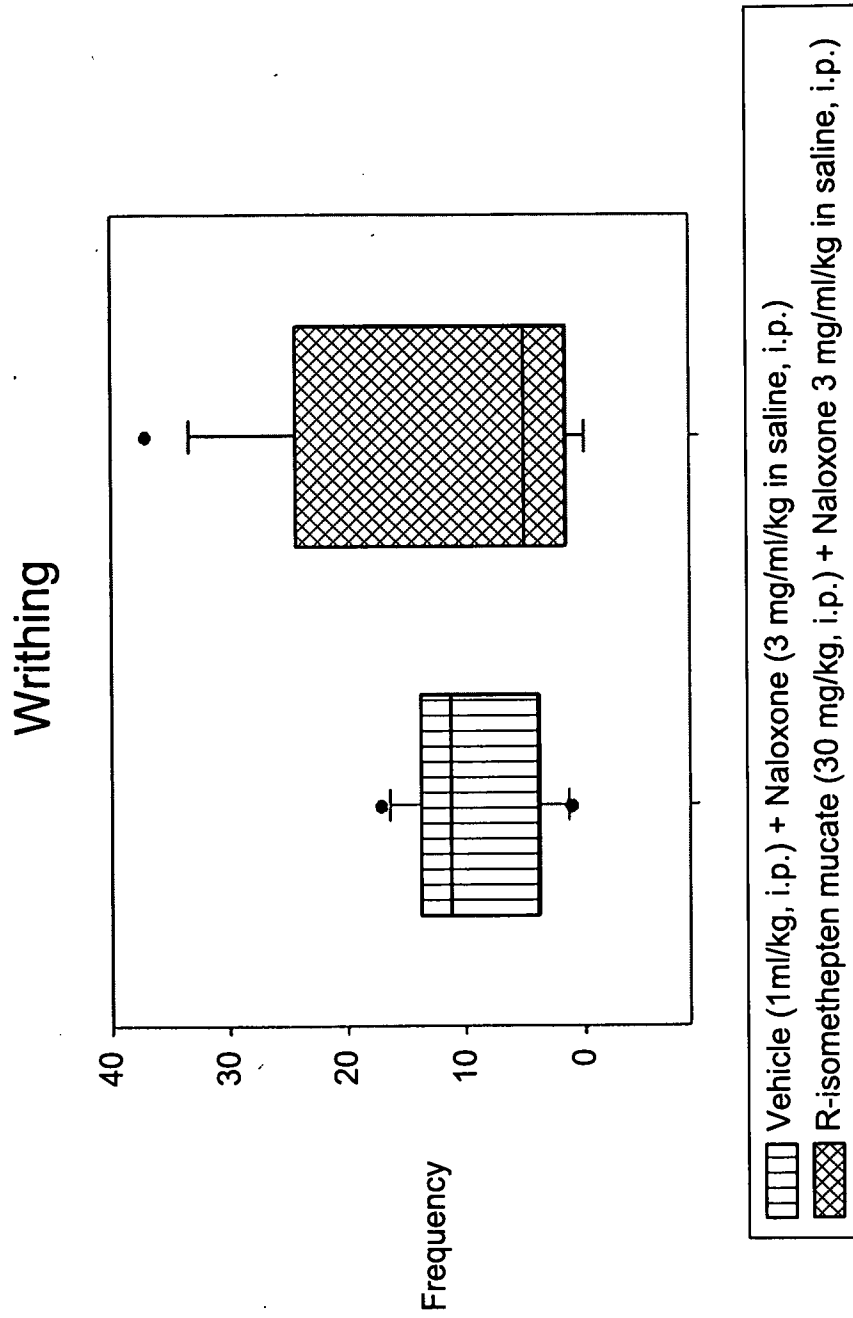


Figure 37

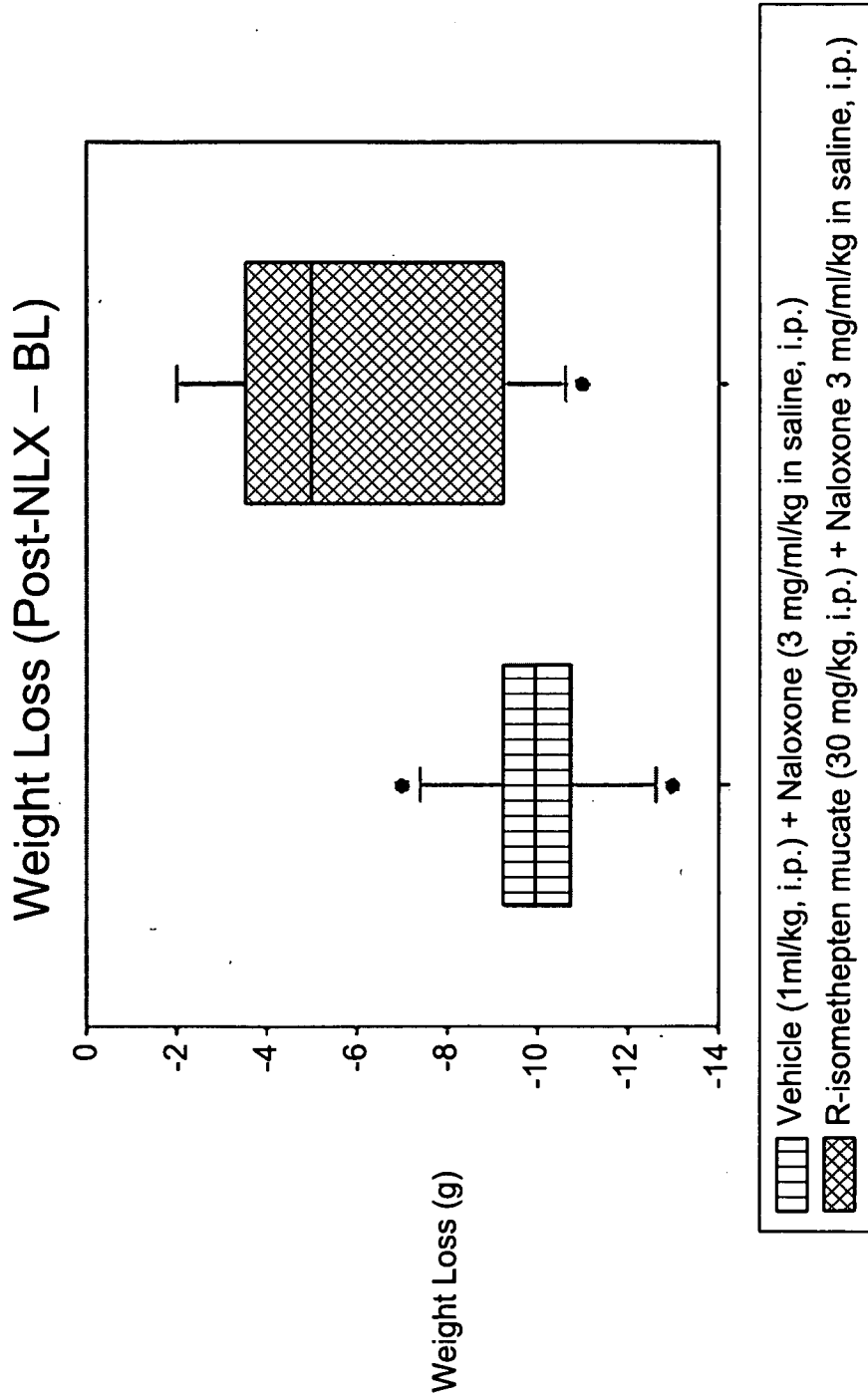


Figure 38

A. CLASSIFICATION OF SUBJECT MATTER

[See Supplemental Sheet]

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

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

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

STN: Registry and CAPlus; CAS RN search for compounds 1-7, 9-10, 12, 14-15, 17, 19, 22-25, 27-30, 32-35 and 49; Exact structure search for compound 48; Keywords - pain, analgesia, nociception and related words.

Espacenet and AusPat: Applicant/inventor name search

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Documents are listed in the continuation of Box C		



Further documents are listed in the continuation of Box C



See patent family annex

* Special categories of cited documents:		
"A" document defining the general state of the art which is not considered to be of particular relevance	"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention	
"E" earlier application or patent but published on or after the international filing date	"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone	
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art	
"O" document referring to an oral disclosure, use, exhibition or other means	"&" document member of the same patent family	
"P" document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search
27 April 2016Date of mailing of the international search report
27 April 2016

Name and mailing address of the ISA/AU

AUSTRALIAN PATENT OFFICE
PO BOX 200, WODEN ACT 2606, AUSTRALIA
Email address: pct@ipaaustralia.gov.au

Authorised officer

Scott Makin
AUSTRALIAN PATENT OFFICE
(ISO 9001 Quality Certified Service)
Telephone No. +61 2 6283 7971

INTERNATIONAL SEARCH REPORT		International application No.
C (Continuation).		PCT/US2015/000154
DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	GENTILI, F. et al, " α_2 -Adrenoreceptors Profile Modulation and High Antinociceptive Activity of (S)-(-)-2-[1-(Biphenyl-2-yloxy)ethyl]-4,5-dihydro-1H-imidazole", Journal of Medicinal Chemistry, 2002, vol. 45, pp. 32-40 Abstract; Introduction; Compounds 11, 4 and 2, chart 1, p. 33; table 1, p. 34	1, 3-4, 72-78, 100-106
X	GENTILI, F. et al, "Imidazoline Binding Sites (IBS) Profile Modulation: Key Role of the Bridge in Determining I ₁ -IBS or I ₂ -IBS Selectivity within a Series of 2-Phenoxymethylimidazoline Analogues", Journal of Medicinal Chemistry, 2003, vol. 46, pp. 2169-2176 Abstract; Introduction; Conclusions; Compounds (+)-7 and (-)-8, (1R,1R)-(-)-(6), (1S,1S)-(+)-(6), 1, and (-)-8 and (+)-8, chart 1, p. 2170; table 1, p. 2172	1, 3-4, 72-78, 100-106
X	SCHANN, S. et al, "Methylation of imidazoline related compounds leads to loss of α_2 -adrenoceptor affinity. Synthesis and biological evaluation of selective I ₁ imidazoline receptor ligands", Bioorganic & Medicinal Chemistry, 2012, vol. 20, pp. 4710-4715 Abstract; Introduction; Fig.1, clonidine, p. 4710 and compound 11, scheme 3, p. 4711; table 1, p. 4712	1, 3-4, 72-78, 100-106
X	US 5686477 A (JARRY et al) 11 November 1997 Abstract; Claims; Examples 1, 22, 9, 13, 15 and 26	1, 3-4, 72-78 and 100-106
X	GENTILI, F. et al, "Involvement of I ₂ -imidazoline binding sites in positive and negative morphine analgesia modulatory effects", European Journal of Pharmacology, 2006, vol. 553, pp. 73-81 Abstract; Introduction; Tracizoline, Diphenzoline (2) and Phenyzoline (1), Fig. 1, p. 74; Section 3.1.2 and 3.2, pp. 52-53; Section 2.5, pp. 75-76, table 1, p. 75; figs. 2-4, p. 76-77	1, 3-5, 9, 15, 30, 36, 51, 57, 72-78, 93, 99, 100-106
X	WO 2007/025613 A2 (LABORATORIOS DEL DR. ESTEVE, S.A.) 08 March 2007 Abstract; Claims, esp. claim 9	1, 3-5, 9-10, 30-31, 51-52, 72-78, 93-94, 100-106
X	BAURIN, N. et al, "3D-QSAR CoMFA Study on Imidazolinergic I ₂ Ligands: A Significant Model through a Combined Exploration of Structural Diversity and Methodology", Journal of Medicinal Chemistry, 2000, vol. 43, pp. 1109-1122 Abstract; Introduction; Compounds C9, C10, C14 and C13, table 3, p. 1113; Fig. 1	1, 3-4, 72-78, 100-106
X	WO 2010/031819 A1 (BIOALLIANCE PHARMA) 25 March 2010 Abstract; Claims; Clonidine and p-aminoclonidine, p. 20, lines 16-25; Examples; p. 26, lines 20-24	1, 3-5, 9, 12-14, 30, 33-35, 51, 54-56, 72-78, 93, 96-98, 100-106
X	WO 2011/127586 A1 (THE ROYAL INSTITUTION FOR THE ADVANCEMENT OF LEARNING / MCGILL UNIVERSITY) 20 October 2011 Abstract; Claims; Examples; Moxonidine, clonidine, apraclonidine, p. 13, lines 6-10, inter alia; p. 32;	1, 3-5, 9-10, 12-13, 15, 30-31, 33-34, 51, 54-55, 72-78, 93-94, 96-97, 100-106
X	DRAGAN, U. et al, "LNP 906, the first high-affinity photoaffinity ligand selective for I ₁ imidazoline receptors", British Journal of Pharmacology, 2004, vol. 142, pp. 609-617 Abstract; Introduction; Table 1, compounds LNP906 and LNP011; clonidine, p-iodoclonidine	1, 3-4, 72-78, 100-106
X	US 2002/0177592 A1 (OLNEY et al) 28 November 2002 Abstract; Claims; Clonidine, iodoclonidine, para. [0149]; para. [0070]-[0071]	1, 3-5, 9, 12, 30, 33, 51, 54, 72-78, 93, 96, 100-106

INTERNATIONAL SEARCH REPORT C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		International application No. PCT/US2015/000154
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2014/160077 A1 (ALLODYNIC THERAPEUTICS, LLC) 02 October 2014 Abstract; Claims; Para. [00106]; Examples; Claims; Para. [0048]	1, 3-5, 9-11, 15, 30-36, 51-57, 72-78, 93-95, 100-106

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
the subject matter listed in Rule 39 on which, under Article 17(2)(a)(i), an international search is not required to be carried out, including
2. Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a)

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

See Supplemental Box for Details

1. As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.
3. As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:
1-15, 23-43, 51-57, 65-78, 86-106 (all in part)

Remark on Protest

- The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
- The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- No protest accompanied the payment of additional search fees.

Supplemental Box**Continuation of: Box III**

This International Application does not comply with the requirements of unity of invention because it does not relate to one invention or to a group of inventions so linked as to form a single general inventive concept.

This Authority has found that there are twelve different inventions based on the following features that separate the claims into distinct groups:

1. Claims 1-15, 23-43, 51-57, 65-78, 86-106 (all in part) are directed to the use of compounds 1-7, 9-10, 12, 14-15, 17, 19, 22-25, 27-30, 32-35 and 48-49 and compositions thereof in treating various forms of pain and other conditions. The feature of compounds comprising a five-membered nitrogen-containing ring attached to a substituted or unsubstituted phenyl or pyrimidinyl ring through a 1- or 2-atom linking group is specific to this group of claims.
2. Claim 1, 3-5, 9-15, 51-57, 72-78 and 93-106 (all in part) are directed to the use of compound 20, 21 and 53 and compositions thereof in treating various forms of pain and other conditions. The feature of compounds comprising a dicyclopropylmethylamine linked to a five-membered unsaturated nitrogen-containing ring is specific to this group of claims.
3. Claim 1-15, 23-43, 51-57, 65-78, 86-106 (all in part) are directed to the use of compound 13, 16, 31, 36, 37, 40-42, 44, 46, 50 and 52 and compositions thereof in treating various forms of pain and other conditions. The feature of compounds comprising a substituted amino-dihydropyrrole is specific to this group of claims.
4. Claim 1, 3-5, 9-15, 51-57, 72-78 and 93-106 (all in part) are directed to the use of compound 31, 36-37, 44, 46 and 50 and compositions thereof in treating various forms of pain and other conditions. The feature of compounds comprising a dihydroimidazole directly attached to an aryl or heteroaryl group is specific to this group of claims.
5. Claim 1, 3-5, 9-15, 51-57, 72-78 and 93-106 (all in part) are directed to the use of compound 18 and 38 and compositions thereof in treating various forms of pain and other conditions. The feature of a 2-aminoethyl substituted dihydroimidazole is specific to this group of claims.
6. Claim 1, 3-5, 9-15, 51-57, 72-78 and 93-106 (all in part) are directed to the use of compound 11 and compositions thereof in treating various forms of pain and other conditions. The feature of a propargylamino-substituted indane is specific to this group of claims.
7. Claim 1, 3-5, 9-15, 51-57, 72-78 and 93-106 (all in part) are directed to the use of compound 39 and 54 and compositions thereof in treating various forms of pain and other conditions. The feature of a guanidine compound is specific to this group of claims.
8. Claim 1, 3-5, 9-15, 51-57, 72-78 and 93-106 (all in part) are directed to the use of compound 43 and compositions thereof in treating various forms of pain and other conditions. The feature of 3-isopropylbicyclo[2.2.1]heptan-2-amine is specific to this group of claims.
9. Claim 1, 3-5, 9-15, 51-57, 72-78 and 93-106 (all in part) are directed to the use of compound 45 and compositions thereof in treating various forms of pain and other conditions. The feature of 1-methyl-4,4a,9,9a-tetrahydro-3H-pyrido[3,4-b]indole is specific to this group of claims.
10. Claim 1, 3-5, 9-15, 51-57, 72-78 and 93-106 (all in part) are directed to the use of compound 47 and compositions thereof in treating various forms of pain and other conditions. The feature of the nucleotide of formula 47 is specific to this group of claims.
11. Claim 1, 3-5, 9-15, 51-57, 72-78 and 93-106 (all in part) are directed to the use of compound 51 and compositions thereof in treating various forms of pain and other conditions. The feature of 1-(2,5-dioxoimidazolidin-4-yl)urea is specific to this group of claims.
12. Claim 16-22, 44-50, 58-64, 79-85 (all in full) and 93-106 (all in part) are directed to the use of compounds 8 and 26 and compositions thereof in treating various forms of pain and other conditions. The feature of the isomethheptene compounds of formulae 8 and 26 is specific to this group of claims.

Supplemental Box

PCT Rule 13.2, first sentence, states that unity of invention is only fulfilled when there is a technical relationship among the claimed inventions involving one or more of the same or corresponding special technical features. PCT Rule 13.2, second sentence, defines a special technical feature as a feature which makes a contribution over the prior art.

When there is no special technical feature common to all the claimed inventions there is no unity of invention.

In the above groups of claims, the identified features may have the potential to make a contribution over the prior art but are not common to all the claimed inventions and therefore cannot provide the required technical relationship. Therefore there is no special technical feature common to all the claimed inventions and the requirements for unity of invention are consequently not satisfied *a priori*.

INTERNATIONAL SEARCH REPORT Information on patent family members		International application No. PCT/US2015/000154	
This Annex lists known patent family members relating to the patent documents cited in the above-mentioned international search report. The Australian Patent Office is in no way liable for these particulars which are merely given for the purpose of information.			
Patent Document/s Cited in Search Report		Patent Family Member/s	
Publication Number	Publication Date	Publication Number	Publication Date
US 5686477 A	11 November 1997	US 5686477 A	11 Nov 1997
		AU 689320 B2	26 Mar 1998
		AU 3459395 A	09 May 1996
		CA 2162106 A1	04 May 1996
		CN 1129697 A	28 Aug 1996
		EP 0710658 A1	08 May 1996
		EP 0710658 B1	04 Oct 2001
		FI 955238 A	04 May 1996
		FR 2726558 A1	10 May 1996
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		JP H08208630 A	13 Aug 1996
		JP 3181211 B2	03 Jul 2001
		NO 954381 A	06 May 1996
		NO 305755 B1	19 Jul 1999
		NZ 280387 A	26 Jul 1996
		ZA 9509311 A	29 May 1996
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		EP 1745783 A1	24 Jan 2007
		US 2009325975 A1	31 Dec 2009
		WO 2007009682 A1	25 Jan 2007
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		AU 2009294612 B2	20 Aug 2015
		CA 2732893 A1	25 Mar 2010
		CN 102170877 A	31 Aug 2011
		CN 102170877 B	27 Aug 2014

Due to data integration issues this family listing may not include 10 digit Australian applications filed since May 2001.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.

PCT/US2015/000154

This Annex lists known patent family members relating to the patent documents cited in the above-mentioned international search report. The Australian Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent Document/s Cited in Search Report		Patent Family Member/s	
Publication Number	Publication Date	Publication Number	Publication Date
		EP 2165706 A1	24 Mar 2010
		EP 2395997 A1	21 Dec 2011
		EP 2395997 B1	10 Feb 2016
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		JP 5693455 B2	01 Apr 2015
		JP 2015013889 A	22 Jan 2015
		KR 20110063471 A	10 Jun 2011
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		US 2013274306 A1	17 Oct 2013
		US 9089559 B2	28 Jul 2015
		US 2015148398 A1	28 May 2015
		US 9192599 B2	24 Nov 2015
		US 2011288140 A1	24 Nov 2011

Due to data integration issues this family listing may not include 10 digit Australian applications filed since May 2001.

Form PCT/ISA/210 (Family Annex)(July 2009)

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.

PCT/US2015/000154

This Annex lists known patent family members relating to the patent documents cited in the above-mentioned international search report. The Australian Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent Document/s Cited in Search Report		Patent Family Member/s	
Publication Number	Publication Date	Publication Number	Publication Date
WO 2011/127586 A1	20 October 2011	WO 2011127586 A1	20 Oct 2011
		CA 2796280 A1	20 Oct 2011
		CN 103068394 A	24 Apr 2013
		EP 2558101 A1	20 Feb 2013
		US 2013029989 A1	31 Jan 2013
US 2002/0177592 A1	28 November 2002	US 2002177592 A1	28 Nov 2002
		AU 7576501 A	03 Dec 2001
		US 2002016319 A1	07 Feb 2002
		US 2002068754 A1	06 Jun 2002
		WO 0189448 A2	29 Nov 2001
WO 2014/160077 A1	02 October 2014	WO 2014160077 A1	02 Oct 2014
		AU 2014244152 A1	01 Oct 2015
		EP 2968293 A1	20 Jan 2016
		US 2014275141 A1	18 Sep 2014
		US 9095548 B2	04 Aug 2015
		US 2014275142 A1	18 Sep 2014
		US 9205081 B2	08 Dec 2015
		US 2011269727 A1	03 Nov 2011
		US 2013310412 A1	21 Nov 2013
		US 2014296274 A1	02 Oct 2014
US 2014296275 A1	02 Oct 2014		
US 2016051537 A1	25 Feb 2016		

End of Annex

Due to data integration issues this family listing may not include 10 digit Australian applications filed since May 2001.

Form PCT/ISA/210 (Family Annex)(July 2009)

Supplemental Box – IPC Marks

<i>C07D 263/28 (2006.01)</i>	<i>A61K 31/43 (2006.01)</i>
<i>C07D 207/22 (2006.01)</i>	<i>A61K 31/4725 (2006.01)</i>
<i>C07D 233/06 (2006.01)</i>	<i>A61K 31/506 (2006.01)</i>
<i>C07D 233/20 (2006.01)</i>	<i>A61K 31/7028 (2006.01)</i>
<i>C07D 233/22 (2006.01)</i>	<i>A61P 29/00 (2006.01)</i>
<i>C07D 233/24 (2006.01)</i>	<i>A61P 29/02 (2006.01)</i>
<i>C07D 233/88 (2006.01)</i>	<i>A61P 43/00 (2006.01)</i>
<i>C07D 233/50 (2006.01)</i>	<i>C07C 279/12 (2006.01)</i>
<i>C07D 263/48 (2006.01)</i>	<i>A61K 31/417 (2006.01)</i>
<i>C07D 401/04 (2006.01)</i>	<i>A61K 31/4174 (2006.01)</i>
<i>C07D 403/04 (2006.01)</i>	
<i>C07D 403/12 (2006.01)</i>	
<i>C07D 417/12 (2006.01)</i>	
<i>C07D 471/04 (2006.01)</i>	
<i>C07C 211/38 (2006.01)</i>	
<i>C07D 405/04 (2006.01)</i>	
<i>C07C 211/08 (2006.01)</i>	
<i>C07C 211/21 (2006.01)</i>	
<i>C07C 211/42 (2006.01)</i>	
<i>C07C 279/22 (2006.01)</i>	
<i>C07C 279/04 (2006.01)</i>	
<i>C07H 19/052 (2006.01)</i>	
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<i>A61K 31/4168 (2006.01)</i>	
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