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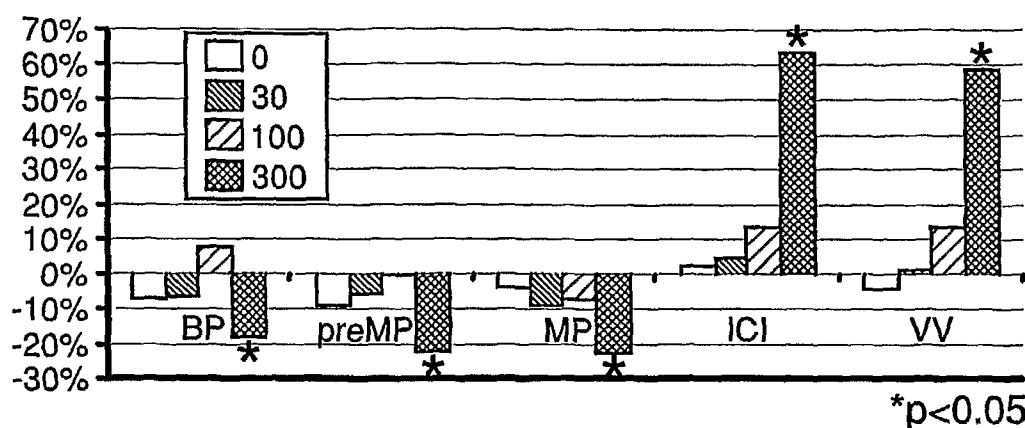
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(54) Title: COMPOSITIONS AND METHODS FOR USE OF A SODIUM CHANNEL BLOCKER



(57) Abstract: The present invention encompasses compositions and methods of using sodium channel blockers to treat bladder and urinary tract diseases, disorder, and conditions such as overactive bladder, urge urinary incontinence, lower urinary tract symptoms due to benign prostatic hyperplasia.

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COMPOSITIONS AND METHODS FOR USE OF A SODIUM CHANNEL BLOCKER

CROSS REFERENCE TO RELATED APPLICATIONS

5 This application claims priority under 35 U.S.C. §119(e) to U.S. Provisional Application Serial Nos. 60/695,134, filed June 29, 2005, and 60/731,677, filed October 31, 2005, the disclosures of which are incorporated by reference in their entirety herein.

10 STATEMENT REGARDING FEDERALLY SPONSORED RESEARCH AND DEVELOPMENT

 This invention was made with United States Government support under Grant No. DK062253-01 awarded by National Institutes of Health. The United States Government may have certain rights in the invention.

15 BACKGROUND

 Overactive bladder (OAB) and urge urinary incontinence are common problems that reduce the quality of life of adults. Up to 16% of adults suffer from OAB. Moreover, up to one in five men develop lower urinary tract symptoms due to benign prostatic hyperplasia. Despite considerable progress in understanding the patho-
20 physiology of bladder dysfunction, there is presently no consistently effective treatment for disorders like the painful or overactive bladder syndromes. Painful bladder syndrome (PBS) is a chronic bladder hypersensitivity disorder that typically presents with suprapubic pain related to bladder filling, accompanied by other symptoms such as increased frequency and nocturia, in the absence of a definable etiology. The overactive
25 bladder syndrome (OABS) is symptom complex characterized by urinary urgency with or without urge incontinence, usually with frequency and nocturia. Detrusor overactivity is often the underlying condition. Detrusor overactivity can be further qualified as neurogenic detrusor overactivity (NDO), when there is a relevant neurologic condition or idiopathic detrusor overactivity (IDO), when there is no defined cause.

30 The pathophysiology of overactive bladder syndrome (OABS) and detrusor overactivity (DO) is complex and involves both peripheral and central nervous system

(CNS) factors. Central in OABS is urgency, the pathophysiology of which is unknown. Increased afferent activity, decreased capacity to process afferent information, decreased suprapontine inhibition, and increased sensitivity to contraction-mediating transmitters are all potential causes of DO and OABS. Because both urgency and initiation of the micturition reflex depend on afferent input from the lower urinary tract, it seems logical that in the search for new therapies for DO and OABS, afferent functions and central control of afferent functions are some of the targets of interest. Voiding and storage reflexes involve several transmitters and transmitter systems that could be targets for the development of drugs that control DO and OABS. Perturbations of these systems are found in CNS disorders associated with DO and OABS, such as stroke, Parkinson's disease, spinal cord injury and multiple sclerosis (see Andersson, Nature Clinical Practice Urology 1:103 - 108, 2004, and Steers, Nature Clinical Practice Urology 3:101 - 110, 2006, for reviews).

The International Continence Society defines OABS as "urgency, with or without incontinence, usually with frequency and nocturia". Urgency, defined as "the complaint of a sudden compelling desire to pass urine, which is difficult to defer", is a central symptom of OABS. It can also be associated with involuntary detrusor contractions, urodynamically demonstrated as DO. It should be noted that urgency is difficult to measure, and no validated tool for its assessment is currently available. Furthermore, there are no animal models of urgency. Because the sensation of desire to void, urgency, and initiation of the micturition reflex depend on afferent input from the lower urinary tract, afferent functions and their central control have been of interest as targets for new therapies.

OAB occurs when smooth muscle of the detrusor muscle of the bladder squeezes or contracts more often than normal and at inappropriate times. Instead of staying at rest as urine fills the bladder, the detrusor contracts while the bladder is filling with urine. By definition, the cause of OAB is unknown. However, identifiable underlying causes can include: drug side effects, nerve damage or neurological disease (e.g., multiple sclerosis, Parkinson's disease, etc.) or stroke. There are also conditions that are associated with urgency and frequency - including bladder cancer, urinary tract

infections, and benign prostatic hyperplasia (BPH) - that must be excluded during an examination. Some experts believe that some individuals are predisposed to OAB. Circumstantial evidence suggests that individuals with depression, anxiety, and attention deficit disorder may experience symptoms of OAB more often than the general population. Some investigators suggest that depression, anxiety, feeding disturbances, pain, irritable bowel syndrome, fibromyalgia and changes in urination are associated with disturbances in brain circuits using specific chemical messengers between nerves known as neurotransmitters, in particular serotonin 5-hydroxytryptamine (5-HT). Fibromyalgia and irritable bowel syndrome are conditions seen more often in patients with OAB and interstitial cystitis (IC) than the general population. These conditions are associated with an overactive bladder, and possibly to depression, which provides a potential link with 5-HT metabolism and OAB.

Urge incontinence is a storage problem which involves a strong, sudden need to urinate immediately followed by a bladder contraction, resulting in an involuntary loss of urine. Often these contractions occur regardless of the amount of urine that is in the bladder. Urge incontinence may result from neurological injuries (such as spinal cord injury or stroke), neurological diseases (such as multiple sclerosis), infection, bladder cancer, bladder stones, bladder inflammation, or bladder outlet obstruction. The majority of cases are classified as idiopathic -- a specific cause cannot be identified. Although urge incontinence may occur in anyone at any age, it is more common in women and the elderly. It is second only to stress incontinence as the most common cause of urinary incontinence (involuntary loss of urine). Approximately 1% to 2% of adult females are affected by urge incontinence. In men, urge incontinence may be due to secondary bladder injuries caused by benign prostatic hypertrophy (BPH) or bladder outlet obstruction from an enlarged prostate. The ability to hold urine and maintain continence is dependent on normal function of the lower urinary tract, the kidneys, and the nervous system -- plus the physical and psychological ability to recognize and appropriately respond to the urge to urinate.

Interstitial cystitis (IC) is a chronic bladder disorder also known as painful bladder syndrome and frequency-urgency-dysuria syndrome. In this disorder, the

bladder wall can become inflamed and irritated.

The bladder's ability to fill and store urine requires a functional sphincter (muscle controlling output) and a stable bladder wall muscle (detrusor). The process of urination involves two phases: the filling and storage phase, and the emptying phase.

5 During the filling and storage phase, the bladder begins to fill, stretching to accommodate the increasing amount of urine. The bladder of an average person can hold 350 mL to 550 mL of urine.

The first sensation of the need to urinate occurs when approximately 200 mL of urine is stored. The nervous system responds by alerting the subject of the need to urinate while also allowing the bladder to continue to fill. The emptying phase requires the ability of the detrusor muscle to appropriately contract, forcing urine out of the bladder. The body must also be able to simultaneously relax the sphincter to allow the urine to exit. The bladder of an infant contracts automatically when a certain volume of urine is collected in the bladder. As the individual learns to control urination, bladder muscle contraction is prevented by constant inhibition from the cerebral cortex (part of the brain). This allows urination to be delayed until the individual is ready. Undesired bladder muscle contraction may occur as the result of a break in the neurological pathway from the brain to the bladder. It can also occur if the bladder is irritated and the normal neurological impulses to inhibit urination are insufficient to keep the bladder relaxed as it fills.

Micturition in the adult is a spinobulbospinal reflex, which is under suprapontine tonic inhibitory control. Voluntary control is dependent on how effectively suprapontine pathways influence (enhance or inhibit) this inhibitory input. Adequate sensory input is the prerequisite for conscious bladder control; changes in sensory mechanisms could disturb bladder function. Thus, it has been proposed that urge incontinence is a "disease of bladder sensors".

Because of the complexity of CNS control of the lower urinary tract, DO and OAB occur as a result of a variety of neurological disorders, as well as in response to changes in peripheral innervation and in the smooth and skeletal muscle components of the lower urinary tract and pelvic floor. Theoretically, the pathophysiology of DO and

OABS might be dependent on increased afferent activity, decreased capacity of the CNS to process afferent information, decreased suprapontine inhibition or increased sensitivity to contraction-mediating transmitters in the target organ.

Recent studies demonstrate that Na channels may be important in the pathogenesis of idiopathic detrusor overactivity or due cystitis and bladder outlet obstruction (Black et al., Brain Res. 2003, 963(1-2):132-8). Evidence for plasticity in afferent nerves has been shown for these conditions. The basis for this plasticity is an alteration of sodium (Na) channels. Knockdown of specific sodium channel isoforms using intrathecal administration of antisense deoxyoligonucleotides reverses detrusor overactivity in the spontaneous hypertensive rat (SHR), cystitis, and urethral obstruction models (Lee et al., J. Urol. 167 (4): 38-38 Suppl. S, APR 2002).

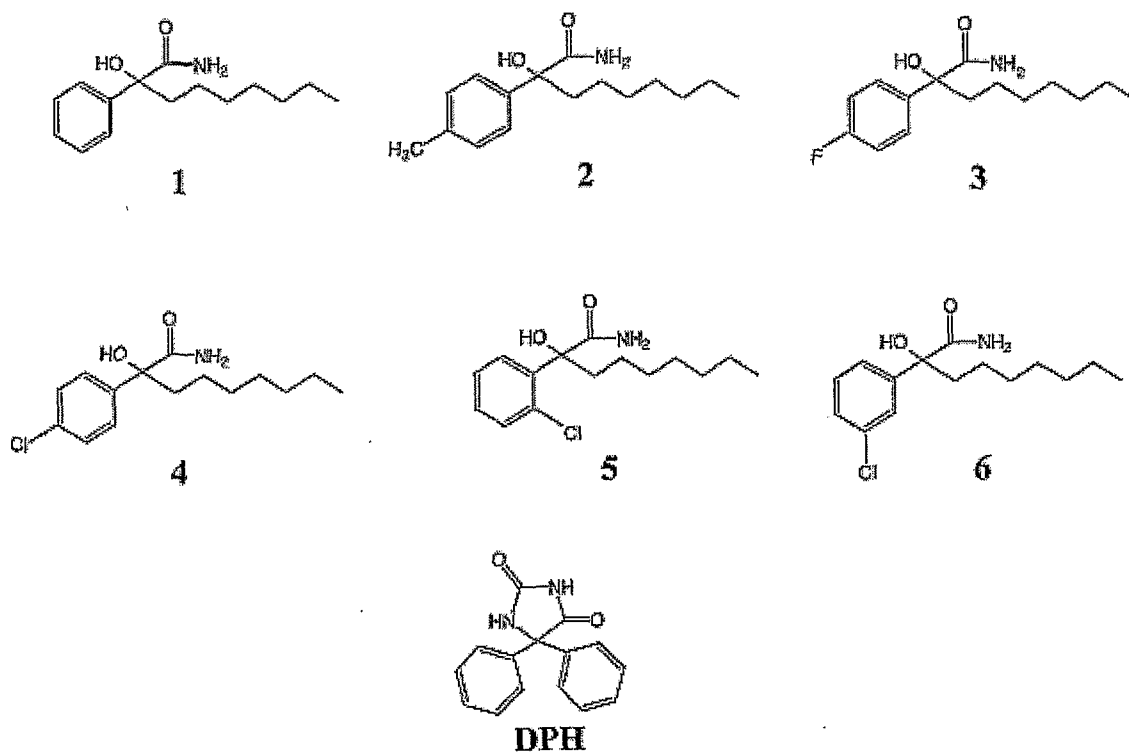
Diphenylhydantoin (DPH) or Phenytoin is a clinically useful anticonvulsant, class 1b antiarrhythmic and has been effectively used in the treatment of neuropathic pain by virtue of its ability to block voltage-gated sodium channels. Sodium channel blockers such as local anesthetics and antiarrhythmics mediate their block of sodium channels by two mechanisms, tonic (resting) block and use-dependent block. Tonic block results from low affinity binding of drug to the resting state of the channel whilst during use-dependent block drugs binds to the inactivated state of the channel with a greater affinity resulting in further inhibition of the current. Because sodium channel isoforms differ in channel gating kinetics these differences are thought to explain different affinities of sodium channel blockers for the various isoforms. For example, lidocaine has been shown to have a higher affinity for the Nav1.5 isoform in comparison to the skeletal muscle specific isoform Nav1.4 and neuronal sodium channel alpha subunits.

There is a long felt need in the art for methods and compounds for treatment of the symptoms and signs of diseases and disorders related to overactive bladder, detrusor overactivity, urge urinary incontinence, and lower urinary tract symptoms caused by problems such as benign prostatic hyperplasia. The present invention satisfies these needs.

SUMMARY OF INVENTION

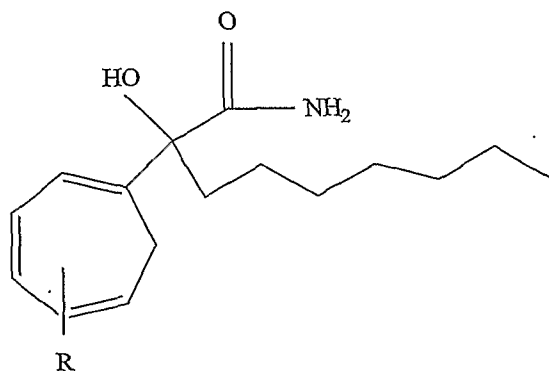
The present invention provides methods and compositions for treating the symptoms and signs or diseases, disorders, and conditions related to overactive bladder (urgency, usually with frequency, with or without nocturia or urge incontinence), urge urinary incontinence, detrusor overactivity, interstitial cystitis, and lower urinary tract symptoms (LUTS) due to benign prostate hypertrophy. In one aspect, the detrusor overactivity is related to bladder outlet obstruction (BOO). It will be understood by one of ordinary skill in the art that overactive bladder and detrusor overactivity can be associated with a variety of disorders, including those listed herein, as well as others known in the art.

In one embodiment, the present invention provides Na channel blockers, including, but not limited to,



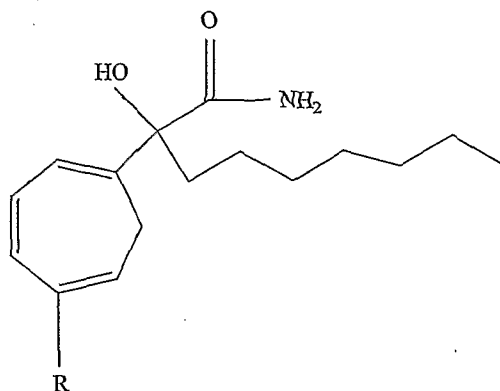
In one aspect, compounds of the invention have a higher affinity for the inactivated state of the sodium channel than phenytoin (DPH) has for the inactivated state of the sodium channel. In one aspect, the sodium channel is Nav1.5.

In another embodiment, the invention provides compounds having the structure:



wherein R is selected from the group consisting of halogen, H, and H₃C, or an analog, derivative, or modification thereof. In one aspect, the halogen is chlorine.

In one aspect, the invention provides a compound having the structure

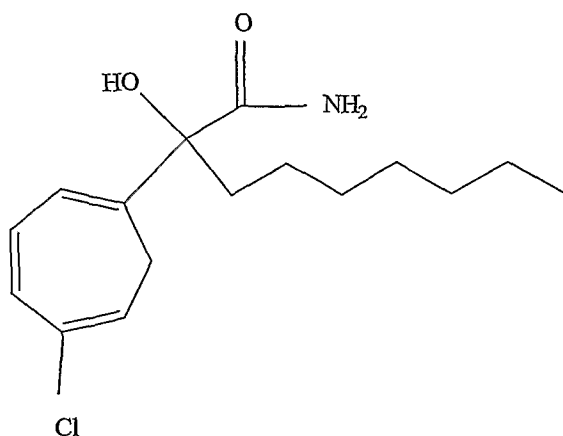


wherein R is selected from the group consisting of halogen, H, and H₃C, or an analog, derivative, or modification thereof. In one aspect, the halogen is chlorine.

ICM-I-136 (see structure 6 above), an alpha-hydroxyamide, is a recently identified new class of potent Na channel blockers with high affinity for the inactivated state as compared to phenytoin (Lenkowski et al. *European J. Pharmaceutical Sciences*, 21:635-644, 2004). ICM-I-136 is structure 6 on page 638 of Lenkowski. The present application discloses the potent effect of ICM-I-136 on voiding function in SHR and in rats with partial urethral obstruction as determined using blinded awake cystometries. The present further discloses the efficacy of this compound in treating detrusor

overactivity.

ICM-I-136 has the following general structure:



5

Other useful compounds of the invention include compounds such as Phenytoin and Carbamazepine, and analogs, derivatives, and modifications thereof, wherein the compounds have the desired biological activity described herein.

10 In one embodiment, the compound used for treating a disease, disorder or condition of the bladder is ICM-I-136. In another aspect, the compound is an analog, derivative, or modification of ICM-I-136. In one aspect, the compounds are alpha-hydroxyamides with the activity described herein. Such compounds have utility in treating diseases associated with inappropriate sodium channel activity.

15 In one embodiment, the present invention provides methods of administering sodium channel blockers for treating diseases, disorders, and conditions related to overactive bladder (urgency, usually with frequency, with or without nocturia or urge incontinence), urge urinary incontinence, detrusor overactivity, and lower urinary tract symptoms (LUTS) due to benign prostate hypertrophy. In one aspect, the present invention provides compositions and method for treating the signs and symptoms of
20 diseases, disorders, and conditions associated with overactive bladder and detrusor overactivity, including, but not limited to, benign prostatic hyperplasia, nocturia, painful bladder syndrome, overactive bladder syndrome, stroke, Parkinson's disease, spinal cord injury, depression, anxiety, feeding disturbances, pain, irritable bowel syndrome,

fibromyalgia, interstitial cystitis, and multiple sclerosis

The invention provides compositions and methods useful for reducing detrusor overactivity, reducing maximum pressure, reducing basal pressure, reducing voiding frequency, increasing intercontraction interval, reducing urge incontinence, nocturia, and increasing voided volume. One of ordinary skill in the art will appreciate that the symptoms and signs described herein can be treated with the compounds of the invention, regardless of whether the particular disease, disorder, or condition associated with those symptoms is described herein, or whether that disease, disorder, or condition is the cause of the symptom or sign.

The invention provides varied doses of compounds of the invention. In one aspect, a compound of the invention can be administered at a dosage of up to about 1000 mg/kg. In another aspect, the dosage can be up to about 300 mg/kg. One of ordinary skill in the art will appreciate that dosages, form of delivery, route of administration, and frequency of administration, may vary depending on a number of conditions, such as the age, sex, weight, and health of the subject, as well as the type and severity of the disease, disorder or condition being treated.

The invention further provides administering one or more compounds of the invention, and using one or more compounds of the invention in combination or in conjunction with other drugs or agents. The other drugs and agents include, but are not limited to, drugs such as pain medication and other types of drugs useful for treating overactive bladder and detrusor overactivity symptoms described herein.

The invention further provides a kit for administering the compositions of the invention.

Various aspects and embodiments of the invention are described in further detail below.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 graphically illustrates the effect of ICM-I-136 on voiding of SHR. The compound was tested at 0, 30, 100, and 300 mg/kg. Measurements analyzed include, BP, preMP, MP ICI, and VV. * indicates a significant difference at the level of

p < 0.05.

Figure 2 graphically illustrates the effect of ICM-I-136 on voiding of WKY. the compound was tested at 0, 100, and 300 mg/kg. Measurements analyzed include BP, preMP, MP, ICI, and VV. * indicates a significant difference at the level of p < 0.05.

Figure 3, comprising Figures 3A and 3B, graphically illustrate the effect of vehicle (Figure 3A; upper panel) and ICM-I-136 at 300 mg/kg (Figure 3B; lower panel) i.p. awake cystometry in obstructed (OBS) rats.

Figure 4 is a schematic representation of the mechanism of detrusor overactivity and the basis for drug therapy with sodium channel antagonists (Upper Panel: Normal Bladder; Lower Panel: Overactive Bladder).

DETAILED DESCRIPTION OF THE INVENTION

In describing and claiming the invention, the following terminology will be used in accordance with the definitions set forth below.

Definitions, Abbreviations, and Eponyms

Basal pressure (BP; also referred to as BsP)

Bladder outlet obstruction (BOO)

Detrusor overactivity (DO)

Dimethyl sulfoxide (DMSO)

Diphenylhydantoin (DPH)

Frequent voiders (F)

Idiopathic detrusor overactivity (IDO)

Intercontraction interval (ICI)

Interstitial cystitis (IC)

Intraperitoneal (i.p.)

Lower urinary tract symptoms (LUTS)

Maximum pressure (MP)

Neurogenic detrusor overactivity (NDO)

Non-frequent voiders (NF)

Obstructed (OBS)

Overactive bladder (OAB); also referred to as Detrusor instability, Detrusor hyperreflexia, Irritable bladder, Spasmodic bladder; Unstable bladder, and Urge Incontinence

5 Overactive bladder syndrome (OABS)

Painful bladder syndrome (PBS)

Postvoid residual volume (RU)

Partial urethral ligation (PUL)

Premicturition pressure (PreMP)

10 Sodium (Na)

Spontaneous hypertensive rat (SHR)

Voided volume (VV)

As used herein, the articles “a” and “an” refer to one or to more than one, i.e., to at least one, of the grammatical object of the article. By way of example, “an element”
15 means one element or more than one element.

As used herein, “affinity for the inactivated state” refers to a drug’s ability to bind to the inactivated state of a voltage-gated sodium channel to inhibit the current.

A disease, condition, or disorder is “alleviated” if the severity of a symptom of the disease, condition, or disorder, or the frequency with which such a symptom is
20 experienced by a subject, or both, are reduced.

As used herein, an “analog” of a chemical compound is a compound that, by way of example, resembles another in structure but is not necessarily an isomer (e.g., 5-fluorouracil is an analog of thymine).

As used herein, “Bladder Outlet Obstruction” is the generic term for obstruction
25 during voiding and is characterized by increased detrusor pressure and reduced urine flow rate. It is usually diagnosed by studying the synchronous values of flowrate and detrusor pressure.

A “control” cell, tissue, sample, or subject is a cell, tissue, sample, or subject of the same type as a test cell, tissue, sample, or subject. The control may, for example, be
30 examined at precisely or nearly the same time the test cell, tissue, sample, or subject is

examined. The control may also, for example, be examined at a time distant from the time at which the test cell, tissue, sample, or subject is examined, and the results of the examination of the control may be recorded so that the recorded results may be compared with results obtained by examination of a test cell, tissue, sample, or subject.

5 The control may also be obtained from another source or similar source other than the test group or a test subject, where the test sample is obtained from a subject suspected of having a disease or disorder for which the test is being performed.

A "test" cell, tissue, sample, or subject is one being examined.

10 A "pathoindicative" cell, tissue, or sample is one which, when present, is an indication that the animal in which the cell, tissue, or sample is located (or from which the tissue was obtained) is afflicted with a disease or disorder. By way of example, the presence of one or more breast cells in a lung tissue of an animal is an indication that the animal is afflicted with metastatic breast cancer.

15 A tissue "normally comprises" a cell if one or more of the cell are present in the tissue in an animal not afflicted with a disease or disorder.

A "compound," as used herein, refers to any type of substance or agent that is commonly considered a drug, or a candidate for use as a drug, as well as combinations and mixtures of the above.

20 As used herein, a "derivative" of a compound refers to a chemical compound that may be produced from another compound of similar structure in one or more steps, as in replacement of H by an alkyl, acyl, or amino group.

25 The use of the word "detect" and its grammatical variants is meant to refer to measurement of the species without quantification, whereas use of the word "determine" or "measure" with their grammatical variants are meant to refer to measurement of the species with quantification. The terms "detect" and "identify" are used interchangeably herein.

30 As used herein, a "detectable marker" or a "reporter molecule" is an atom or a molecule that permits the specific detection of a compound comprising the marker in the presence of similar compounds without a marker. Detectable markers or reporter molecules include, but are not limited to, radioactive isotopes, antigenic determinants,

enzymes, nucleic acids available for hybridization, chromophores, fluorophores, chemiluminescent molecules, electrochemically detectable molecules, and molecules that provide for altered fluorescence polarization or altered light scattering.

The term "Detrusor Overactivity", as used herein, refers to a urodynamic observation characterized by involuntary detrusor contractions during the filling phase which may be spontaneous or provoked. Any detrusor contraction prior to permission to void is abnormal.

The term "Detrusor Overactivity Incontinence" refers to incontinence due to detrusor overactivity.

As used herein, a "derivative" of a compound refers to a chemical compound that may be produced from another compound of similar structure in one or more steps, as in replacement of H by an alkyl, acyl, or amino group.

As used herein, the phrase, "disease, condition, or disorder is characterized by an overactive bladder or detrusor overactivity" refers to any disease, disorder, or condition which is known to be associated with overactive bladder or detrusor overactivity, whether or not the disease, disorder, or condition actually causes overactive bladder or detrusor overactivity.

As used herein, a "disorder" in an animal is a state of health in which in which the animal is able to maintain homeostasis, but in which the subject's state of health is less favorable than it would be in the absence of the disorder. Left untreated, a disorder does not necessarily cause a further decrease in the subject's state of health.

As used herein, an "effective amount" means an amount sufficient to produce a selected or desired effect.

"Filling Cystometry" refers to the method by which the pressure/volume relationship of the bladder is measured during bladder filling.

The term "inhibit," as used herein, refers to the ability of a compound of the invention to reduce or impede a described function. Preferably, inhibition is a reduction of at least 10%, more preferably by at least 25%, even more preferably by at least 50%, and most preferably, the function is inhibited by at least 75%. The term "inhibit" is used interchangeably with "reduce" herein.

As used herein, an "instructional material" includes a publication, a recording, a diagram, or any other medium of expression which can be used to communicate the usefulness of the peptide of the invention in the kit for effecting alleviation of the various diseases or disorders recited herein. Optionally, or alternately, the instructional material may describe one or more methods of alleviating the diseases or disorders in a cell or a tissue of a mammal. The instructional material of the kit of the invention may, for example, be affixed to a container which contains the identified compound invention or be shipped together with a container which contains the identified compound. Alternatively, the instructional material may be shipped separately from the container with the intention that the instructional material and the compound be used cooperatively by the recipient.

As used herein, the term "in vivo" refers to inside a living organism.

As used herein, the term "in vitro" refers to outside a living organism.

As used herein, "modification" of a compound refers to a compound that's structure or composition has been somewhat changed from the original compound.

"Nocturia" refers to the complaint that the individual has to wake at night one or more times to void.

"Overactive bladder syndrome" ("OABS") is symptom complex characterized by urinary urgency with or without urge incontinence, usually with frequency and nocturia.

The term, "parenteral" means not through the alimentary canal but by some other route such as subcutaneous, intramuscular, intraspinal, or intravenous.

As used herein, the term "pharmaceutically acceptable carrier" includes any of the standard pharmaceutical carriers, such as a phosphate buffered saline solution, water, emulsions such as an oil/water or water/oil emulsion, and various types of wetting agents. The term also encompasses any of the agents approved by a regulatory agency of the US Federal government or listed in the US Pharmacopeia for use in animals, including humans.

The term "pharmaceutically acceptable salt" refers to salts which retain the biological effectiveness and properties of the compounds of this invention and which

are not biologically or otherwise undesirable. In many cases, the compounds of this invention are capable of forming acid and/or base salts.

"Premicturition pressure" is the pressure recorded immediately before the initial isovolumetric contraction.

5 A "sample," as used herein, refers preferably to a biological sample from a subject, including, but not limited to, normal tissue samples, diseased tissue samples, biopsies, blood, saliva, feces, semen, tears, and urine. A sample can also be any other source of material obtained from a subject which contains cells, tissues, or fluid of interest. A sample can also be obtained from cell or tissue culture.

10 The term "sign," as used herein, refers to any abnormality indicative of a disease, disorder, or condition, discoverable on examination of the patient; an objective indication of disease, in contrast to a symptom, which is a subjective indication of disease.

The term "sodium channel," as used herein, refers to a structure comprised of
15 integral membrane proteins that functions to allow sodium to equilibrate across a cell membrane according to its electrochemical gradient and at rates that are diffusion limited. A sodium channel can exist in several modes: C (closed resting state); C* (activated closed state); O (open state); and I (inactivated state). The probability that a channel will exist in one of these four states changes with voltage.

20 The term "sodium channel activity," as used herein, refers to activities of sodium channels and the results of activities of a sodium channel, which can be measured or monitored using in vitro and in vivo assays. For example, voltage-gated sodium channels are responsible for the rising phase of the action potential in excitable membranes and certain known anesthetics and anticonvulsants target specific sites in
25 sodium channels to block Na⁺ currents, thus reducing excitability in neuronal, muscle, or central nervous system. Thus, nerve transmission is regulated. Sodium channel activity, or the results of sodium channel activity, can be measured, analyzed, or monitored using various assays such as binding, gating, ion permeation, current, and various methods which measure parameters indicative of pain or reaction, such as motor
30 function, proprioception, nocifensive reaction.

The term "sodium channel blocker" refers to a compound that is able to inhibit sodium channel activity.

The term "standard," as used herein, refers to something used for comparison. For example, it can be a known standard agent or compound which is administered or added to a control sample and used for comparing results when measuring said compound in a test sample. Standard can also refer to an "internal standard", such as an agent or compound which is added at known amounts to a sample and is useful in determining such things as purification or recovery rates when a sample is processed or subjected to purification or extraction procedures before a marker of interest is measured.

A "subject" of analysis, diagnosis, or treatment is an animal. Such animals include mammals, preferably a human. Non-human animals subject to analysis, diagnosis, or treatment include, but are not limited to, primates, cats, dogs, horses, cows, goats, pigs, and sheep.

The term "substantially pure" describes a compound, e.g., a protein or polypeptide which has been separated from components which naturally accompany it. Typically, a compound is substantially pure when at least 10%, more preferably at least 20%, more preferably at least 50%, more preferably at least 60%, more preferably at least 75%, more preferably at least 90%, and most preferably at least 99% of the total material (by volume, by wet or dry weight, or by mole percent or mole fraction) in a sample is the compound of interest. Purity can be measured by any appropriate method, e.g., in the case of polypeptides by column chromatography, gel electrophoresis, or HPLC analysis. A compound, e.g., a protein, is also substantially purified when it is essentially free of naturally associated components or when it is separated from the native contaminants which accompany it in its natural state.

The term "symptom," as used herein, refers to any morbid phenomenon or departure from the normal in structure, function, or sensation, experienced by the patient and indicative of disease. In contrast, a sign is objective evidence of disease. For example, a bloody nose is a sign. It is evident to the patient, doctor, nurse and other observers.

As used herein, the term "treating" includes prophylaxis of the specific disease, disorder, or condition, or alleviation of the symptoms associated with a specific disease, disorder, or condition and/or preventing or eliminating said symptoms.

5 A "prophylactic" treatment is a treatment administered to a subject who does not exhibit signs of a disease or exhibits only early signs of the disease for the purpose of decreasing the risk of developing pathology associated with the disease.

A "therapeutic" treatment is a treatment administered to a subject who exhibits signs of pathology for the purpose of diminishing or eliminating those signs.

10 A "therapeutically effective amount" of a compound is that amount of compound which is sufficient to provide a beneficial effect to the subject to which the compound is administered.

"Urinary incontinence" refers to the complaint of any involuntary leakage of urine.

15 "Urgency" refers to the complaint of a sudden compelling desire to pass urine, which is difficult to defer.

The term "voiding," as used herein, refers to passing urine. The term "voiding" is used interchangeably with "micturition".

Chemical Definitions

20 As used herein, the term "halogen" or "halo" includes bromo, chloro, fluoro, and iodo.

The term "haloalkyl" as used herein refers to an alkyl radical bearing at least one halogen substituent, for example, chloromethyl, fluoroethyl or trifluoromethyl and the like.

25 The term "C₁-C_n alkyl" wherein n is an integer, as used herein, represents a branched or linear alkyl group having from one to the specified number of carbon atoms. Typically, C₁-C₆ alkyl groups include, but are not limited to, methyl, ethyl, n-propyl, iso-propyl, butyl, iso-butyl, sec-butyl, tert-butyl, pentyl, hexyl, and the like.

30 The term "C₂-C_n alkenyl" wherein n is an integer, as used herein, represents an olefinically unsaturated branched or linear group having from 2 to the specified number of carbon atoms and at least one double bond. Examples of such groups include, but are

not limited to, 1-propenyl, 2-propenyl, 1,3-butadienyl, 1-butenyl, hexenyl, pentenyl, and the like.

The term " C_2-C_n alkynyl" wherein n is an integer refers to an unsaturated branched or linear group having from 2 to the specified number of carbon atoms and at least one triple bond. Examples of such groups include, but are not limited to, 1-propynyl, 2-propynyl, 1-butyne, 2-butyne, 1-pentyne, and the like.

The term " C_3-C_n cycloalkyl" wherein $n = 3-8$, represents cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, and cyclooctyl.

As used herein, the term "optionally substituted" refers to from zero to four substituents, wherein the substituents are each independently selected. Each of the independently selected substituents may be the same or different than other substituents.

As used herein the term "aryl" refers to an optionally substituted mono- or bicyclic carbocyclic ring system having one or two aromatic rings including, but not limited to, phenyl, benzyl, naphthyl, tetrahydronaphthyl, indanyl, indenyl, and the like. "Optionally substituted aryl" includes aryl compounds having from zero to four substituents, and "substituted aryl" includes aryl compounds having one or more substituents. The term $(C_5-C_8 \text{ alkyl})\text{aryl}$ refers to any aryl group which is attached to the parent moiety via the alkyl group.

The term "heterocyclic group" refers to an optionally substituted mono- or bicyclic carbocyclic ring system containing from one to three heteroatoms wherein the heteroatoms are selected from the group consisting of oxygen, sulfur, and nitrogen.

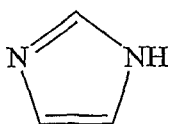
As used herein the term "heteroaryl" refers to an optionally substituted mono- or bicyclic carbocyclic ring system having one or two aromatic rings containing from one to three heteroatoms and includes, but is not limited to, furyl, thienyl, pyridyl and the like.

The term "bicyclic" represents either an unsaturated or saturated stable 7- to 12-membered bridged or fused bicyclic carbon ring. The bicyclic ring may be attached at any carbon atom which affords a stable structure. The term includes, but is not limited to, naphthyl, dicyclohexyl, dicyclohexenyl, and the like.

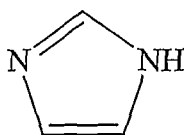
The compounds of the present invention may contain one or more asymmetric

centers in the molecule. In accordance with the present invention a structure that does not designate the stereochemistry is to be understood as embracing all the various optical isomers, as well as racemic mixtures thereof.

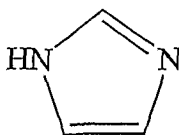
The compounds of the present invention may exist in tautomeric forms and the invention includes both mixtures and separate individual tautomers. For example the following structure:



is understood to represent a mixture of the structures:



and



10

The term "pharmaceutically-acceptable salt" refers to salts which retain the biological effectiveness and properties of the compounds of the present invention and which are not biologically or otherwise undesirable. In many cases, the compounds of the present invention are capable of forming acid and/or base salts by virtue of the presence of amino and/or carboxyl groups or groups similar thereto.

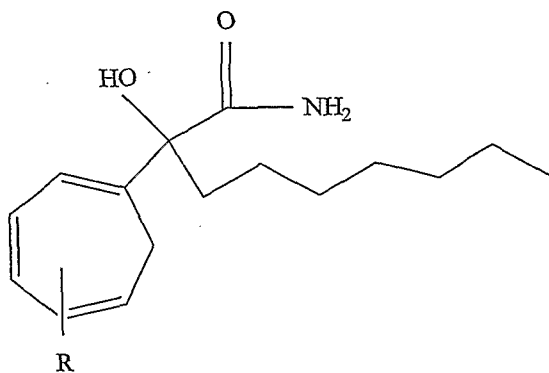
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The present invention provides compositions and methods for treating overactive bladder and detrusor overactivity-associated diseases, disorders, and conditions with compounds which regulate sodium channel activity.

20

The compounds of the invention useful for treating diseases and conditions described herein, such as overactive bladder syndrome, may also be used in conjunction with other drugs, behavioral modification, surgery, and neuromodulation.

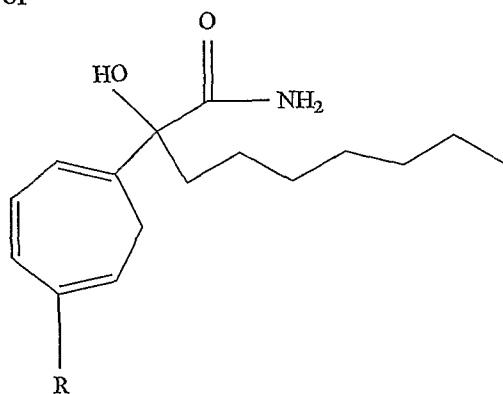
In one aspect, the compound has the general structures:



wherein R is selected from the group consisting of halogen, H, and H₃C,

5

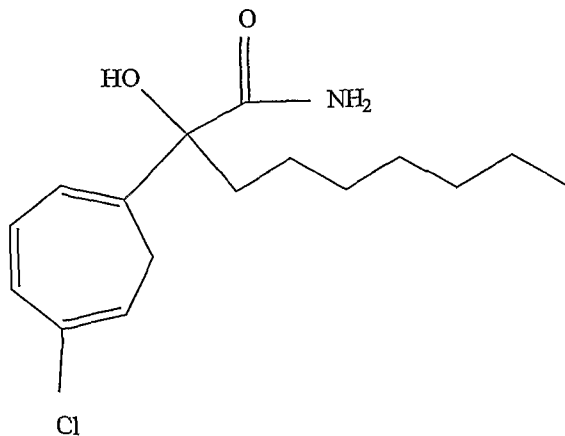
or



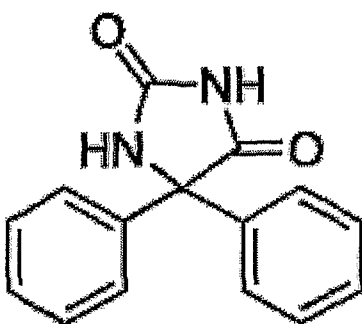
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wherein R is selected from the group consisting of halogen, H, and H₃C. In one aspect, halogen is chlorine.

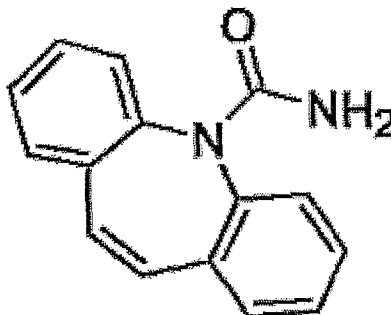
In one aspect, the compound is ICM-I-136, which has the following general structure:



The structures of phenytoin and carbamazepine are as follows:



Phenytoin



Carbamazepine

5

10

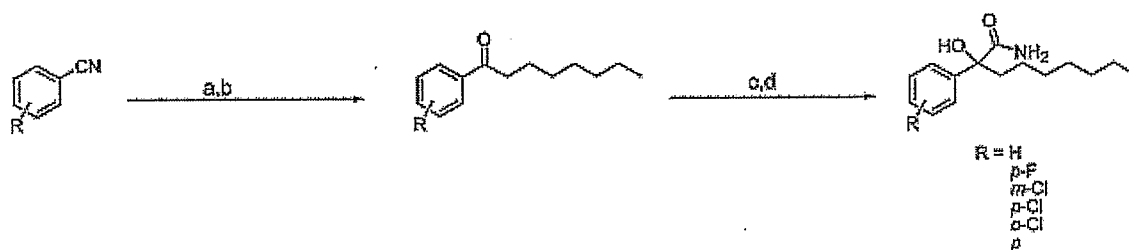
Carbamazepine, an iminostilbene derivative of tricyclic antidepressants, exhibits a spectrum of anticonvulsant activity very similar to that of phenytoin. In humans, it is effective against partial and generalized tonic-clonic seizures, but not against absence seizures. Lamotrigine has been used for treating partial and generalized tonic-clonic seizure. Such compounds, as well as analogs, derivatives, and modifications thereof are useful in the method of the invention.

15

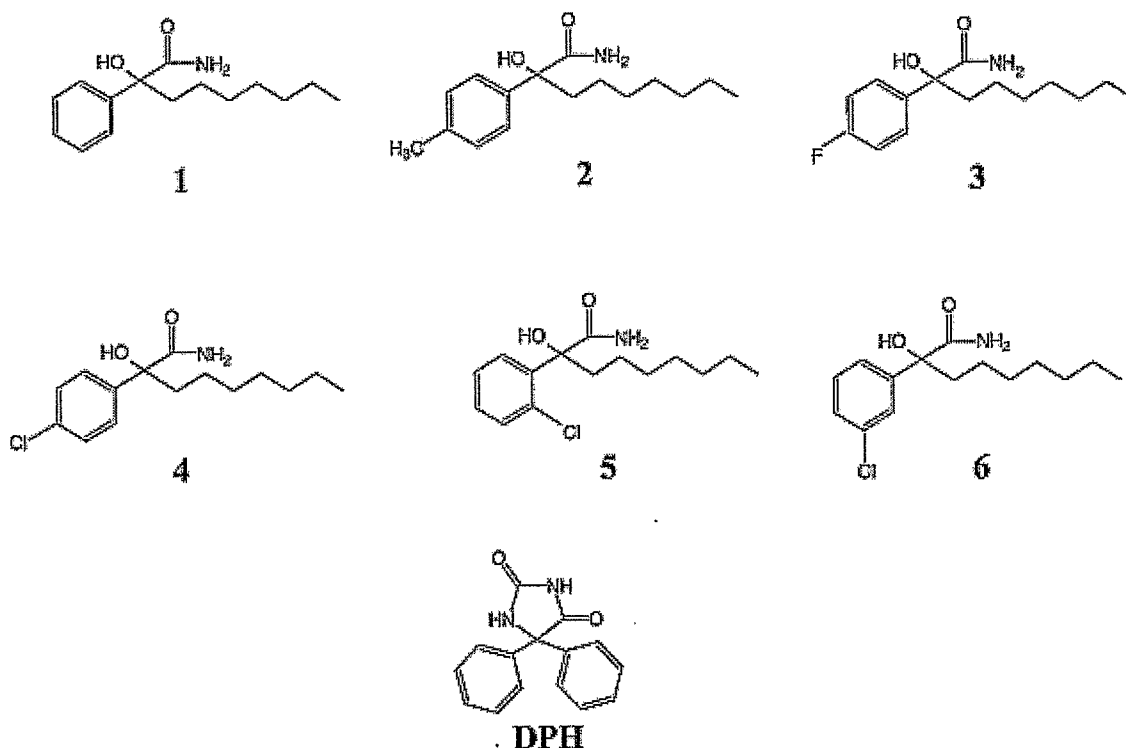
Techniques for preparing analogs, derivative, and modifications of compounds such as phenytoin and ICM-I-136 are known in the art (see for example, Lenkowski et al., *European Journal of Pharmaceutical Sciences* 21 (2004) 635–644, Schenck et al., *Bioorg. Med. Chem.*, 2004, 12(5):979-93, and Anderson et al., *Mol Cancer Ther.* 2003, 2:1149–1154). Other techniques for preparing and testing compounds for use in treating lower urinary tract conditions are also known (Barbanti et al., WO 2005/070405).

20

A general synthetic scheme is described in Lenkowski et al. (*European Journal of Pharmaceutical Sciences* 21 (2004) 635–644) and is as follows:



Some of the compounds described in Lenkowski are as follows:



5

For the Lenkowski structures, DPH and novel α -hydroxyphenylamide substitutions were examined in that study. Structures showed differences in phenyl ring substitution. Compound 1 (see above) is unsubstituted. Compounds 2, 3 and 4 are the para-methyl, para-fluoro and para-chloro substitutions, respectively. Compounds 5 and 6 are the ortho- and meta-chloro substitutions, respectively.

Molecular modeling can be employed when designing and studying new compounds useful in the invention (see Lenkowski et al., *European Journal of Pharmaceutical Sciences* 21 (2004) 635–644). For example, the X-ray coordinates for

phenytoin (DPH) can be utilized. α -hydroxyphenylamides can be modified from the X-ray structure and energy-minimized with the Tripos force field using conjugate gradient approach and 0.05 kCal/mol energy cutoff, without solvent, using default bond distances and angles and neglecting electrostatics. The minimization can be completed by aggregating using the SYBYL/AGGREGATE module for only the X-ray structure atoms and allowing the modified portion to minimize. For internal consistency, the R-configuration for all chiral compounds can be used. Plane angles can be calculated using the phenyl ring for plane 1 and the carbonyl and nitrogen of the amide for plane 2. Plane 1 for DPH can be constructed with phenyl ring atoms and plane 2 using all hydantoin ring atoms. The plane angle can be calculated as the angle between planes 1 and 2. Molecular volume can be determined using the volume contour option within SYBYL/VIEW presented with default options.

Methods for testing and studying sodium channels are known (see Lenkowski et al.; U.S. Pat. No. 6,420,354). Chinese Hamster Ovary (CHO-K1) cells stably expressing Nav1.5 can be grown in DMEM/F12 media (Invitrogen Corp., CA, USA) supplemented with 10% fetal bovine serum, penicillin (100 U/ml), streptomycin (100 μ g/ml) and G418 (500 μ g/ml; Sigma, MO, USA). Cells can be grown in a humidified atmosphere of 5% CO₂ and 95% air at 37 °C. For electrophysiology experiments, sodium currents can be recorded using the whole-cell configuration of the patch clamp recording technique with an Axopatch 200B amplifier (Axon Instruments, Foster City, CA). All voltage protocols can be applied using pCLAMP 8 software (Axon, USA) and a Digidata 1322A (Axon, USA). Currents were amplified and low pass filtered (2 kHz) and sampled at 33 kHz. Borosilicate glass pipettes can be pulled using a Brown-Flaming puller (model P87, Sutter Instruments Co., Novato, CA) and heat polished to produce electrode resistances of 0.5–1.5 M Ω when filled with the following electrode solution (in mM): CsCl 130, MgCl₂ 1, MgATP 5, BAPTA 10, HEPES 5 (pH adjusted to 7.4 with CsOH). Cells can be plated on glass coverslips and superfused with solution containing the following composition (in mM) NaCl 130, KCl 4, CaCl₂ 1, MgCl₂ 5, HEPES 5, and glucose 5 (pH adjusted to 7.4 with NaOH). Compounds can be prepared as 100 mM stock solutions in dimethyl sulfoxide (DMSO) and diluted to desired

concentration in perfusion solution. The maximum DMSO concentration might be 0.3% because it usually has no effect on current amplitude. Experiments can be performed at room temperature (20–22 °C). After establishing whole-cell, a minimum series resistance compensation of 75% can be applied and cells can be held at –80 mV for 5 min to account for equilibrium gating shifts. Voltage error can be calculated using the following equation:

$$\Delta V = I_p(1-a)R$$

where ΔV is the voltage error, I_p the peak current, a the series resistance compensation and R the series resistance. Data from cells with a voltage error greater than 3 mV may be excluded. Activation and steady-state inactivation data can be fitted by the equation:

$$y = \frac{1}{1 + \exp((V - V_{1/2})/k)}$$

where y is the normalized conductance ($g/g_{\max}$) or the normalized current for activation and inactivation, respectively, $V_{1/2}$ the voltage of half-maximal activation or inactivation and k the slope factor. The difference between the $V_{1/2}$ value in the presence and absence of compound can be shown as $\Delta V_{1/2}$ (mV). Time constants for recovery from inactivation were obtained using a double exponential function:

$$y = A_1 \left(1 - \exp \left(-\frac{t}{\tau_1} \right) \right) + A_2 \left(1 - \exp \left(-\frac{t}{\tau_2} \right) \right)$$

A_1 and A_2 are the coefficients for the fast and slow exponentials, t the time (ms) and τ_1 and τ_2 the fast and slow time constants. The percentage of the current represented by the fast time constant can be calculated from the equation $100\% \times A_1/(A_1+A_2)$, where A_1 and A_2 are the amplitudes of the fast and slow gating modes, respectively. Time constants for use-dependent block can be obtained using the equation:

$$y = A \exp \left(-\frac{t}{\tau} \right) + C$$

where A is the coefficient of the exponential, t the time (ms), τ the time constant (ms) and C the fraction of unblocked current at the end of the time course.

Data analysis for these experiments can be performed using Clampfit software (v8, Axon Instruments, CA, USA), Origin (v5, Microcal Software, MA, USA), and Excel (Microsoft). Statistical analyses can be performed using a t-test for normally distributed data as determined by the Kolmogorov-Smirnov test, or the Rank Sum test for non-normalized data (Sigma Stat, Jandel). Averaged data can be presented as mean $\pm$ standard error of the mean (S.E.M.). Values of $P < 0.05$ can be considered to indicate significance.

Other techniques for such analyses not described herein are known in the art.

Pharmaceutically-acceptable base addition salts can be prepared from inorganic and organic bases. Salts derived from inorganic bases, include by way of example only, sodium, potassium, lithium, ammonium, calcium and magnesium salts. Salts derived from organic bases include, but are not limited to, salts of primary, secondary and tertiary amines, such as alkyl amines, dialkyl amines, trialkyl amines, substituted alkyl amines, di(substituted alkyl) amines, tri(substituted alkyl) amines, alkenyl amines, dialkenyl amines, trialkenyl amines, substituted alkenyl amines, di(substituted alkenyl) amines, tri(substituted alkenyl) amines, cycloalkyl amines, di(cycloalkyl) amines, tri(cycloalkyl) amines, substituted cycloalkyl amines, disubstituted cycloalkyl amine, trisubstituted cycloalkyl amines, cycloalkenyl amines, di(cycloalkenyl) amines, tri(cycloalkenyl) amines, substituted cycloalkenyl amines, disubstituted cycloalkenyl amine, trisubstituted cycloalkenyl amines, aryl amines, diaryl amines, triaryl amines, heteroaryl amines, diheteroaryl amines, triheteroaryl amines, heterocyclic amines, diheterocyclic amines, triheterocyclic amines, mixed di- and tri-amines where at least two of the substituents on the amine are different and are selected from the group consisting of alkyl, substituted alkyl, alkenyl, substituted alkenyl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, aryl, heteroaryl, heterocyclic, and the like. Also included are amines where the two or three substituents, together with the amino nitrogen, form a heterocyclic or heteroaryl group. Examples of suitable amines include, by way of example only, isopropylamine, trimethyl amine, diethyl amine,

tri(iso-propyl) amine, tri(n-propyl) amine, ethanolamine, 2-dimethylaminoethanol, tromethamine, lysine, arginine, histidine, caffeine, procaine, hydrabamine, choline, betaine, ethylenediamine, glucosamine, N-alkylglucamines, theobromine, purines, piperazine, piperidine, morpholine, N-ethylpiperidine, and the like. It should also be understood that other carboxylic acid derivatives would be useful in the practice of this invention, for example, carboxylic acid amides, including carboxamides, lower alkyl carboxamides, dialkyl carboxamides, and the like.

Pharmaceutically acceptable acid addition salts may be prepared from inorganic and organic acids. Salts derived from inorganic acids include hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, and the like. Salts derived from organic acids include acetic acid, propionic acid, glycolic acid, pyruvic acid, oxalic acid, malic acid, malonic acid, succinic acid, maleic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, p-toluene-sulfonic acid, salicylic acid, and the like.

The present invention is also directed to pharmaceutical compositions comprising the compounds of the present invention. More particularly, such compounds can be formulated as pharmaceutical compositions using standard pharmaceutically acceptable carriers, fillers, solubilizing agents and stabilizers known to those skilled in the art. For example, a pharmaceutical composition comprising a compound of the invention, or analog, derivative, or modification thereof, as described herein, is used to administer the appropriate compound to a subject.

Pharmaceutical compositions comprising the a compound of the invention are administered to a subject in need thereof by any number of routes and means including, but not limited to, topical, oral, buccal, intravenous, intramuscular, intra arterial, intramedullary, intrathecal, intraventricular, transdermal, subcutaneous, intraperitoneal, intranasal, enteral, topical, sublingual, vaginal, ophthalmic, pulmonary, or rectal means. The oral route is typically employed for most conditions requiring the compounds of the invention. Preference is given to intravenous injection or infusion for the acute treatments. For maintenance regimens, the oral or parenteral, e.g. intramuscular or subcutaneous, route is preferred.

In accordance with one embodiment, a composition is provided that comprises a compound of the invention, or an analog, derivative, or modification thereof, and albumin, more particularly, the composition comprises a compound of the present invention, a pharmaceutically acceptable carrier and 0.1-1.0% albumin. Albumin
5 functions as a buffer and improves the solubility of the compounds. In one aspect, albumin is not added.

In one embodiment, the pharmaceutical compositions useful for practicing the invention may be administered to deliver a dose of between 1 ng/kg/day and 100 mg/kg/day. In another embodiment, the pharmaceutical compositions useful for
10 practicing the invention may be administered to deliver a dose of between 1 ng/kg/day and 100 g/kg/day.

Pharmaceutically acceptable carriers which are useful include, but are not limited to, glycerol, water, saline, ethanol, and other pharmaceutically acceptable salt solutions such as phosphates and salts of organic acids. Examples of these and other
15 pharmaceutically acceptable carriers are described in Remington's Pharmaceutical Sciences (1991, Mack Publication Co., New Jersey).

The pharmaceutical compositions may be prepared, packaged, or sold in the form of a sterile injectable aqueous or oily suspension or solution. This suspension or solution may be formulated according to the known art, and may comprise, in addition
20 to the active ingredient, additional ingredients such as the dispersing agents, wetting agents, or suspending agents described herein. Such sterile injectable formulations may be prepared using a non toxic parenterally acceptable diluent or solvent, such as water or 1,3 butane diol, for example. Other acceptable diluents and solvents include, but are not limited to, Ringer's solution, isotonic sodium chloride solution, and fixed oils such
25 as synthetic mono- or di-glycerides.

Compounds which are identified using any of the methods described herein may be formulated and administered to a subject for treatment of any of the diseases and disorders described herein. However, the use of compounds of the invention should not be construed to include only the diseases and disorder described herein. Preferably, the
30 subject is a human.

The formulations of the pharmaceutical compositions described herein may be prepared by any method known or hereafter developed in the art of pharmacology. In general, such preparatory methods include the step of bringing the active ingredient into association with a carrier or one or more other accessory ingredients, and then, if
5 necessary or desirable, shaping or packaging the product into a desired single- or multi-dose unit.

Although the descriptions of pharmaceutical compositions provided herein are principally directed to pharmaceutical compositions which are suitable for ethical administration to humans, it will be understood by the skilled artisan that such
10 compositions are generally suitable for administration to animals of all sorts.

Modification of pharmaceutical compositions suitable for administration to humans in order to render the compositions suitable for administration to various animals is well understood, and the ordinarily skilled veterinary pharmacologist can design and perform such modification with merely ordinary, if any, experimentation.
15 Subjects to which administration of the pharmaceutical compositions of the invention is contemplated include, but are not limited to, humans and other primates, and mammals, including commercially relevant mammals such as cattle, pigs, horses, sheep, cats, and dogs.

A pharmaceutical composition of the invention may be prepared, packaged, or
20 sold in bulk, as a single unit dose, or as a plurality of single unit doses. As used herein, a "unit dose" is a discrete amount of the pharmaceutical composition comprising a predetermined amount of the active ingredient. The amount of the active ingredient is generally equal to the dosage of the active ingredient which would be administered to a subject or a convenient fraction of such a dosage such as, for example, one-half or one-
25 third of such a dosage.

The relative amounts of the active ingredient, the pharmaceutically acceptable carrier, and any additional ingredients in a pharmaceutical composition of the invention will vary, depending upon the identity, size, and condition of the subject treated and further depending upon the route by which the composition is to be administered. By
30 way of example, the composition may comprise between 0.1% and 100% (w/w) active

ingredient.

In addition to the active ingredient, a pharmaceutical composition of the invention may further comprise one or more additional pharmaceutically active agents. Particularly contemplated additional agents include anti-emetics and scavengers such as cyanide and cyanate scavengers.

Controlled- or sustained-release formulations of a pharmaceutical composition of the invention may be made using conventional technology.

In some cases, the dosage forms to be used can be provided as slow or controlled-release of one or more active ingredients therein using, for example, hydropropylmethyl cellulose, other polymer matrices, gels, permeable membranes, osmotic systems, multilayer coatings, microparticles, liposomes, or microspheres or a combination thereof to provide the desired release profile in varying proportions. Suitable controlled-release formulations known to those of ordinary skill in the art, including those described herein, can be readily selected for use with the pharmaceutical compositions of the invention. Thus, single unit dosage forms suitable for oral administration, such as tablets, capsules, gelcaps, and caplets that are adapted for controlled-release are encompassed by the present invention.

Most controlled-release formulations are designed to initially release an amount of drug that promptly produces the desired therapeutic effect, and gradually and continually release of other amounts of drug to maintain this level of therapeutic effect over an extended period of time. In order to maintain this constant level of drug in the body, the drug must be released from the dosage form at a rate that will replace the amount of drug being metabolized and excreted from the body.

Controlled-release of an active ingredient can be stimulated by various inducers, for example pH, temperature, enzymes, water, or other physiological conditions or compounds.

Powdered and granular formulations of a pharmaceutical preparation of the invention may be prepared using known methods. Such formulations may be administered directly to a subject, used, for example, to form tablets, to fill capsules, or to prepare an aqueous or oily suspension or solution by addition of an aqueous or oily

vehicle thereto. Each of these formulations may further comprise one or more of dispersing or wetting agent, a suspending agent, and a preservative. Additional excipients, such as fillers and sweetening, flavoring, or coloring agents, may also be included in these formulations.

5 As used herein, an "oily" liquid is one which comprises a carbon-containing liquid molecule and which exhibits a less polar character than water.

A formulation of a pharmaceutical composition of the invention suitable for oral administration may be prepared, packaged, or sold in the form of a discrete solid dose unit including, but not limited to, a tablet, a hard or soft capsule, a cachet, a troche, or a
10 lozenge, each containing a predetermined amount of the active ingredient. Other formulations suitable for oral administration include, but are not limited to, a powdered or granular formulation, an aqueous or oily suspension, an aqueous or oily solution, a paste, a gel, a toothpaste, a mouthwash, a coating, an oral rinse, or an emulsion. The terms oral rinse and mouthwash are used interchangeably herein.

15 A tablet comprising the active ingredient may, for example, be made by compressing or molding the active ingredient, optionally with one or more additional ingredients. Compressed tablets may be prepared by compressing, in a suitable device, the active ingredient in a free flowing form such as a powder or granular preparation, optionally mixed with one or more of a binder, a lubricant, an excipient, a surface-active
20 agent, and a dispersing agent. Molded tablets may be made by molding, in a suitable device, a mixture of the active ingredient, a pharmaceutically acceptable carrier, and at least sufficient liquid to moisten the mixture. Pharmaceutically acceptable excipients used in the manufacture of tablets include, but are not limited to, inert diluents, granulating and disintegrating agents, binding agents, and lubricating agents. Known
25 dispersing agents include, but are not limited to, potato starch and sodium starch glycollate. Known surface-active agents include, but are not limited to, sodium lauryl sulphate. Known diluents include, but are not limited to, calcium carbonate, sodium carbonate, lactose, microcrystalline cellulose, calcium phosphate, calcium hydrogen phosphate, and sodium phosphate. Known granulating and disintegrating agents
30 include, but are not limited to, corn starch and alginic acid. Known binding agents

include, but are not limited to, gelatin, acacia, pre-gelatinized maize starch, polyvinylpyrrolidone, and hydroxypropyl methylcellulose. Known lubricating agents include, but are not limited to, magnesium stearate, stearic acid, silica, and talc.

Tablets may be non-coated or they may be coated using known methods to achieve delayed disintegration in the gastrointestinal tract of a subject, thereby providing sustained release and absorption of the active ingredient. By way of example, a material such as glyceryl monostearate or glyceryl distearate may be used to coat tablets. Further by way of example, tablets may be coated using methods described in U.S. Patents numbers 4,256,108; 4,160,452; and 4,265,874 to form osmotically-controlled release tablets. Tablets may further comprise a sweetening agent, a flavoring agent, a coloring agent, a preservative, or some combination of these in order to provide for pharmaceutically elegant and palatable preparation.

Hard capsules comprising the active ingredient may be made using a physiologically degradable composition, such as gelatin. Such hard capsules comprise the active ingredient, and may further comprise additional ingredients including, for example, an inert solid diluent such as calcium carbonate, calcium phosphate, or kaolin.

Soft gelatin capsules comprising the active ingredient may be made using a physiologically degradable composition, such as gelatin. Such soft capsules comprise the active ingredient, which may be mixed with water or an oil medium such as peanut oil, liquid paraffin, or olive oil.

Liquid formulations of a pharmaceutical composition of the invention which are suitable for oral administration may be prepared, packaged, and sold either in liquid form or in the form of a dry product intended for reconstitution with water or another suitable vehicle prior to use.

Injectable formulations may be prepared, packaged, or sold in unit dosage form, such as in ampules or in multi dose containers containing a preservative. Formulations for parenteral administration include, but are not limited to, suspensions, solutions, emulsions in oily or aqueous vehicles, pastes, and implantable sustained-release or biodegradable formulations. Such formulations may further comprise one or more additional ingredients including, but not limited to, suspending, stabilizing, or

dispersing agents. In one embodiment of a formulation for parenteral administration, the active ingredient is provided in dry (i.e., powder or granular) form for reconstitution with a suitable vehicle (e.g., sterile pyrogen free water) prior to parenteral administration of the reconstituted composition.

5 A pharmaceutical composition of the invention may be prepared, packaged, or sold in a formulation suitable for buccal administration. Such formulations may, for example, be in the form of tablets or lozenges made using conventional methods, and may, for example, 0.1 to 20% (w/w) active ingredient, the balance comprising an orally dissolvable or degradable composition and, optionally, one or more of the additional
10 ingredients described herein. Alternately, formulations suitable for buccal administration may comprise a powder or an aerosolized or atomized solution or suspension comprising the active ingredient. Such powdered, aerosolized, or aerosolized formulations, when dispersed, preferably have an average particle or droplet size in the range from about 0.1 to about 200 nanometers, and may further comprise one
15 or more of the additional ingredients described herein.

As used herein, "additional ingredients" include, but are not limited to, one or more of the following: excipients; surface active agents; dispersing agents; inert diluents; granulating and disintegrating agents; binding agents; lubricating agents; sweetening agents; flavoring agents; coloring agents; preservatives; physiologically
20 degradable compositions such as gelatin; aqueous vehicles and solvents; oily vehicles and solvents; suspending agents; dispersing or wetting agents; emulsifying agents, demulcents; buffers; salts; thickening agents; fillers; emulsifying agents; antioxidants; antibiotics; antifungal agents; stabilizing agents; and pharmaceutically acceptable polymeric or hydrophobic materials. See Genaro, ed., 1985, Remington's
25 Pharmaceutical Sciences, Mack Publishing Co., Easton, PA, which is incorporated herein by reference.

The compound can be administered to a subject as frequently as several times daily, or it may be administered less frequently, such as twice a day (b.i.d.), once a day (q.i.d.), once a week, once every two weeks, once a month, or even less frequently, such
30 as once every several months or even once a year or less. The frequency of the dose will

be readily apparent to the skilled artisan and will depend upon any number of factors, such as, but not limited to, the type and severity of the disease being treated, the type, and age of the subject, etc.

5 The invention also provides a pharmaceutical pack or kit comprising one or more containers filled with one or more of the ingredients of the pharmaceutical compositions of the invention. In accordance with one embodiment, a kit is provided for treating a subject in need of immuno-modulation. Preferably, the subject is a human. In one embodiment, the kit comprises one or more of the analogs or derivatives of the present invention and may also include one or more known immuno-suppressants.

10 These pharmaceuticals can be packaged in a variety of containers, e.g., vials, tubes, microtiter well plates, bottles, and the like. Other reagents can be included in separate containers and provided with the kit; e.g., positive control samples, negative control samples, buffers, cell culture media, etc. Preferably, the kits will also include instructions for use.

15 Although any methods and materials similar or equivalent to those described herein can be used in the practice or testing of the present invention, the preferred methods and materials are described herein.

 One skilled in the art will readily appreciate that the present invention is well adapted to carry out the objects and obtain the ends and advantages mentioned, as well

20 as those inherent therein. The present invention may be embodied in other specific forms without departing from the spirit or essential attributes thereof and, accordingly, reference should be made to the appended claims, rather than to the foregoing specification, as indicating the scope of the invention.

25 Examples

 The invention is now described with reference to the following Examples and Embodiments. Without further description, it is believed that one of ordinary skill in the art can, using the preceding description and the following illustrative examples, make and utilize the present invention and practice the claimed methods. The following

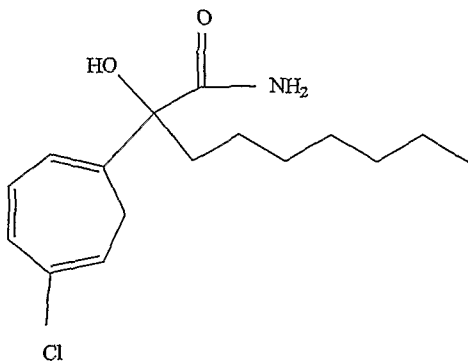
30 working examples therefore, are provided for the purpose of illustration only and

specifically point out some embodiments of the present invention, and are not to be construed as limiting in any way the remainder of the disclosure. Therefore, the examples should be construed to encompass any and all variations which become evident as a result of the teaching provided herein.

5 **Example 1**

Methods

 All experiments were approved by the institutional animal care and use committee. Animals of the SHR (model for OAB) and WKY (control), as well as animals with partial urethral ligation (OBS) or sham surgery prepared for voiding
10 function studies by placing intravesical catheters for cystometry and intraperitoneal catheters for drug administration. Three days following surgery, studies were performed in awake, unrestrained animals with normal saline infusion (10 ml/hr). Animals were randomized to receive vehicle or 30, 100 or 300 mg/kg of ICM-I-136. ICM-I-136 has the general structure as described in Lenkowski et al.:



15

 The randomization scheme was established as a blind scheme. Basal pressure (BP), premicturition pressure (PreMP), Maximum pressure (MP), intercontraction interval (ICI), voided volume (VV), and postvoid residual volume (RU) were recorded.
20 In each animal, results after treatment were compared to results obtained after a stable baseline voiding pattern was achieved.

Results

 In SHR, intraperitoneal treatment with 300 mg/kg ICM-I-136 (N=5) resulted in a 22.5% reduction in maximum pressure, a 63.2% increase in intercontraction interval,
25 and a 58.8% increase in voided volume (p<0.05; see Figure 1 and Table 1). Similar

effects on voiding function were observed after treatment with 100 mg/kg ICM-I-136 (N=6); however, results did not reach statistical significance. No effects on voiding function were observed after treatment with vehicle (N=5) and 30 mg/Kg ICM-I-136 (N=6; see Figure 1).

5

Table 1. Effects of intraperitoneal administration of ICM-I-136 (300 mg/kg) on voiding of SHR and WKY

	SHR (n=5)			WKY (n=6)		
	Baseline	Treatment	Mean % changes	Baseline	Treatment	Mean % changes
Basal Pr. (cm H ₂ O)	24.8±12.2	19.7±8.7 *	-20.5%	13.7±4.2	11.3±2.6 *	-17.5%
Maximum Pr. (cm H ₂ O)	70.6±6.1	54.2±15.1*	-23.2%	45.1±14.8	32.5±11.3 *	-27.9%
Intercontraction interval (sec.)	72.4±19.4	106.2±12.7 *	46.8%	236.1±43.1	235.1±33.5	-0.4%
Voided volume (ml)	0.19±0.07	0.26±0.04*	34.6%	0.69±0.12	0.68±0.09	-1.6%

* P< 0.05 on Wilcoxon Signed Ranks Test

10

In WKY, modest reductions in maximum pressure were observed with minimal effects noted on intercontraction interval and voided volume. Effects were most pronounced after treatment with 300 mg/kg ICM-I-136 (N=6) where micturition pressure was reduced by 27.9% (P<0.05; see Figure 2 and Table 1). After cystometry, all rats had minimal post void residual volumes regardless of treatment type.

15

In SHR and OBS rats, intraperitoneal administration of high-dose (300 mg/kg) ICM-I-136 decreased maximum pressure and increased intercontraction interval and voided volume in a dose-dependent manner. In WKY and SHAM surgery rats, administration of ICM-I-136 decreased the maximum pressure in a dose-dependent manner, however, no significant effects on intercontraction interval and voided volume were observed. These results suggest that systemic treatment with Na channel blockers such as ICM-I-136 may be effective in the treatment of overactive bladder.

20

Intraperitoneal administration of the novel Na channel blocker ICM-I-136

reduced detrusor overactivity in both the SHR and OBS models. These results support the hypothesis that Na channels may play a role in the pathogenesis of afferent plasticity giving rise to detrusor overactivity and aberrant urinary frequency. The present application is the first to disclose that systemic administration of a Na channel blocker is
5 useful for treatment of detrusor overactivity.

Example 2- Effects of ICM-I-136 on detrusor overactivity (DO) in a rat model of bladder outlet obstruction (BOO)

The next study was designed to examine the effects of systemically administered ICM-I-136, a Na channel blocker, on DO in a rat model of BOO created by partial
10 urethral ligation (PUL).

Methods

PUL was created in female Wister-Kyoto rats. After 3 weeks, cystometry experiments were performed in awake, unrestrained animals with saline infusion (10 ml/hr). Intravesical and intraperitoneal (i.p.) catheters were placed 3 days prior. After a
15 stable voiding pattern was achieved (30-45 min), animals received either: vehicle, 30, 100 or 300 mg/kg of ICM-I-136 via i.p. injection. Basal pressure (BP), maximum pressure (MP), intercontraction interval (ICI), voided volume (VV), and postvoid residual volume (RV) were recorded. Rats were grouped according to baseline voiding frequency (less than 2 voids/10 min vs. 2 or more voids/10 min). Drug effects were
20 compared between non-frequent voiders (NF) and frequent voiders (F).

Results

ICM-I-136 was well tolerated with no gross toxicity or motor impairment. Bladder hypertrophy was similar in NF and F groups based on bladder weights. In the F group (N=6), 300 mg/kg ICM-I-136 resulted in a 24.1% reduction in BP, a 26.3%
25 reduction in MP, a 26.6% increase in ICI, and a 25.6% increase in VV ($p < 0.05$). Similar effects were seen with 100 mg/kg ICM-I-136 ($n=6$); however, no effects were observed after treatment with 30 mg/kg ($n=5$) or vehicle ($n=5$). In the NF group, small statistically insignificant reductions in BP, MP, ICI and VV were observed after treatment with 300 mg/Kg ($n=5$), 100 mg/kg ($n=6$) and 30 mg/kg ($n=6$). No effects on
30 voiding function were observed after treatment with vehicle (N=6). After cystometry,

measured RV of the F and NF group were approximately 20% of VV and did not differ between groups or vary with treatment doses.

Conclusion

These results demonstrate that ICM-I-136 reduced DO in a rat model of BOO.
5 Significant effects were identified only in animals displaying elevated baseline voiding frequency. Clinically, BOO associated with conditions such as BPH also induces a variable spectrum of storage symptoms. Therefore, this work is an important first step in the identification of novel drugs possibly targeting afferents that can selectively treat these symptoms.

10 The disclosures of each and every patent, patent application, and publication cited herein are hereby incorporated by reference herein in their entirety. One of skill in the art will appreciate that the superiority of the compositions and methods of the invention relative to the compositions and methods of the prior art are unrelated to the physiological accuracy of the theory explaining the superior results.

15 Headings are included herein for reference and to aid in locating certain sections. These headings are not intended to limit the scope of the concepts described therein under, and these concepts may have applicability in other sections throughout the entire specification.

Other methods which were used but not described herein are well known and
20 within the competence of one of ordinary skill in the art of clinical, chemical, cellular, histochemical, biochemical, molecular biology, microbiology and recombinant DNA techniques.

The description of the disclosed embodiments is provided to enable any person skilled in the art to make or use the present invention. Various modifications to these
25 embodiments will be readily apparent to those skilled in the art, and the generic principles defined herein may be applied to other embodiments without departing from the spirit or scope of the invention. Accordingly, the present invention is not intended to be limited to the embodiments shown herein but is to be accorded the widest scope consistent with the principles and novel features disclosed herein.

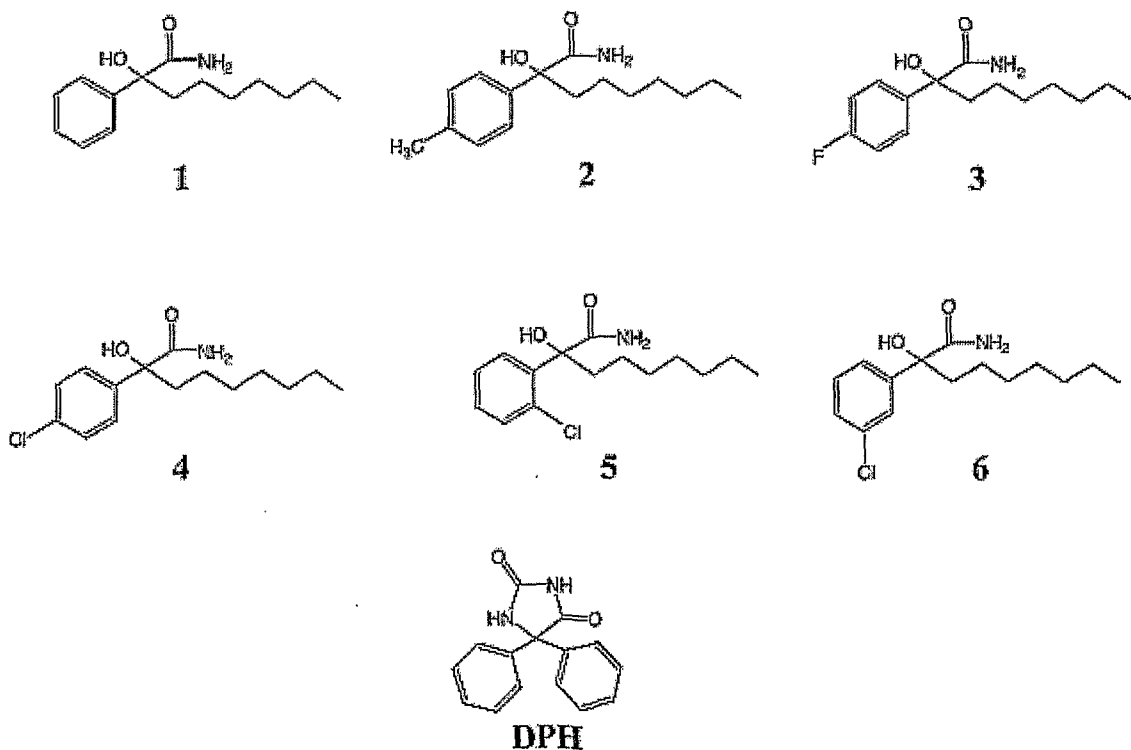
Claims

What is claimed is:

- 5 1. A method of treating an overactive bladder or detrusor overactivity in a subject having a disease, condition, or disorder characterized by an overactive bladder or detrusor overactivity, said method comprising administering to said subject a pharmaceutical composition comprising a therapeutically effective amount of at least one compound, or analog, derivative, or modification thereof, wherein said compound is
10 a sodium channel blocker, thereby treating overactive bladder or detrusor overactivity in said subject.

2. The method of claim 1, wherein said compound is selected from the group consisting of

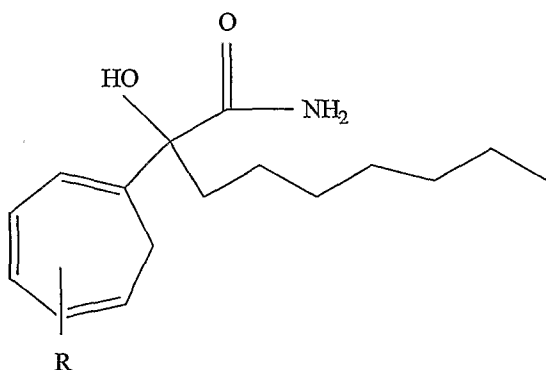
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or an analog, derivative, or modification thereof.

3. The method of claim 1, wherein said compound is an alpha-hydroxyamide, or an analog, derivative, or modification thereof.

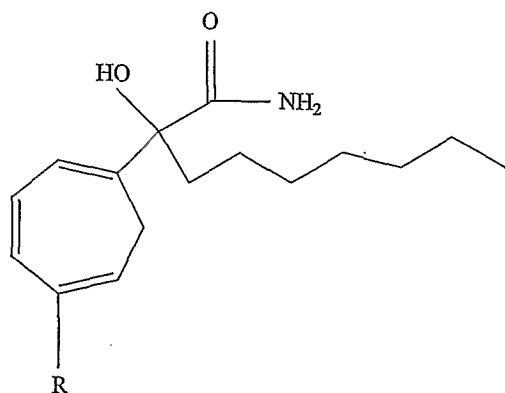
5 4. The method of claim 3, wherein said compound is



10 wherein R is selected from the group consisting of halogen, H, and H₃C, or an analog, derivative, or modification thereof.

5. The method of claim 4, wherein said halogen is chlorine.

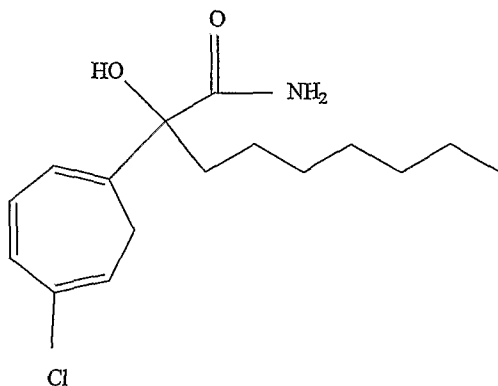
15 6. The method of claim 4, wherein the compound is



wherein R is selected from the group consisting of halogen, H, and H₃C,

or an analog, derivative, or modification thereof.

7. The method of claim 6, wherein said compound is ICM-I-136:



or an analog, derivative, or modification thereof.

8. The method of claim 1, wherein said subject is a human.

9. The method of claim 1, wherein said overactive bladder is characterized by at least one symptom or sign selected from the group consisting of urethral obstruction, increased maximum pressure, increased basal pressure, increased voiding frequency, decreased intercontraction interval, increased urgency, nocturia, urge incontinence, and decreased voided volume.

10. The method of claim 9, wherein said treatment alleviates at least one symptom or sign selected from the group consisting of urethral obstruction, increased maximum pressure, increased basal pressure, increased voiding frequency, decreased intercontraction interval, increased urgency, nocturia, urge incontinence and decreased voided volume.

11. The method of claim 1, wherein said detrusor overactivity is characterized by at least one symptom or sign selected from the group consisting of urethral

obstruction, increased maximum pressure, increased basal pressure, increased voiding frequency, decreased intercontraction interval, increased urgency, nocturia, urge incontinence and decreased voided volume.

5 12. The method of claim 11, wherein said treatment alleviates at least one symptom or sign selected from the group consisting of urethral obstruction, increased maximum pressure, increased basal pressure, increased voiding frequency, decreased intercontraction interval, increased urgency, nocturia, urge incontinence and decreased voided volume.

10

 13. The method of claim 1, wherein said pharmaceutical composition is administered via a route selected from the group consisting of topical, oral, buccal, intravenous, intramuscular, intra-arterial, intramedullary, intrathecal, intraventricular, transdermal, subcutaneous, intraperitoneal, intranasal, enteral, sublingual, vaginal, 15 ophthalmic, pulmonary, and rectal.

 14. The method of claim 13, wherein said route is oral.

 15. The method of claim 1, wherein said sodium channel is Nav1.5.

20

 16. The method of claim 1, wherein said overactive bladder or detrusor overactivity is associated with a disease, disorder, or condition selected from the group consisting of benign prostatic hyperplasia, nocturia, painful bladder syndrome, overactive bladder syndrome, stroke, Parkinson's disease, spinal cord injury, depression, 25 anxiety, feeding disturbances, pain, irritable bowel syndrome, fibromyalgia, interstitial cystitis, and multiple sclerosis.

30

 17. The method of claim 16, wherein said disease, disorder, or condition is overactive bladder syndrome.

18. The method of claim 1, wherein said detrusor overactivity is selected from the group consisting of neurogenic detrusor overactivity (NDO) and idiopathic detrusor overactivity (IDO).

5 19. The method of claim 1, wherein said compound is administered at a dose of about 30 mg/kg to about 1,000 mg/kg.

 20. A kit for administering a pharmaceutical composition to a subject to treat an overactive bladder or detrusor overactivity in a subject in need thereof, said kit
10 comprising a pharmaceutical composition comprising at least one compound of claim 1, an applicator, and an instructional material for the use thereof.

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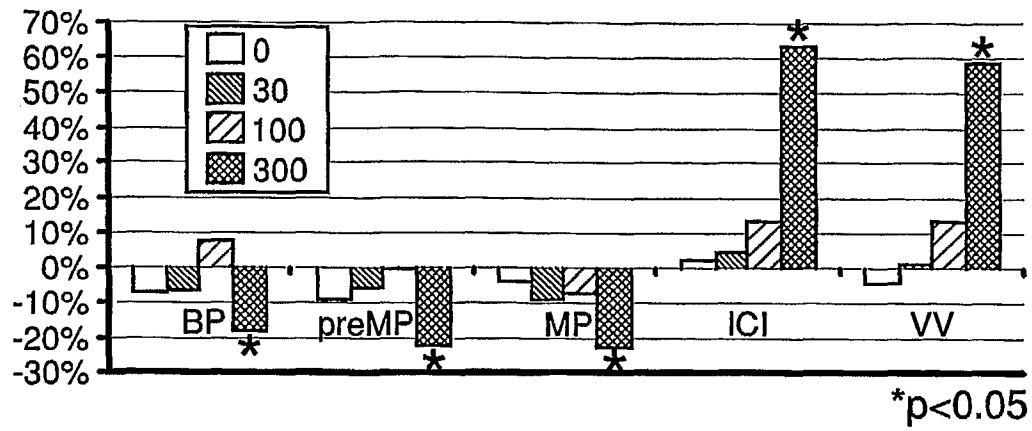


FIG. 1

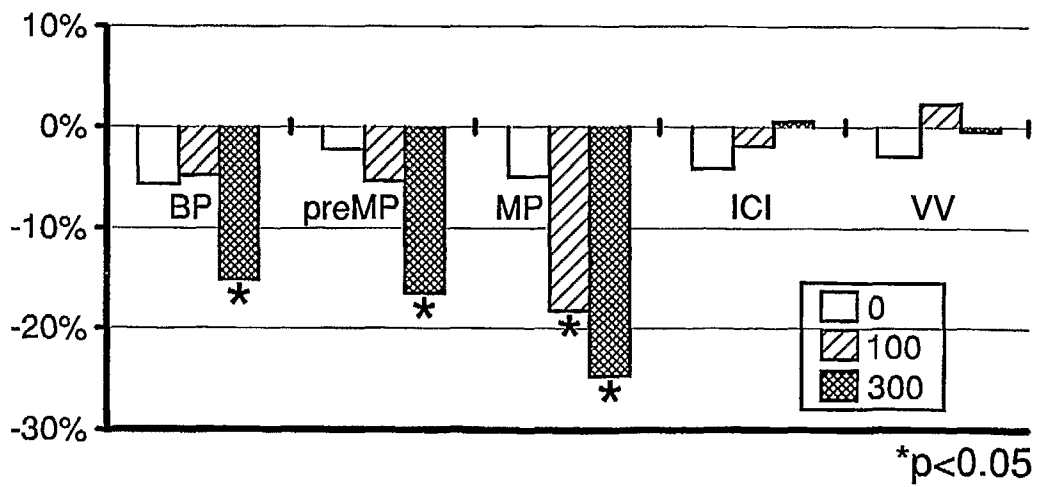


FIG. 2

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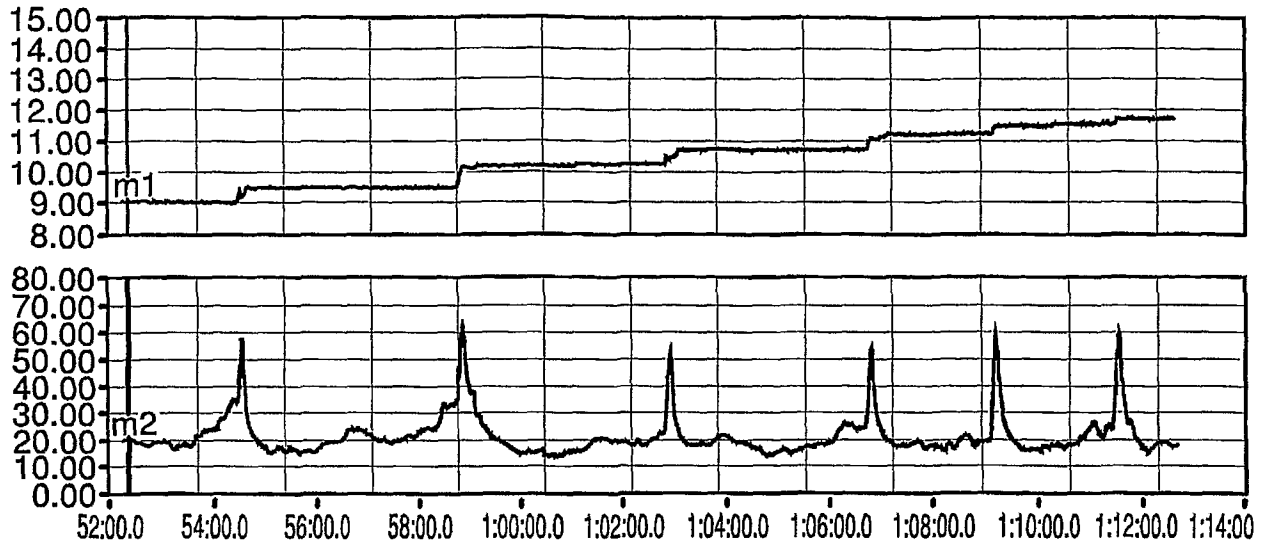


FIG. 3A

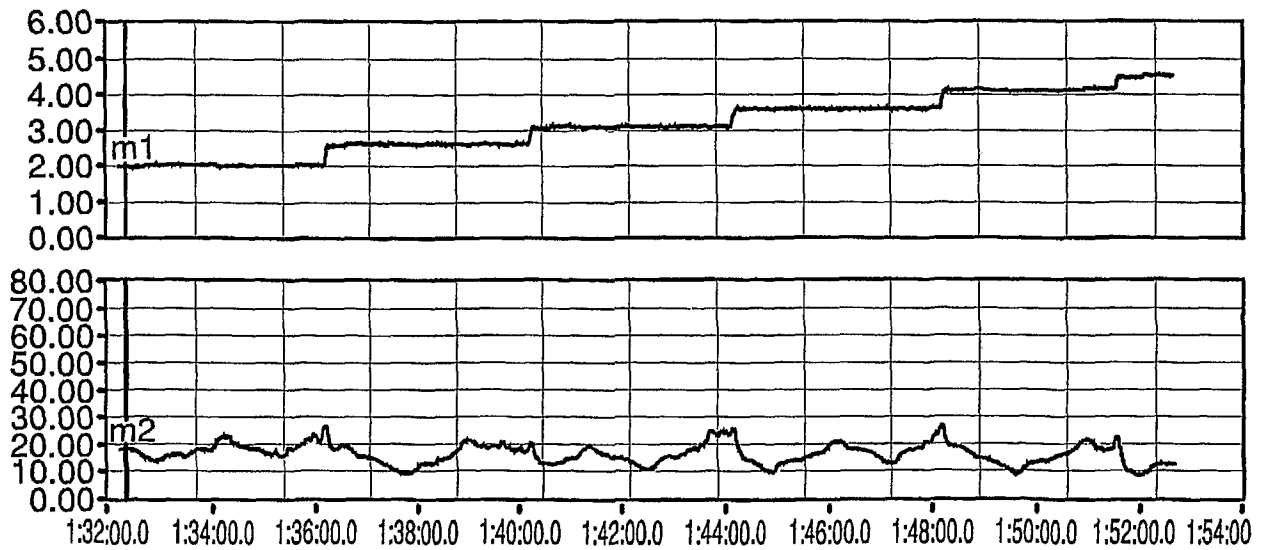


FIG. 3B

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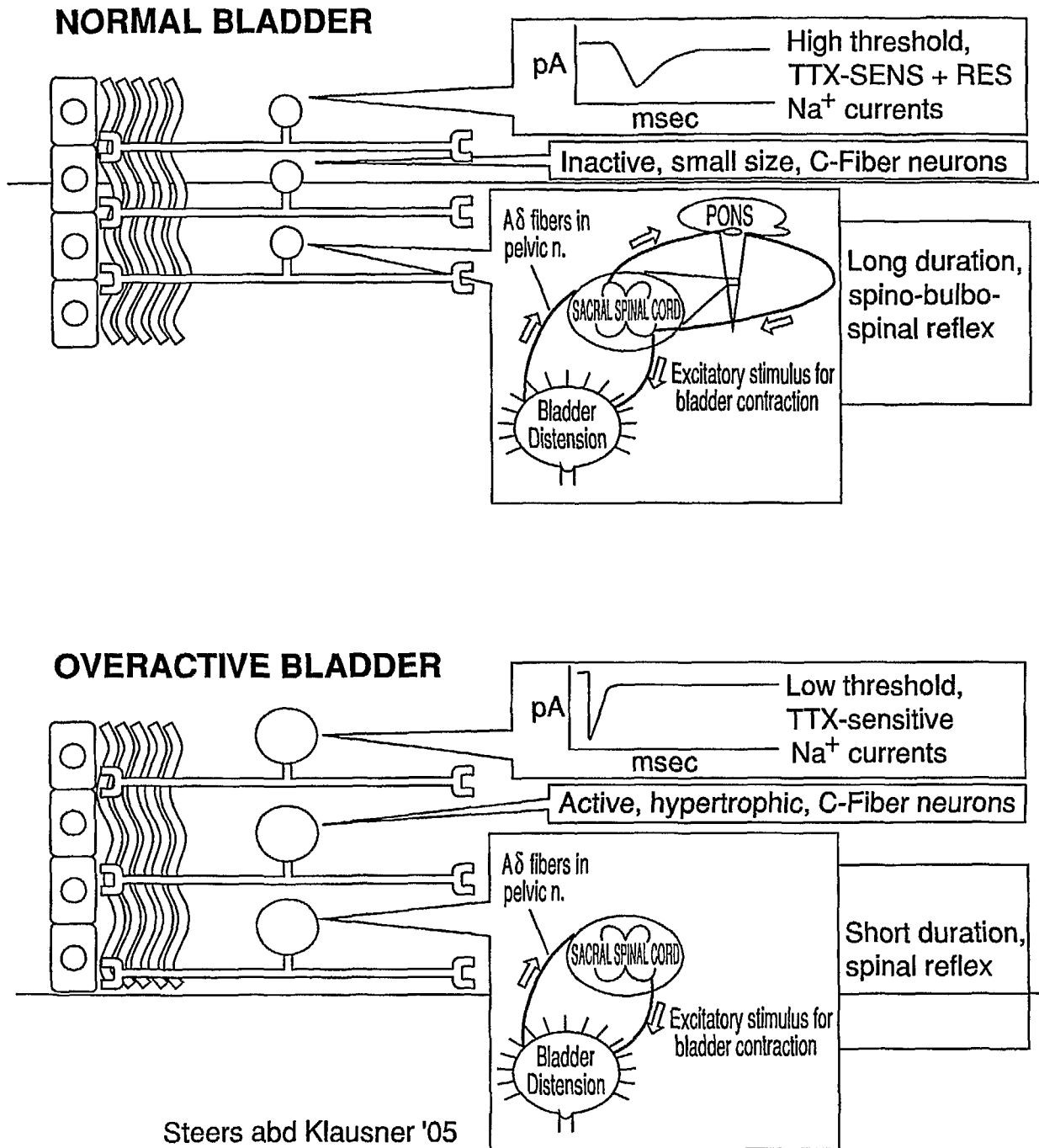


FIG. 4