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(54) Title: VANILLOID RECEPTOR ANTAGONISTS, AND METHODS OF MAKING AND USING THEM

(57) Abstract: One aspect of the invention relates to antagonists of mammalian vanilloid receptors. Another aspect of the invention relates to a method of modulating the activity of a vanilloid receptor in a mammal, comprising administering a compound of the invention. A third aspect of the invention relates to a method of treating a mammal suffering from pain associated with a malady selected from the group consisting of bladder hyperreflexia, detrusor instability, post-mastectomy pain, mucositis, interstitial cystitis, pharyngitis, pancreatitis, enteritis, cellulitis, postherpetic neuralgia, peripheral neuropathy, arthritis, and bony fractures, comprising administering a compound of the invention.

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VANILLOID RECEPTOR ANTAGONISTS, AND METHODS OF MAKING AND USING THEM

Related Applications

This application claims the benefit of the filing date of United States Provisional Patent Application serial number 60/471,210, filed May 16, 2003.

Background of the Invention

The concentration of free Ca^{+2} in the cytosol of any cell is extremely low (approximately 10^{-7} M), whereas the concentration of free Ca^{+2} in the extracellular fluid (approximately 10^{-3} M) and in the endoplasmic reticulum is quite high. Thus, there is a large gradient tending to drive Ca^{+2} into the cytosol across both the plasma membrane and the endoplasmic reticulum membrane. It is believed that when a signal transiently opens Ca^{+2} channels in either of these membranes, Ca^{+2} rushes into the cytosol, dramatically increasing the local Ca^{+2} concentration and triggering Ca^{+2} -responsive proteins in the cell. Ca^{+2} has been demonstrated to act as an intracellular messenger in a wide variety of cellular responses, such as, for example, transmission of an action potential in nerve cells, muscular contraction, and cell secretion, activation, survival, proliferation, migration, and differentiation.

Pain is initiated when a subgroup of sensory neurons, called nociceptors, are activated by noxious chemical, thermal or mechanical stimuli. The activated nociceptors convey information regarding the noxious stimuli to pain processing centers in the spinal cord and brain. Fields, H., *Pain*, McGraw-Hill, New York, **1987**. Nociceptors are characterized in part, by their sensitivity to vanilloids (i.e., chemicals containing vanillyl groups), such as, for example, capsaicin, the main pungent ingredient in capsaicin peppers. In mammals, exposure of nociceptor terminals to capsaicin leads to excitation of the neuron and the consequent perception of pain and local release of inflammatory mediators. Prolonged exposure of nociceptor terminals to capsaicin leads to the desensitization of these neurons to capsaicin and other noxious stimuli. Szolcsanyi, Y., *Capsaicin and the Study of Pain*, ed. Wood J., 255-272, Academic, London, **1993**. This phenomenon of desensitization has led to the use of capsaicin as an analgesic agent in the treatment of painful disorders ranging from viral and diabetic neuropathies to rheumatoid arthritis. Campbell, E.,

Capsaicin and the Study of Pain, ed. Wood J., 255-272, Academic, London, **1993**; Szallasi et al., *Pain* 68:195-208, **1996**.

Recently, a cDNA encoding vanilloid receptor subtype-1 (VR1), has been isolated from a rodent dorsal root ganglion plasmid cDNA library. Caterina et al., *Nature* 389:816-824 **1997**. This clone encodes a polytopic integral membrane protein containing six transmembrane domains, four extracellular domains, four intracellular domains, and an additional short hydrophobic region between transmembrane domains five and six that may contribute to an ion permeation path. Hardie et al., Trends *Neurosci.* 16:371-376, **1993**. The product of this clone is a calcium permeable, non-selective cation channel that is structurally related to members of the TRP family of ion channels. See, e.g., Montell et al., *Neuron* 2:1313-1333, **1989**; and Hardie et al., *Trends Neurosci.* 16:371-376, **1993**.

VR1 is activated (i.e., the VR1 cation-selective channel is opened), by capsaicin, capsaicin agonists, and other vanilloid compounds (e.g., resiniferatoxin), and antagonized by capsaicin antagonists (e.g., capsazepine and ruthenium red). Further, hydrogen ions potentiate the response of VR1 to low concentrations of capsaicin: thus, VR1 may be involved in the detection of noxious stimuli that accompany such conditions as inflammation and ischemia. Caterina et al, *Nature* 389:819-824, **1997**.

Additionally, VR1 is activated when ambient temperatures are elevated to elicit pain in humans or pain associated behaviors in animals, indicating that, in addition to its role in transducing noxious chemical stimuli, VR1 functions as a transducer of painful thermal stimuli in vivo. Caterina et al., *Nature* 389:816-824, **1997**.

The involvement of a vanilloid receptor family member in transducing thermal and chemical stimuli suggests that members of this family of cation channels are involved in diverse human disease states ranging from congenital pain insensitivity, to chronic pain syndromes and more generally that members of this family mediate cellular responses such as cell secretion, activation, survival, proliferation, migration and differentiation; that vanilloid receptor family members provide an important model system for the in vitro study of hyperalgesia; and that vanilloid receptors provide defined targets for the development of new analgesic agents.

Summary of the Invention

In another embodiment, the compounds of the present invention are vanilloid receptor modifiers. In another embodiment, the compounds of the present invention are vanilloid receptor antagonists. In another embodiment, the compounds of the present invention are vanilloid receptor agonists.

In part, the present invention relates to a method of changing a vanilloid receptor antagonist to an agonist, or a vanilloid receptor agonist to an antagonist, comprising substituting an iodide substituent on either the antagonist or agonist with an acetylenic group.

In part, the present invention relates to a pharmaceutical composition comprising a compound of the present invention and a pharmaceutical carrier.

In part, the present invention relates to a pharmaceutical composition comprising a compound of the present invention, wherein the pharmaceutical composition provides effective pain relief in a mammal for 3, 6, 12, 24, 48, 72, or more hours.

In part, the present invention relates to a method of treating a mammal for pain comprising administering to the mammal a compound or composition of the present invention.

The subject compositions may be administered by one of a variety of means known to those of skill in the art. The subject compounds may be prepared as described herein and as known to those of skill in the art.

In one embodiment, the compositions of the present invention have a minimum inhibitory concentration (MIC) of less than 256 μg/mL. In other embodiments, the compositions of the present invention may have a MIC value of less than 128 μg/mL, or even less than 64 μg/mL.

In certain embodiments, the present invention provides pharmaceutical compositions of the present invention, and methods of using the same, for the reduction and abatement of at least one pain disorder or conditions based on a therapeutic regimen. In certain aspects, the present invention contemplates monitoring such disorders or conditions as part of any therapeutic regimen, which may be administered over the short-term and/or

long-term. These aspects of the invention may be particularly helpful in preventive care regimes.

In another aspect of the present invention, the pharmaceutical compositions of the present invention may be used in the manufacture of a medicament to treat pain disorders. In certain embodiments, the present invention is directed to a method for formulating compositions of the present invention in a pharmaceutically acceptable carrier.

In certain embodiments, the pharmaceutical compositions are formulated as a tablet, pill capsule or other appropriate ingestible formulation, to provide a therapeutic dose in 10 tablets or fewer. In another example, a therapeutic dose is provided in 50, 40, 30, 20, 15, 10, 5 or 3 tablets.

In another aspect, the present invention also provides for kits containing at least one dose of a subject composition, and often many doses, and other materials for a treatment regimen. For example, in one embodiment, a kit of the present invention contains sufficient subject composition for from five to thirty days and optionally equipment and supplies necessary to measure one or more indices relevant to the treatment regiment. In another embodiment, kits of the present invention contain all the materials and supplies, including subject compositions, for carrying out any methods of the present invention. In still another embodiment, kits of the present invention, as described above, additionally include instructions for the use and administration of the subject compositions.

The dosage may be selected to assuage pain in a subject in such a way as to provide at least partial relief if not complete relief. The skilled artisan may identify this amount as provided herein as well as by using other methods known in the art.

As explained herein in greater detail, the invention will readily enable the design and implementation of trials in warm-blooded animals, including humans and mammals, necessary for easily determining or tailoring the form and dose for any composition of the present invention.

These embodiments of the present invention, other embodiments, and their features and characteristics, will be apparent from the description, drawings and claims that follow.

Brief Description of the Drawings

Figure 1 depicts vanilloids capsaicin, capsazepine resiniferatoxin, 5-iodo-resiniferatoxin, and the A, B, and C, moieties of compound **1**.

Detailed Description of the Invention

The vanilloid receptor VR1 is a polymodal integrator of noxious stimuli, including low pH, heat, and ligands such as capsaicin, the pungent constituent in red pepper. Caterina, M.J., Schumacher, M.A., Tominaga, M., Rosen, T.A., Levine, J.D., and Julius, D., *Nature*, **1997**, *389*, 816-824; Caterina, M.J., Leffler, A., Malmberg, A.B., Martin, W.J., Trafton, J., Petersen-Zeitz, K.R., Koltzenburg, M., Basbaum, A.I., and Julius, D., *Science*, **2000**, *288*, 306-313; Tominaga, M., Caterina, M.J., Malmberg, A.B., Rosen, T.A., Gilbert, H., Skinner, K., Raumann, B.E., Basbaum, A.I., and Julius, D., *Neuron*, **1998**, *21*, 531-543. Because of its function as a nociceptor, VR1 has attracted much attention as a novel, potential therapeutic target for the treatment of pain and other conditions involving C fiber sensory neurons. Kress, M. and Zeilhofer, H.U., *Trends Pharmacol Sci*, **1999**, *20*, 112-118, Szallasi, A. and Blumberg, P.M., *Pharmacol Rev*, **1999**, *51*, 159-212. Caterina, M.J. and Julius, D., *Annu Rev Neurosci*, **2001**, *24*, 487-517. Such applications include bladder hyperreflexia, detrusor instability, post-mastectomy pain, mucositis, interstitial cystitis, pharyngitis, pancreatitis, enteritis, cellulitis, postherpetic neuralgia, peripheral neuropathy, arthritis, and bony fractures. Robbins, W., *Clin J Pain*, **2000**, *16*, S86-S89.

Among a number of VR agonists studied, only a few compounds are currently marketed (e.g. capsaicin) or undergoing clinical trial (e.g. resiniferatoxin, DA-5018). Wrigglesworth, R.; Walpole, C. S. J., *Drug of the Future*, **1998**, *23*, 531. The primary mechanistic rationale of vanilloids for treatment of pain is through C-fiber desensitization. The initial response of VR1 to vanilliods is to permit a large influx of Ca^{2+} and C-fiber depolarization. Subsequently, depending on dose of vanilloid, time of exposure, and other factors, desnsitization, potentially reflecting multiple mechanisms, develops. For capsaicin, the initial phase of acute stimulation, causing a severe burning sensation, represents the limiting toxicity. Apparently, pungency, reflecting the acute pain response, and the subsequent desensitization are not directly coupled. Thus, the vanilloid resiniferatoxin (RTX) is more potent as a ligand at VR1 but is only modestly more pungent. Szallasi, A.; Blumberg, P. M., *Pharmacol. Rev.*, **1999**, *51*, 159. One direction for drug development, therefore, is design of anlogues in which pungency and desensitization have been dissociated. An inherent advantage/problem in this approach is the potential long duration of desensitization. A single treatment with RTX, for example, can cause desensitization for multiple weeks. Szallasi, A.; Blumberg, P. M., *Pharmacol. Rev.*, **1999**, *51*, 159.

An alternative strategy, optimal when only a short duration of inhibition is desirable, is to block the VR1 function either through a channel blocker specific for VR1 or else through a competitive receptor antagonist. Chizh, B. A.; Dickenson, A. H.; Wnendt, S., *TIPS*, **1999**, *20*, 354; Kress, M.; Zeilhofer, H. U., *TIPS*, **1999**, *20*, 112. This approach has the potential benefit of rapid reversibility. Another characteristic is that antagonism should show greater specificity, since it would not be expected to cause heterologous blockade of other activation pathways for the C fiber neurons. Currently, capsazepine is the only commercially available competitive antagonist for VR1, inhibiting biological responses of capsaicin and RTX in competitive manner in a variety of bioassays. Capsazepine has several drawbacks, such as moderate potency, susceptibility to metabolic clearance, inhibitory activity on several channels other than VR1, and poor solubility. Nonetheless, the inhibition of nociceptive and hyperalgesic responses by capsazepine proves in principle that VR1 antagonists have an analgesic potential. Kwak, J. Y.; Jung, J. Y.; Hwang, S. W.; Lee, W. T.; Oh, U., *Neuroscience*, **1998**, *86*, 619.

It has recently been shown that Iodo-RTX (I-RTX) is the most potent known vanilloid receptor antagonist. Wahl P, Foged C, Tullin S, Thomsen C., *Mol. Pharmacol.* **2001**, *59*(1):9-15. I-RTX has been shown to completely block capsaicin-induced currents (IC_{50} = 3.9 nM). In vivo, I-RTX effectively blocked the pain responses elicited by capsaicin (ED_{50} = 16 ng/mouse, intrathecally). This study thus reveals that I-RTX is at least 40-fold more potent than the previously known VR antagonist, capsazepine. Based in part upon this finding one aspect of the present invention is to explore the effect of iodination on the activity of capsaicin and its analogs.

Based on structure-activity relationships for stimulation of Ca^{2+} uptake by capsaicin derivatives, a model for ligand interaction at the receptor has been proposed in which three pharmacophoric elements, the so-called A, B, and C regions, are crucial for activity (See Figure 1). Szolcsanyi, A.; Jancso-Gabor, A., *Arzneimittel-Forsch*, **1975**, *25*, 1877; Walpole, C. S. J.; Wrigglesworth, R.; Bevan, S. J.; Campell, E. A.; Dray, A.; James, I. F.; Perkins, M. N.; Masdin, K. J.; Winter, J., *J. Med. Chem.*, **1993**, *36*, 2373; Klopman, G.; Li, Y. J., *J. Comp-Aided Mol. Design*, **1995**, *9*, 283. Therefore, because capsazepine contains a thiourea as part of its structure, one aspect of the present invention is to make capsaicin analogues in which the A region (aromatic ring) is linked to the C region (hydrophobic moiety) using a thiourea as the B region. Variations in the C region are also examined. Moreover, the iodo group can be used as a handle to introduce acetylenic groups into the

core aromatic nucleus through use of the Sonogashira coupling. Such modification appears valuable in light of the finding that introduction of an acetylene group into epibatidine converted it from agonist to antagonist. Introduction of a cannabinoid receptor ligand into the C-region will also likely generate a ligand showing dual cannibinoid (CB) and VR activity.

Following the identification of capsazepine, which proved that it was possible to develop competitive antagonists of VR1, several distinct approaches have afforded antagonists. Competitive antagonists or partial antagonists derivatives in which the p-hydroxy group on the A region of capsaicin analogs has been replaced with a methylsulfonamide residue have been characterized. These antagonists now permit evaluation of their potential effects in therapeutic models. In addition to blockade of capsaicin action, antagonists of VR1 have been shown to block nociceptive responses, supporting their potential utility. This inhibition could be visualized as arising either from antagonism of endogenous VR1 ligands such as anandamide or lipoxygenase products or from stabilization of a closed receptor conformation, as implied from our demonstration that [N-(4-*tert*-butylbenzyl)-N'-[3-fluoro-4-(methylsulfonylamino)benzyl]-thiourea blocked response to heat and pH as well as to vanilloids in cultured cell systems.

The evaluation of the novel vanilloids emerging for the current robust medicinal chemical efforts has been complicated by distinct differences in the structure activity relations as revealed by different *in vitro* assays. In particular, an approximately 20 fold differences in potencies of vanilloids as assayed by inhibition of [^{3}H]resiniferatoxin binding and by induction of $^{45}Ca^{2+}$ uptake has been described. Although these results suggested distinct receptors mediating these responses, cloned, heterologously expressed VR1 was able to account both for [^{3}H]resiniferatoxin binding as well as for $^{45}Ca^{2+}$ uptake. Conversely, mice in which VR1 was genetically knocked out fully lost response to vanilloids. It would thus appear that the distinct structure activity relations revealed by the [^{3}H]resiniferatoxin binding and $^{45}Ca^{2+}$ uptake assays reflect differently modified fractions of the same VR1 receptor.

Subsequent to the cloning of VR1, it has become apparent that VR1 is localized to internal sites within the cell as well as to the plasma membrane and that, indeed, the internal localization is often predominant. It has been shown that heterologously expressed green fluorescent protein labeled VR1 is predominantly located in the endoplasmic reticulum, with very little actually evident at the plasma membrane. This pattern of localization

depends somewhat of the specific expression system, but is also seen with unmodified, heterologously expressed VR1 in various systems as well as with endogenous VR1 in dorsal root ganglion cells, as detected with specific VR1 antibodies. Consistent with internal VR1 being functional, resiniferatoxin and, to a lesser degree capsaicin, can release calcium from internal pools in the absence of external calcium.

Here, the synthesis and characterization of compound **1**, a novel VR1 antagonist with a unique pattern of selectivity is described. Although compound **1** displays very weak activity as an inhibitor of [^{3}H]resiniferatoxin binding to VR1, compound **1** is a potent antagonist of $^{45}Ca^{2+}$ uptake in response to resiniferatoxin or capsaicin. By calcium imaging, compound **1** was found to block the increase in intracellular calcium from the medium in response to resiniferatoxin but not that released from internal stores. These results suggest that the basis for the difference in structure activity relations in the assays may be ascribable to differences in the VR1 at the plasma membrane and internally. In any case, compound **1** provides a tool to dissect the roles of those pools of VR1 as detected in the different assays and to explore the implications of this selectivity.

Definitions

For convenience, before further description of the present invention, certain terms employed in the specification, examples and appended claims are collected here. These definitions should be read in light of the remainder of the disclosure and understood as by a person of skill in the art. Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by a person of ordinary skill in the art.

The articles "a" and "an" are used herein to 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" means one element or more than one element.

The terms "comprise" and "comprising" are used in the inclusive, open sense, meaning that additional elements may be included.

The term "including" is used to mean "including but not limited to". "Including" and "including but not limited to" are used interchangeably.

The term "cis" is art-recognized and refers to the arrangement of two atoms or groups around a double bond such that the atoms or groups are on the same side of the double bond. Cis configurations are often labeled as (Z) configurations.

The term "trans" is art-recognized and refers to the arrangement of two atoms or groups around a double bond such that the atoms or groups are on the opposite sides of a double bond. Trans configurations are often labeled as (E) configurations.

The term "covalent bond" is art-recognized and refers to a bond between two atoms where electrons are attracted electrostatically to both nuclei of the two atoms, and the net effect of increased electron density between the nuclei counterbalances the internuclear repulsion. The term covalent bond includes coordinate bonds when the bond is with a metal ion.

The term "therapeutic agent" is art-recognized and refers to any chemical moiety that is a biologically, physiologically, or pharmacologically active substance that acts locally or systemically in a subject. Examples of therapeutic agents, also referred to as "drugs", are described in well-known literature references such as the Merck Index, the Physicians Desk Reference, and The Pharmacological Basis of Therapeutics, and they include, without limitation, medicaments; vitamins; mineral supplements; substances used for the treatment, prevention, diagnosis, cure or mitigation of a disease or illness; substances which affect the structure or function of the body; or pro-drugs, which become biologically active or more active after they have been placed in a physiological environment. Antibiotic agents and Fab I/Fab K inhibitors are examples of therapeutic agents.

The term "therapeutic effect" is art-recognized and refers to a local or systemic effect in animals, particularly mammals, and more particularly humans caused by a pharmacologically active substance. The term thus means any substance intended for use in the diagnosis, cure, mitigation, treatment or prevention of disease or in the enhancement of desirable physical or mental development and/or conditions in an animal or human. The phrase "therapeutically-effective amount" means that amount of such a substance that produces some desired local or systemic effect at a reasonable benefit/risk ratio applicable to any treatment. The therapeutically effective amount of such substance will vary depending upon the subject and disease condition being treated, the weight and age of the subject, the severity of the disease condition, the manner of administration and the like,

which can readily be determined by one of ordinary skill in the art. For example, certain compositions of the present invention may be administered in a sufficient amount to produce a at a reasonable benefit/risk ratio applicable to such treatment.

The terms "combinatorial library" or "library" are art-recognized and refer to a plurality of compounds, which may be termed "members," synthesized or otherwise prepared from one or more starting materials by employing either the same or different reactants or reaction conditions at each reaction in the library. There are a number of other terms of relevance to combinatorial libraries (as well as other technologies). The term "identifier tag" is art-recognized and refers to a means for recording a step in a series of reactions used in the synthesis of a chemical library. The term "immobilized" is art-recognized and, when used with respect to a species, refers to a condition in which the species is attached to a surface with an attractive force stronger than attractive forces that are present in the intended environment of use of the surface, and that act on the species. The term "solid support" is art-recognized and refers to a material which is an insoluble matrix, and may (optionally) have a rigid or semi-rigid surface. The term "linker" is art-recognized and refers to a molecule or group of molecules connecting a support, including a solid support or polymeric support, and a combinatorial library member. The term "polymeric support" is art-recognized and refers to a soluble or insoluble polymer to which a chemical moiety can be covalently bonded by reaction with a functional group of the polymeric support. The term "functional group of a polymeric support" is art-recognized and refers to a chemical moiety of a polymeric support that can react with an chemical moiety to form a polymer-supported amino ester.

The term "synthetic" is art-recognized and refers to production by in vitro chemical or enzymatic synthesis.

The term "meso compound" is art-recognized and refers to a chemical compound which has at least two chiral centers but is achiral due to a plane or point of symmetry.

The term "chiral" is art-recognized and refers to molecules which have the property of non-superimposability of the mirror image partner, while the term "achiral" refers to molecules which are superimposable on their mirror image partner. A "prochiral molecule" is a molecule which has the potential to be converted to a chiral molecule in a particular process.

The term "stereoisomers" is art-recognized and refers to compounds which have identical chemical constitution, but differ with regard to the arrangement of the atoms or groups in space. In particular, "enantiomers" refer to two stereoisomers of a compound which are non-superimposable mirror images of one another. "Diastereomers", on the other hand, refers to stereoisomers with two or more centers of dissymmetry and whose molecules are not mirror images of one another.

Furthermore, a "stereoselective process" is one which produces a particular stereoisomer of a reaction product in preference to other possible stereoisomers of that product. An "enantioselective process" is one which favors production of one of the two possible enantiomers of a reaction product.

The term "regioisomers" is art-recognized and refers to compounds which have the same molecular formula but differ in the connectivity of the atoms. Accordingly, a "regioselective process" is one which favors the production of a particular regioisomer over others, e.g., the reaction produces a statistically significant increase in the yield of a certain regioisomer.

The term "epimers" is art-recognized and refers to molecules with identical chemical constitution and containing more than one stereocenter, but which differ in configuration at only one of these stereocenters.

The term "ED_{50}" is art-recognized. In certain embodiments, ED_{50} means the dose of a drug which produces 50% of its maximum response or effect, or alternatively, the dose which produces a pre-determined response in 50% of test subjects or preparations. The term "LD_{50}" is art-recognized. In certain embodiments, LD_{50} means the dose of a drug which is lethal in 50% of test subjects. The term "therapeutic index" is an art-recognized term which refers to the therapeutic index of a drug, defined as LD_{50}/ED_{50}.

The term "structure-activity relationship" or "SAR" is art-recognized and refers to the way in which altering the molecular structure of a drug or other compound alters its interaction with a receptor, enzyme, nucleic acid or other target and the like.

The term "agonist" is art-recognized and refers to a compound that mimics the action of natural transmitter or, when the natural transmitter is not known, causes changes at the receptor complex in the absence of other receptor ligands.

The term "antagonist" is art-recognized and refers to a compound that binds to a receptor site, but does not cause any physiological changes unless another receptor ligand is present.

The term "competitive antagonist" is art-recognized and refers to a compound or that binds to a receptor site; its effects may be overcome by increased concentration of the agonist.

The term "partial agonist" is art-recognized and refers to a compound or that binds to a receptor site but does not produce the maximal effect regardless of its concentration.

The term "aliphatic" is art-recognized and refers to a linear, branched, cyclic alkane, alkene, or alkyne. In certain embodiments, aliphatic groups in the present invention are linear or branched and have from 1 to about 20 carbon atoms.

The term "alkyl" is art-recognized, and includes saturated aliphatic groups, including straight-chain alkyl groups, branched-chain alkyl groups, cycloalkyl (alicyclic) groups, alkyl substituted cycloalkyl groups, and cycloalkyl substituted alkyl groups. In certain embodiments, a straight chain or branched chain alkyl has about 30 or fewer carbon atoms in its backbone (e.g., C_1-C_{30} for straight chain, C_3-C_{30} for branched chain), and alternatively, about 20 or fewer. Likewise, cycloalkyls have from about 3 to about 10 carbon atoms in their ring structure, and alternatively about 5, 6 or 7 carbons in the ring structure.

Unless the number of carbons is otherwise specified, "lower alkyl" refers to an alkyl group, as defined above, but having from one to about ten carbons, alternatively from one to about six carbon atoms in its backbone structure. Likewise, "lower alkenyl" and "lower alkynyl" have similar chain lengths.

The term "aralkyl" is art-recognized and refers to an alkyl group substituted with an aryl group (e.g., an aromatic or heteroaromatic group).

The terms "alkenyl" and "alkynyl" are art-recognized and refer to unsaturated aliphatic groups analogous in length and possible substitution to the alkyls described above, but that contain at least one double or triple bond respectively.

The term "heteroatom" is art-recognized and refers to an atom of any element other than carbon or hydrogen. Illustrative heteroatoms include boron, nitrogen, oxygen, phosphorus, sulfur and selenium.

The term "aryl" is art-recognized and refers to 5-, 6- and 7-membered single-ring aromatic groups that may include from zero to four heteroatoms, for example, benzene, naphthalene, anthracene, pyrene, pyrrole, furan, thiophene, imidazole, oxazole, thiazole, triazole, pyrazole, pyridine, pyrazine, pyridazine and pyrimidine, and the like. Those aryl groups having heteroatoms in the ring structure may also be referred to as "aryl heterocycles" or "heteroaromatics." The aromatic ring may be substituted at one or more ring positions with such substituents as described above, for example, halogen, azide, alkyl, aralkyl, alkenyl, alkynyl, cycloalkyl, hydroxyl, alkoxyl, amino, nitro, sulfhydryl, imino, amido, phosphonate, phosphinate, carbonyl, carboxyl, silyl, ether, alkylthio, sulfonyl, sulfonamido, ketone, aldehyde, ester, heterocyclyl, aromatic or heteroaromatic moieties, $-CF_3$, -CN, or the like. The term "aryl" also includes polycyclic ring systems having two or more cyclic rings in which two or more carbons are common to two adjoining rings (the rings are "fused rings") wherein at least one of the rings is aromatic, e.g., the other cyclic rings may be cycloalkyls, cycloalkenyls, cycloalkynyls, aryls and/or heterocyclyls.

The terms ortho, meta and para are art-recognized and refer to 1,2-, 1,3- and 1,4-disubstituted benzenes, respectively. For example, the names 1,2-dimethylbenzene and ortho-dimethylbenzene are synonymous.

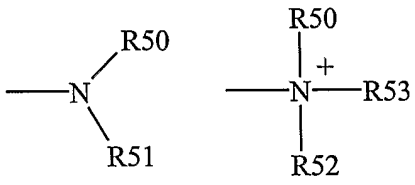
The terms "heterocyclyl" or "heterocyclic group" are art-recognized and refer to 3- to about 10-membered ring structures, alternatively 3- to about 7-membered rings, whose ring structures include one to four heteroatoms. Heterocycles may also be polycycles. Heterocyclyl groups include, for example, thiophene, thianthrene, furan, pyran, isobenzofuran, chromene, xanthene, phenoxanthene, pyrrole, imidazole, pyrazole, isothiazole, isoxazole, pyridine, pyrazine, pyrimidine, pyridazine, indolizine, isoindole, indole, indazole, purine, quinolizine, isoquinoline, quinoline, phthalazine, naphthyridine, quinoxaline, quinazoline, cinnoline, pteridine, carbazole, carboline, phenanthridine, acridine, pyrimidine, phenanthroline, phenazine, phenarsazine, phenothiazine, furazan, phenoxazine, pyrrolidine, oxolane, thiolane, oxazole, piperidine, piperazine, morpholine, lactones, lactams such as azetidinones and pyrrolidinones, sultams, sultones, and the like. The heterocyclic ring may be substituted at one or more positions with such substituents as described above, as for example, halogen, alkyl, aralkyl, alkenyl, alkynyl, cycloalkyl, hydroxyl, amino, nitro, sulfhydryl, imino, amido, phosphonate, phosphinate, carbonyl, carboxyl, silyl, ether, alkylthio, sulfonyl, ketone, aldehyde, ester, a heterocyclyl, an aromatic or heteroaromatic moiety, $-CF_3$, -CN, or the like.

The terms "polycyclyl" or "polycyclic group" are art-recognized and refer to two or more rings (e.g., cycloalkyls, cycloalkenyls, cycloalkynyls, aryls and/or heterocyclyls) in which two or more carbons are common to two adjoining rings, e.g., the rings are "fused rings". Rings that are joined through non-adjacent atoms are termed "bridged" rings. Each of the rings of the polycycle may be substituted with such substituents as described above, as for example, halogen, alkyl, aralkyl, alkenyl, alkynyl, cycloalkyl, hydroxyl, amino, nitro, sulfhydryl, imino, amido, phosphonate, phosphinate, carbonyl, carboxyl, silyl, ether, alkylthio, sulfonyl, ketone, aldehyde, ester, a heterocyclyl, an aromatic or heteroaromatic moiety, $-CF_3$, -CN, or the like.

The term "carbocycle" is art-recognized and refers to an aromatic or non-aromatic ring in which each atom of the ring is carbon.

The term "nitro" is art-recognized and refers to $-NO_2$; the term "halogen" is art-recognized and refers to -F, -Cl, -Br or -I; the term "sulfhydryl" is art-recognized and refers to -SH; the term "hydroxyl" means -OH; and the term "sulfonyl" is art-recognized and refers to $-SO_2^-$. "Halide" designates the corresponding anion of the halogens, and "pseudohalide" has the definition set forth on page 560 of "Advanced Inorganic Chemistry" by Cotton and Wilkinson.

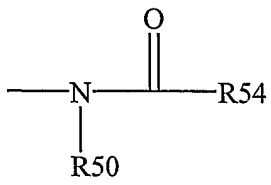
The terms "amine" and "amino" are art-recognized and refer to both unsubstituted and substituted amines, e.g., a moiety that may be represented by the general formulas:



wherein R50, R51 and R52 each independently represent a hydrogen, an alkyl, an alkenyl, $-(CH_2)_m$-R61, or R50 and R51, taken together with the N atom to which they are attached complete a heterocycle having from 4 to 8 atoms in the ring structure; R61 represents an aryl, a cycloalkyl, a cycloalkenyl, a heterocycle or a polycycle; and m is zero or an integer in the range of 1 to 8. In certain embodiments, only one of R50 or R51 may be a carbonyl, e.g., R50, R51 and the nitrogen together do not form an imide. In other embodiments, R50 and R51 (and optionally R52) each independently represent a hydrogen, an alkyl, an alkenyl, or $-(CH_2)_m$-R61. Thus, the term "alkylamine" includes an amine group, as defined

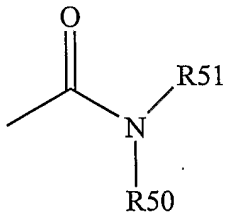
above, having a substituted or unsubstituted alkyl attached thereto, i.e., at least one of R50 and R51 is an alkyl group.

The term "acylamino" is art-recognized and refers to a moiety that may be represented by the general formula:



wherein R50 is as defined above, and R54 represents a hydrogen, an alkyl, an alkenyl or -$(CH_2)_m$-R61, where m and R61 are as defined above.

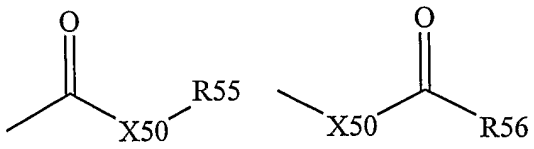
The term "amido" is art recognized as an amino-substituted carbonyl and includes a moiety that may be represented by the general formula:



wherein R50 and R51 are as defined above. Certain embodiments of the amide in the present invention will not include imides which may be unstable.

The term "alkylthio" refers to an alkyl group, as defined above, having a sulfur radical attached thereto. In certain embodiments, the "alkylthio" moiety is represented by one of -S-alkyl, -S-alkenyl, -S-alkynyl, and -S-$(CH_2)_m$-R61, wherein m and R61 are defined above. Representative alkylthio groups include methylthio, ethyl thio, and the like.

The term "carbonyl" is art recognized and includes such moieties as may be represented by the general formulas:

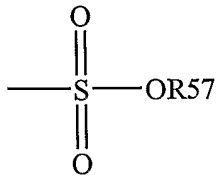


wherein X50 is a bond or represents an oxygen or a sulfur, and R55 and R56 represents a hydrogen, an alkyl, an alkenyl, -$(CH_2)_m$-R61or a pharmaceutically acceptable salt, R56 represents a hydrogen, an alkyl, an alkenyl or -$(CH_2)_m$-R61, where m and R61 are defined

above. Where X50 is an oxygen and R55 or R56 is not hydrogen, the formula represents an "ester". Where X50 is an oxygen, and R55 is as defined above, the moiety is referred to herein as a carboxyl group, and particularly when R55 is a hydrogen, the formula represents a "carboxylic acid". Where X50 is an oxygen, and R56 is hydrogen, the formula represents a "formate". In general, where the oxygen atom of the above formula is replaced by sulfur, the formula represents a "thiolcarbonyl" group. Where X50 is a sulfur and R55 or R56 is not hydrogen, the formula represents a "thiolester." Where X50 is a sulfur and R55 is hydrogen, the formula represents a "thiolcarboxylic acid." Where X50 is a sulfur and R56 is hydrogen, the formula represents a "thiolformate." On the other hand, where X50 is a bond, and R55 is not hydrogen, the above formula represents a "ketone" group. Where X50 is a bond, and R55 is hydrogen, the above formula represents an "aldehyde" group.

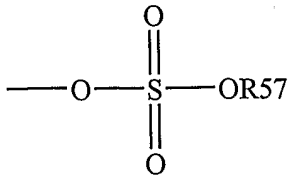
The terms "alkoxyl" or "alkoxy" are art-recognized and refer to an alkyl group, as defined above, having an oxygen radical attached thereto. Representative alkoxyl groups include methoxy, ethoxy, propyloxy, tert-butoxy and the like. An "ether" is two hydrocarbons covalently linked by an oxygen. Accordingly, the substituent of an alkyl that renders that alkyl an ether is or resembles an alkoxyl, such as may be represented by one of -O-alkyl, -O-alkenyl, -O-alkynyl, -O--$(CH_2)_m$-R61, where m and R61 are described above.

The term "sulfonate" is art recognized and refers to a moiety that may be represented by the general formula:



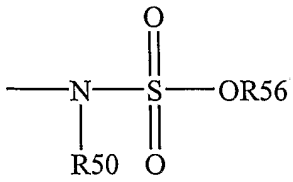
in which R57 is an electron pair, hydrogen, alkyl, cycloalkyl, or aryl.

The term "sulfate" is art recognized and includes a moiety that may be represented by the general formula:



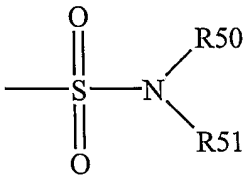
in which R57 is as defined above.

The term "sulfonamido" is art recognized and includes a moiety that may be represented by the general formula:



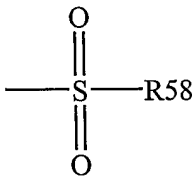
in which R50 and R56 are as defined above.

The term "sulfamoyl" is art-recognized and refers to a moiety that may be represented by the general formula:



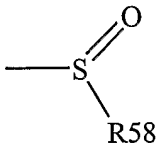
in which R50 and R51 are as defined above.

The term "sulfonyl" is art-recognized and refers to a moiety that may be represented by the general formula:



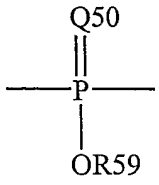
in which R58 is one of the following: hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl or heteroaryl.

The term "sulfoxido" is art-recognized and refers to a moiety that may be represented by the general formula:

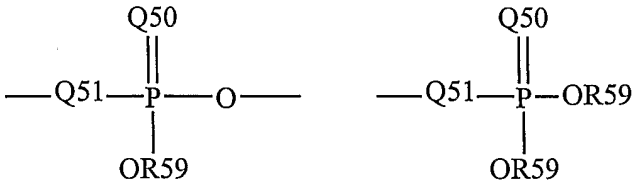


in which R58 is defined above.

The term "phosphoryl" is art-recognized and may in general be represented by the formula:

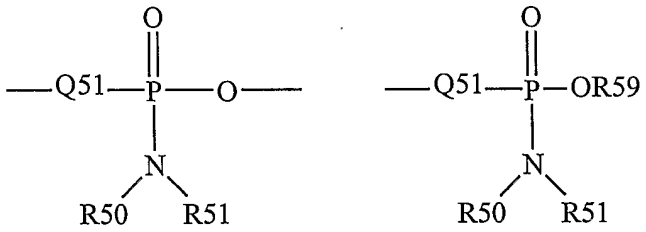


wherein Q50 represents S or O, and R59 represents hydrogen, a lower alkyl or an aryl. When used to substitute, e.g., an alkyl, the phosphoryl group of the phosphorylalkyl may be represented by the general formulas:



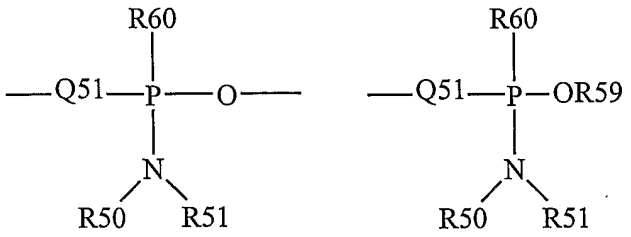
wherein Q50 and R59, each independently, are defined above, and Q51 represents O, S or N. When Q50 is S, the phosphoryl moiety is a "phosphorothioate".

The term "phosphoramidite" is art-recognized and may be represented in the general formulas:



wherein Q51, R50, R51 and R59 are as defined above.

The term "phosphonamidite" is art-recognized and may be represented in the general formulas:



wherein Q51, R50, R51 and R59 are as defined above, and R60 represents a lower alkyl or an aryl.

Analogous substitutions may be made to alkenyl and alkynyl groups to produce, for example, aminoalkenyls, aminoalkynyls, amidoalkenyls, amidoalkynyls, iminoalkenyls, iminoalkynyls, thioalkenyls, thioalkynyls, carbonyl-substituted alkenyls or alkynyls.

The definition of each expression, e.g. alkyl, m, n, and the like, when it occurs more than once in any structure, is intended to be independent of its definition elsewhere in the same structure.

The term "selenoalkyl" is art-recognized and refers to an alkyl group having a substituted seleno group attached thereto. Exemplary "selenoethers" which may be substituted on the alkyl are selected from one of -Se-alkyl, -Se-alkenyl, -Se-alkynyl, and -Se-$(CH_2)_m$-R61, m and R61 being defined above.

The terms triflyl, tosyl, mesyl, and nonaflyl are art-recognized and refer to trifluoromethanesulfonyl, *p*-toluenesulfonyl, methanesulfonyl, and nonafluorobutanesulfonyl groups, respectively. The terms triflate, tosylate, mesylate, and nonaflate are art-recognized and refer to trifluoromethanesulfonate ester, *p*-toluenesulfonate ester, methanesulfonate ester, and nonafluorobutanesulfonate ester functional groups and molecules that contain said groups, respectively.

The abbreviations Me, Et, Ph, Tf, Nf, Ts, and Ms represent methyl, ethyl, phenyl, trifluoromethanesulfonyl, nonafluorobutanesulfonyl, *p*-toluenesulfonyl and methanesulfonyl, respectively. A more comprehensive list of the abbreviations utilized by organic chemists of ordinary skill in the art appears in the first issue of each volume of the Journal of Organic Chemistry; this list is typically presented in a table entitled Standard List of Abbreviations.

Certain compounds contained in compositions of the present invention may exist in particular geometric or stereoisomeric forms. In addition, polymers of the present invention may also be optically active. The present invention contemplates all such compounds, including cis- and trans-isomers, *R*- and *S*-enantiomers, diastereomers, (D)-isomers, (L)-isomers, the racemic mixtures thereof, and other mixtures thereof, as falling within the scope of the invention. Additional asymmetric carbon atoms may be present in a substituent such as an alkyl group. All such isomers, as well as mixtures thereof, are intended to be included in this invention.

If, for instance, a particular enantiomer of compound of the present invention is desired, it may be prepared by asymmetric synthesis, or by derivation with a chiral

auxiliary, where the resulting diastereomeric mixture is separated and the auxiliary group cleaved to provide the pure desired enantiomers. Alternatively, where the molecule contains a basic functional group, such as amino, or an acidic functional group, such as carboxyl, diastereomeric salts are formed with an appropriate optically-active acid or base, followed by resolution of the diastereomers thus formed by fractional crystallization or chromatographic means well known in the art, and subsequent recovery of the pure enantiomers.

It will be understood that "substitution" or "substituted with" includes the implicit proviso that such substitution is in accordance with permitted valence of the substituted atom and the substituent, and that the substitution results in a stable compound, e.g., which does not spontaneously undergo transformation such as by rearrangement, cyclization, elimination, or other reaction.

The term "substituted" is also contemplated to include all permissible substituents of organic compounds. In a broad aspect, the permissible substituents include acyclic and cyclic, branched and unbranched, carbocyclic and heterocyclic, aromatic and nonaromatic substituents of organic compounds. Illustrative substituents include, for example, those described herein above. The permissible substituents may be one or more and the same or different for appropriate organic compounds. For purposes of this invention, the heteroatoms such as nitrogen may have hydrogen substituents and/or any permissible substituents of organic compounds described herein which satisfy the valences of the heteroatoms. This invention is not intended to be limited in any manner by the permissible substituents of organic compounds.

For purposes of this invention, the chemical elements are identified in accordance with the Periodic Table of the Elements, CAS version, Handbook of Chemistry and Physics, 67th Ed., 1986-87, inside cover.

The term "protecting group" is art-recognized and refers to temporary substituents that protect a potentially reactive functional group from undesired chemical transformations. Examples of such protecting groups include esters of carboxylic acids, silyl ethers of alcohols, and acetals and ketals of aldehydes and ketones, respectively. The field of protecting group chemistry has been reviewed by Greene and Wuts in Protective Groups in Organic Synthesis (2^{nd} ed., Wiley: New York, 1991).

The term "hydroxyl-protecting group" is art-recognized and refers to those groups intended to protect a hydroxyl group against undesirable reactions during synthetic procedures and includes, for example, benzyl or other suitable esters or ethers groups known in the art.

The term "carboxyl-protecting group" is art-recognized and refers to those groups intended to protect a carboxylic acid group, such as the C-terminus of an amino acid or peptide or an acidic or hydroxyl azepine ring substituent, against undesirable reactions during synthetic procedures and includes. Examples for protecting groups for carboxyl groups involve, for example, benzyl ester, cyclohexyl ester, 4-nitrobenzyl ester, t-butyl ester, 4-pyridylmethyl ester, and the like.

The term "amino-blocking group" is art-recognized and refers to a group which will prevent an amino group from participating in a reaction carried out on some other functional group, but which can be removed from the amine when desired. Such groups are discussed by in Ch. 7 of Greene and Wuts, cited above, and by Barton, Protective Groups in Organic Chemistry ch. 2 (McOmie, ed., Plenum Press, New York, 1973). Examples of suitable groups include acyl protecting groups such as, to illustrate, formyl, dansyl, acetyl, benzoyl, trifluoroacetyl, succinyl, methoxysuccinyl, benzyl and substituted benzyl such as 3,4-dimethoxybenzyl, o-nitrobenzyl, and triphenylmethyl; those of the formula -COOR where R includes such groups as methyl, ethyl, propyl, isopropyl, 2,2,2-trichloroethyl, 1-methyl-1-phenylethyl, isobutyl, t-butyl, t-amyl, vinyl, allyl, phenyl, benzyl, p-nitrobenzyl, o-nitrobenzyl, and 2,4-dichlorobenzyl; acyl groups and substituted acyl such as formyl, acetyl, chloroacetyl, dichloroacetyl, trichloroacetyl, trifluoroacetyl, benzoyl, and p-methoxybenzoyl; and other groups such as methanesulfonyl, p-toluenesulfonyl, p-bromobenzenesulfonyl, p-nitrophenylethyl, and p-toluenesulfonyl-aminocarbonyl. Preferred amino-blocking groups are benzyl ($-CH_2C_6H_5$), acyl [C(O)R1] or $SiR1_3$ where R1 is C_1-C_4 alkyl, halomethyl, or 2-halo-substituted-(C_2-C_4 alkoxy), aromatic urethane protecting groups as, for example, carbonylbenzyloxy (Cbz); and aliphatic urethane protecting groups such as t-butyloxycarbonyl (Boc) or 9-fluorenylmethoxycarbonyl (FMOC).

The definition of each expression, e.g. lower alkyl, m, n, p and the like, when it occurs more than once in any structure, is intended to be independent of its definition elsewhere in the same structure.

The term "electron-withdrawing group" is art-recognized, and refers to the tendency of a substituent to attract valence electrons from neighboring atoms, i.e., the substituent is electronegative with respect to neighboring atoms. A quantification of the level of electron-withdrawing capability is given by the Hammett sigma (σ) constant. This well known constant is described in many references, for instance, March, Advanced Organic Chemistry 251-59 (McGraw Hill Book Company: New York, 1977). The Hammett constant values are generally negative for electron donating groups ($\sigma(P) = -0.66$ for NH_2) and positive for electron withdrawing groups ($\sigma(P) = 0.78$ for a nitro group), $\sigma(P)$ indicating para substitution. Exemplary electron-withdrawing groups include nitro, acyl, formyl, sulfonyl, trifluoromethyl, cyano, chloride, and the like. Exemplary electron-donating groups include amino, methoxy, and the like.

The term "small molecule" is art-recognized and refers to a composition which has a molecular weight of less than about 2000 amu, or less than about 1000 amu, and even less than about 500 amu. Small molecules may be, for example, nucleic acids, peptides, polypeptides, peptide nucleic acids, peptidomimetics, carbohydrates, lipids or other organic (carbon containing) or inorganic molecules. Many pharmaceutical companies have extensive libraries of chemical and/or biological mixtures, often fungal, bacterial, or algal extracts, which can be screened with any of the assays of the invention. The term "small organic molecule" refers to a small molecule that is often identified as being an organic or medicinal compound, and does not include molecules that are exclusively nucleic acids, peptides or polypeptides.

A "target" shall mean a site to which a molecule binds or at which a molecule has a biological effect. A target may be either in vivo or in vitro. In certain embodiments, a target may be a tumor (e.g., tumors of the brain, lung (small cell and non-small cell), ovary, prostate, breast and colon as well as other carcinomas and sarcomas). In other embodiments, a target may be a site of infection (e.g., by bacteria, viruses (e.g., HIV, herpes, hepatitis) and pathogenic fungi (Candida sp.). In still other embodiments, a target may refer to a molecular structure to which a targeting moiety binds, such as a hapten, epitope, receptor, dsDNA fragment, carbohydrate or enzyme. Additionally, a target may be a type of tissue, e.g., neuronal tissue, intestinal tissue, pancreatic tissue etc.

The term "targeting moiety" refers to any molecular structure which assists the molecule in localizing to a particular target area, entering a target cell(s), and/or binding to

a target receptor. For example, lipids (including cationic, neutral, and steroidal lipids, virosomes, and liposomes), antibodies, lectins, ligands, sugars, steroids, hormones, nutrients, and proteins may serve as targeting moieties.

The term "modulation" is art-recognized and refers to up regulation (i.e., activation or stimulation), down regulation (i.e., inhibition or suppression) of a response, or the two in combination or apart.

The term "treating" is art-recognized and refers to curing as well as ameliorating at least one symptom of any condition or disease.

The term "prophylactic" or "therapeutic" treatment is art-recognized and refers to administration to the host of one or more of the subject compositions. If it is administered prior to clinical manifestation of the unwanted condition (e.g., disease or other unwanted state of the host animal) then the treatment is prophylactic, i.e., it protects the host against developing the unwanted condition, whereas if administered after manifestation of the unwanted condition, the treatment is therapeutic (i.e., it is intended to diminish, ameliorate or maintain the existing unwanted condition or side effects therefrom).

A "patient," "subject" or "host" to be treated by the subject method may mean either a human or non-human animal.

The term "mammal" is known in the art, and exemplary mammals include humans, primates, bovines, porcines, canines, felines, and rodents (e.g., mice and rats).

The term "bioavailable" is art-recognized and refers to a form of the subject invention that allows for it, or a portion of the amount administered, to be absorbed by, incorporated to, or otherwise physiologically available to a subject or patient to whom it is administered.

The term "pharmaceutically-acceptable salts" is art-recognized and refers to the relatively non-toxic, inorganic and organic acid addition salts of compounds, including, for example, those contained in compositions of the present invention.

The term "pharmaceutically acceptable carrier" is art-recognized and refers to a pharmaceutically-acceptable material, composition or vehicle, such as a liquid or solid filler, diluent, excipient, solvent or encapsulating material, involved in carrying or transporting any subject composition or component thereof from one organ, or portion of the body, to another organ, or portion of the body. Each carrier must be "acceptable" in the

sense of being compatible with the subject composition and its components and not injurious to the patient. Some examples of materials which may 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 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; (14) buffering agents, such as magnesium hydroxide and aluminum hydroxide; (15) alginic acid; (16) pyrogen-free water; (17) isotonic saline; (18) Ringer's solution; (19) ethyl alcohol; (20) phosphate buffer solutions; and (21) other non-toxic compatible substances employed in pharmaceutical formulations.

The terms "systemic administration," "administered systemically," "peripheral administration" and "administered peripherally" are art-recognized and refer to the administration of a subject composition, therapeutic or other material other than directly into the central nervous system, such that it enters the patient's system and, thus, is subject to metabolism and other like processes, for example, subcutaneous administration.

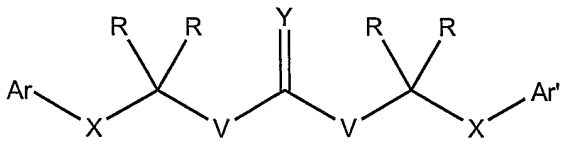
The terms "parenteral administration" and "administered parenterally" are art-recognized and refer to modes of administration other than enteral and topical administration, usually by injection, and includes, without limitation, intravenous, intramuscular, intraarterial, intrathecal, intracapsular, intraorbital, intracardiac, intradermal, intraperitoneal, transtracheal, subcutaneous, subcuticular, intra-articulare, subcapsular, subarachnoid, intraspinal, and intrasternal injection and infusion.

Contemplated equivalents of the compositions described herein include compositions which otherwise correspond thereto, and which have the same general properties thereof (such as other compositions comprising vanilloid receptor modifiers), wherein one or more simple variations of substituents or components are made which do not adversely affect the characteristics of the compositions of interest. In general, the components of the compositions of the present invention may be prepared by the methods illustrated in the general reaction schema as, for example, described below, or by modifications thereof, using readily available starting materials, reagents and conventional

synthesis procedures. In these reactions, it is also possible to make use of variants which are in themselves known, but are not mentioned here.

Compounds & Methods of the Invention

In part, the present invention relates to compounds of formula **I**:



I

wherein, independently for each occurrence:

Y is O, S, or $N(R_1)$;

V is O, S, or $N(R_4)$;

X is a bond, O, S, N(R), or $C(R)_2$;

R is H, alkyl, cycloalkyl, aryl, or aralkyl;

R_1 is alkyl, cycloalkyl, aryl, or aralkyl;

R_4 is H, alkyl, cycloalkyl, aryl, or aralkyl;

Ar is a monocyclic or bicyclic aromatic moiety of 5 to 12 atoms, unsubstituted or substituted with one or more R_3;

Ar' is a monocyclic or bicyclic aromatic moiety of 5 to 12 atoms, unsubstituted or substituted with one or more R_3; and

R_3 is alkyl, cycloalkyl, alkenyl, alkynyl, aryl, aralkyl, hydroxy, alkoxy, acetyl, acetyloxy, nitro, cyano, aryloxy, amino, halogen, methanesulfonylamino, -$NHCO_2CH_3$, -$NHCOCH_3$, -CF_3, sulfamoyl, or -OCH_2OCH_3.

In another embodiment, the present invention relates to compounds of formula **I** and the attendant definitions, wherein Y is S or O.

In another embodiment, the present invention relates to compounds of formula **I** and the attendant definitions, wherein Y is S.

In another embodiment, the present invention relates to compounds of formula **I** and the attendant definitions, wherein V is $N(R_4)$.

In another embodiment, the present invention relates to compounds of formula **I** and the attendant definitions, wherein V is $N(R_4)$; and R_4 is H.

In another embodiment, the present invention relates to compounds of formula **I** and the attendant definitions, wherein X is a bond.

In another embodiment, the present invention relates to compounds of formula **I** and the attendant definitions, wherein R is H or alkyl.

In another embodiment, the present invention relates to compounds of formula **I** and the attendant definitions, wherein Ar represents unsubstituted or substituted phenyl or naphthalenyl.

In another embodiment, the present invention relates to compounds of formula **I** and the attendant definitions, wherein Ar' represents unsubstituted or substituted phenyl or naphthalenyl.

In another embodiment, the present invention relates to compounds of formula **I** and the attendant definitions, wherein Ar represents substituted phenyl.

In another embodiment, the present invention relates to compounds of formula **I** and the attendant definitions, wherein Ar' represents substituted phenyl.

In another embodiment, the present invention relates to compounds of formula **I** and the attendant definitions, wherein Ar represents 4-chlorophenyl.

In another embodiment, the present invention relates to compounds of formula **I** and the attendant definitions, wherein Ar' represents 3-methoxy-4-hydroxy-5-iodophenyl.

In another embodiment, the present invention relates to compounds of formula **I** and the attendant definitions, wherein Y is S; and V is $N(R_4)$.

In another embodiment, the present invention relates to compounds of formula **I** and the attendant definitions, wherein Y is S; V is $N(R_4)$; and R_4 is H.

In another embodiment, the present invention relates to compounds of formula **I** and the attendant definitions, wherein Y is S; V is $N(R_4)$; R_4 is H; and X is a bond.

In another embodiment, the present invention relates to compounds of formula **I** and the attendant definitions, wherein Y is S; V is $N(R_4)$; R_4 is H; X is a bond; and R is H or alkyl.

In another embodiment, the present invention relates to compounds of formula **I** and the attendant definitions, wherein Y is S; V is $N(R_4)$; R_4 is H; X is a bond; R is H or alkyl; Ar represents unsubstituted or substituted phenyl or naphthalenyl; and Ar' represents unsubstituted or substituted phenyl or naphthalenyl.

In another embodiment, the present invention relates to compounds of formula **I** and the attendant definitions, wherein Y is S; V is $N(R_4)$; R_4 is H; X is a bond; and R is H or alkyl; Ar represents unsubstituted or substituted phenyl or naphthalenyl; and Ar' represents 3-methoxy-4-hydroxy-5-iodophenyl.

In another embodiment, the present invention relates to compounds of formula **I** and the attendant definitions, wherein Y is S; V is $N(R_4)$; R_4 is H; X is a bond; and R is H or alkyl; Ar represents substituted phenyl; and Ar' represents 3-methoxy-4-hydroxy-5-iodophenyl.

In another embodiment, the present invention relates to compounds of formula **I** and the attendant definitions, wherein Y is S; V is $N(R_4)$; R_4 is H; X is a bond; and R is H or alkyl; Ar represents 4-chlorophenyl; and Ar' represents 3-methoxy-4-hydroxy-5-iodophenyl.

In another embodiment, the present invention relates to compounds of formula **I** and the attendant definitions, wherein the compound has an IC_{50} less than 1 μM in a $^{45}Ca^{2+}$ uptake assay.

In another embodiment, the present invention relates to compounds of formula **I** and the attendant definitions, wherein the compound has an IC_{50} less than 100 nM in a $^{45}Ca^{2+}$ uptake assay.

In another embodiment, the present invention relates to compounds of formula **I** and the attendant definitions, wherein the compound has an IC_{50} less than 10 nM in a $^{45}Ca^{2+}$ uptake assay.

In another embodiment, the present invention relates to a pharmaceutical composition, comprising a compound of claim 1; and a pharmaceutically acceptable excipient.

The present invention also relates to a method of modulating the activity of a vanilloid receptor in a mammal, comprising administering to the mammal a therapeutically effective amount of a compound of the invention.

A method of treating a mammal suffering from pain associated with a malady selected from the group consisting of bladder hyperreflexia, detrusor instability, post-mastectomy pain, mucositis, interstitial cystitis, pharyngitis, pancreatitis, enteritis, cellulitis, postherpetic neuralgia, peripheral neuropathy, arthritis, and bony fractures, comprising administering to the mammal a therapeutically effective amount of a compound of the invention.

In certain embodiments of any of the aforementioned methods, the mammal is primate, equine, canine or feline.

In certain embodiments of any of the aforementioned methods, the mammal is a human.

In certain embodiments of any of the aforementioned methods, the compound is administered orally.

In certain embodiments of any of the aforementioned methods, the compound is administered intravenously.

In certain embodiments of any of the aforementioned methods, the compound is administered sublingually.

In certain embodiments of any of the aforementioned methods, the compound is administered ocularly.

In certain embodiments of any of the aforementioned methods, the compound is administered transdermally.

In certain embodiments of any of the aforementioned methods, the compound is administered rectally.

In certain embodiments of any of the aforementioned methods, the compound is administered vaginally.

In certain embodiments of any of the aforementioned methods, the compound is administered topically.

In certain embodiments of any of the aforementioned methods, the compound is administered intramuscularly.

In certain embodiments of any of the aforementioned methods, the compound is administered subcutaneously.

In certain embodiments of any of the aforementioned methods, the compound is administered buccally.

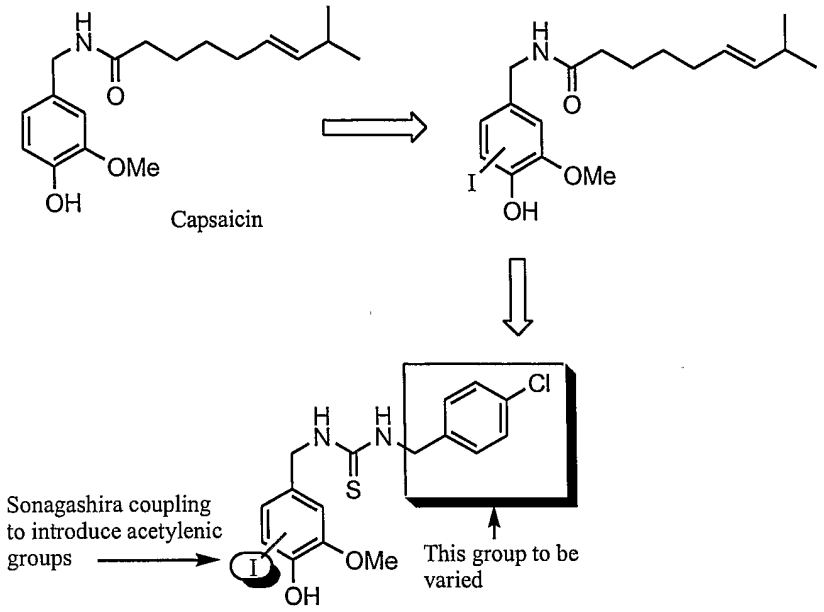
In certain embodiments of any of the aforementioned methods, the compound is administered nasally.

Also included in the compounds and compositions of the present invention are pharmaceutically acceptable addition salts of the compounds of formula **I**. In cases wherein the compounds may have one or more chiral centers, unless specified, the present invention comprises each unique racemic compound, as well as each unique non-racemic compound.

In cases in which the compounds have unsaturated carbon-carbon double bonds, both the cis (Z) and trans (E) isomers are within the scope of this invention. In cases wherein compounds may exist in tautomeric forms, such as keto-enol tautomers, such as  and  , each tautomeric form is contemplated as being included within this invention, whether existing in equilibrium or locked in one form by appropriate substitution with R'. The meaning of any substituent at any one occurrence is independent of its meaning, or any other substituent's meaning, at any other occurrence.

Also included in the compounds and compositions of the present invention are prodrugs of the compounds of formula **I**. Prodrugs are considered to be any covalently bonded carriers which release the active parent drug *in vivo*.

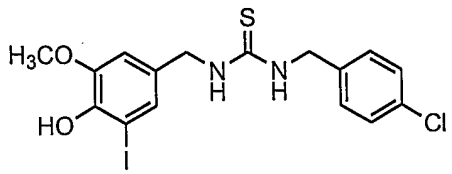
Examples of the compounds of formula **I** may be prepared by the general method described in Scheme 1.



Scheme 1. General synthetic route for compounds of formula **I**.

Acid addition salts of the compounds are prepared in a standard manner in a suitable solvent from the parent compound and an excess of an acid, such as hydrochloric, hydrobromic, hydrofluoric, sulfuric, phosphoric, acetic, trifluoroacetic, maleic, succinic or methanesulfonic. Certain of the compounds form inner salts or zwitterions which may be acceptable. Cationic salts are prepared by treating the parent compound with an excess of an alkaline reagent, such as a hydroxide, carbonate or alkoxide, containing the appropriate cation; or with an appropriate organic amine. Cations such as Li^+, Na^+, K^+, Ca^{++}, Mg^{++} and NH_4^+ are specific examples of cations present in pharmaceutically acceptable salts.

Compound 1 Assay Results



Compound **1**

Compound **1** exploits the A region found in iodo-resiniferatoxin, which conferred antagonism to that RTX derivative, together with a B region thiourea, which enhances

affinity in the calcium uptake assay, and a C region similar to that of capsazepine (Figure 1). Wahl, P., Foged, C., Tullin, S., and Thomsen, C., *Mol Pharmacol,* **2001**, *59*, 9-15; Lee, J., Park, S.U., Kim, J.Y., Kim, J.K., Oh, U., Marquez, V.E., Beheshti, M., Wang, Q.J., Modarres, S., and Blumberg, P.M., *Bioorg Med Chem Lett*, **1999**, *9*, 2909-2914; Bevan, S., Hothi, S., Hughes, G., James, I.F., Rang, H.P., Shah, K., Walpole, C.S., and Yeats, J.C., *Br J Pharmacol*, **1992**, *107*, 544-552. As described elsewhere, however, these regions cannot be considered as independent, and in other structural series the C-region has been clearly shown to modulate the extent of antagonism conferred by the A-region substitution.

The binding potency of the compound **1** to VR1 was determined by inhibition of [^{3}H]RTX binding. There was almost no [^{3}H]RTX binding inhibition detected at a 30 micromolar concentration of compound **1** and none at lower concentrations, suggesting an inactive compound. Surprisingly, in contrast to the inability of compound **1** to replace [^{3}H]RTX from the membranes of CHO-VR1 cells, it was a potent inhibitor of the $^{45}Ca^{2+}$ uptake induced by capsaicin (IC_{50} = 99 + 23 nM; p = 1.28 +/- 0.39, n = 4 experiments). To exclude the possibility that the apparent difference in activity depended on the ligand with which compound **1** was competing, we similarly tested the ability of compound **1** to inhibit the RTX induced $^{45}Ca^{2+}$ uptake of the CHO-VR1 cells. The potency of compound **1** under these circumstances (IC_{50} = 93 + 34 nM; p = 1.52 +/- 0.12) was almost identical to that determined using capsaicin. Since we have described vanilloids which function as partial antagonists/partial agonists, the activity of compound **1** as an agonist of VR1 was also assayed. At 30 uM of the level of stimulation of $^{45}Ca^{2+}$ uptake over baseline compared to capsaicin (300 nM) was detected. Although it can be concluded that compound **1** was a full antagonist under these assay conditions, it is now described that the extent of agonism for partial agonists depends on the level of VR1 and on the level of modulation by other factors, such as protein kinase C. It is therefore possible that compound **1** may show a low level of agonism under other conditions.

To clarify the mechanism of the compound **1** inhibition, whether the compound **1** was a competitive, noncompetitive or mixed type inhibitor of RTX or capsaicin induced $^{45}Ca^{2+}$ uptake was tested. The dose-response curves for capsaicin and RTX were determined in the presence of different concentrations of compound **1** (0, 100, 300, 1000 nM). Qualitatively consistent with a competitive mechanism for the antagonism, the maximal responses remained constant but the dose response curves shifted to the right as a function

of compound **1** concentration. Quantitatively consistent with a competitive mechanism, the apparent EC_{50} values fitted the equation

$$EC_{50} \text{ (apparent)} = EC_{50} + I/K_i,$$

where I = concentration of the antagonist and K_i = dissociation constant for the antagonist. In the case of capsaicin, the equation yielded a EC_{50} for capsaicin of 98 nM (n = 3 experiments), similar to previous determinations, and a K_i value for compound **1** of 148 nM (n = 3 experiments), likewise similar to previously determined K_i of 99 + 23 nM. For RTX, the equation yielded a EC_{50} for RTX of 32 nM (n = 4 experiments), similar to our previous determinations, and a K_i value for compound **1** of 80 nM (n = 4 experiments), likewise similar to previously determined K_i of 93 + 34 nM. From this it is concluded that compound **1** is a competitive antagonist of capsaicin and RTX action on VR1 in the $^{45}Ca^{2+}$ uptake assays.

To further explore the mechanism and kinetics of antagonism by compound **1**, its activity on VR1 was evaluated by intracellular Ca^{2+} imaging. CHO-VR1 cells were pretreated with different concentrations of compound **1** (0 - 6500 nM) for 4 min, 50 nM capsaicin was then added, and the intracellular Ca^{2+} concentration was monitored as a function of time. The maximal signals (ratio of fluorescence) were plotted as a function of the compound **1** concentration. Under these conditions, compound **1** blocked the elevation in intracellular Ca^{2+} concentration with a similar potency (IC_{50} = 106 +/- 36 nM; p = 1.91 +/- 0.20, n = 3 experiments) to that in the $^{45}Ca^{2+}$ experiments (IC_{50} = 99 +/- 23 nM). Conversely, the ability of compound **1** to reverse the action of capsaicin when the compound **1** was added after the capsaicin was tested. The cells were treated for 5 min with 50 nM, after which 10 μM compound **1** was added in the continued presence of the capsaicin. The compound **1** antagonized the capsaicin, with an immediate onset of action.

Since the receptor for compound **1** is most likely the VR1, the remarkable difference (more than 300-fold) between the binding inhibition and the functional assays suggests, that the two methods measure somewhat different properties of the VR1. From the data it is clear, that the plasmamembrane localized VR1 is a receptor for all of the compounds tested here. It is believed that one could measure the binding to all of the expressed receptors using the ^{3}H-RTX binding assay, while the properties of the intracellular membrane located VR1 are somewhat different. To test the idea of different pharmacological properties for receptors regarding their localization, intracellular Ca^{2+} imaging experiments were

performed. To be able to detect different receptor behavior RTX as a VR1 agonist was used. At the beginning, the experiment was performed in the presence of 1.8 mM Ca^{2+} in the extracellular solution. First, the RTX response was characterized. Cells were incubated in buffer for 4 min, then 100 pM RTX was added. The elevation in the intracellular Ca^{2+} concentrations could be detected. To detect the maximal response under these circumstances a consecutive RTX treatment was applied using a maximal dose of RTX (100 nM). The response of CHO-VR1 cells to 100 pM RTX was almost maximal. Next, the question of the inhibition with compound **1** was addressed. Application of 100 pM RTX after 4 min pretreatment with 600 nM compound **1** was without effect. The inhibition was competitive, because the application of 100 nM RTX lead to similar maximal response that could be seen in case of experiments without compound **1**. It is again consistent with the results from the inhibition of $^{45}Ca^{2+}$ uptake.

To address the question of the regulation of the intracellular membrane localized VR1 the experiments were performed in the absence of extracellular Ca^{2+} (experiments in the absence of Ca^{2+}, but in the presence of 100 micromole EDTA in the extracellular solution). First, the intracellular RTX sensitive Ca^{2+} pools were identified as the same as the thapsigargin operated pools (data not shown). Using this method the release of Ca^{2+} using 100 pM RTX at 4 min was detected. The effect was about half maximal, since the application of thapsigargin yielded similar signal indicating, that just half of the intracellular pools were released by RTX. It is noteworthy, that the signals were transient in contrast with the signals in the presence of extracellular Ca^{2+}, where the elevated intracellular Ca^{2+} concentration was maintained over a long period of time. The reason for the difference is presumably the limited Ca^{2+} content of the intracellular pools in the absence of extracellular Ca^{2+}. Next, the cells were pretreated with 600 nM compound **1** for 4 min before 100 pM RTX application, followed by thapsigargin challenge. Indeed, indistinguishable results from the control experiment (pretreatment with buffer alone, were obtained. To rule out the nonspecific effects of RTX and compound **1** on the release of Ca^{2+} from the intracellular pools of Ca^{2+}, the cells were pretreated with 10 nM I-RTX, which is probably the most potent specific antagonist of VR1 known so far. The RTX effect was completely antagonized under these circumstances suggesting that the overall response is specific to the VR1.

This difference detected in the Ca^{2+} imaging experiments could rationalize the difference between results from ^{3}H-RTX binding experiments and $^{45}Ca^{2+}$ uptake

experiments. The data suggest, that the intracellular membrane located VR1 is the receptor measured by the ^{3}H-RTX binding assay and by the intracellular Ca^{2+} imaging in the absence of extracellular Ca^{2+}. In contrast, the plasmamembrane located VR1 is the receptor measured by the $^{45}Ca^{2+}$ uptake experiments and by the intracellular Ca^{2+} imaging experiments in the presence of extraceellular 1.8 mM extracellular Ca^{2+}.

Discussion

The regulation of VR1 attracted particular interest in the past decade. Kress, M. and Zeilhofer, H.U., *Trends Pharmacol Sci*, **1999**, *20*, 112-118; Szallasi, A. and Blumberg, P.M., *Pharmacol Rev*, **1999**, *51*, 159-212; Caterina, M.J. and Julius, D., *Annu Rev Neurosci*, **2001**, *24*, 487-517; Robbins, W., *Clin J Pain*, **2000**, *16*, S86-S89; Szallasi, A. and Blumberg, P.M., *Pain JID - 7508686*, **1996**, *68*, 195-208; Di, M., V, Blumberg, P.M., and Szallasi, A., *Curr Opin Neurobiol*, **2002**, *12*, 372-379. The clue to this attention could be, that the treatment and the prevention pain is a challenge of modern medicine. So far most of the analgesics belong to two groups: the aspirin like cyclooxygenase inhibitors, and the morphin like narcotic analgesics. The receptors of these drugs (i.e., cyclooxygenases and opioid receptors) are widely expressed in the body. Therefore the treatments through these targets induce a great deal of side effect on cells that are not involved in the pain prescription. In contrast, the VR1 found to be expressed almost specifically on the 'pain pathway'. Caterina, M.J., Schumacher, M.A., Tominaga, M., Rosen, T.A., Levine, J.D., and Julius, D., *Nature*, **1997**, *389*, 816-824.

One concept in the development of new compounds acting on the VR1 is the modification or combination of motifs known to be important in the determination of activity and potency. The most active compound, the RTX and the historical activator capsaicin contain the same A region (Figure 1). An important observation is, that the introduction of iodine into the A region could modify the physiological activity of the ultrapotent full agonist RTX to a potent full antagonist or to a partial agonist/antagonist. Wahl, P., Foged, C., Tullin, S., and Thomsen, C., *Mol Pharmacol*, **2001**, *59*, 9-15; McDonnell, M.E., Zhang, S.P., Dubin, A.E., and Dax, S.L., *Bioorg Med Chem Lett*, **2002**, *12*, 1189-1192. In the B region a modification leading to the replacement to a thiourea moiety were suggested as the most effective group to improve the potency of different RTX analogues. Lee, J., Park, S.U., Kim, J.Y., Kim, J.K., Oh, U., Marquez, V.E., Beheshti, M.,

Wang, Q.J., Modarres, S., and Blumberg, P.M., *Bioorg Med Chem Lett*, **1999**, *9*, 2909-2914. Finally the modification of the different regions of capsaicin, including the replacement of the C region with a group containing a chlorobenzol moiety led to the development of the capsazepine, a well-known competitive antagonist of VR1. Bevan, S., Hothi, S., Hughes, G., James, I.F., Rang, H.P., Shah, K., Walpole, C.S., and Yeats, J.C., *Br J Pharmacol*, **1992**, *107*, 544-552. Taken together, we synthesized compound **1** to achieve a potent competitive antagonist, using the considerations mentioned above: (i) in the A region we introduced the 4-iodine to get full inhibition, (ii) in the B region we used the thiourea modification to get high potency, and (iii) in the C region we used the chlorobenzol moiety to get relatively high potency, not effecting the competitive mechanism. As a matter of fact, compound **1** is a relatively potent competitive antagonist having about 4 fold higher potency than the capsazepine and about 25 fold lower potency than the iodo-RTX determined in our functional assays.

During the drug development on VR1, two of the widely accepted methods to measure the structure-activity of compounds acting on the VR1 are the ^{3}H-RTX binding assay and the $^{45}Ca^{2+}$ uptake assay. Szallasi, A. and Blumberg, P.M., *Pharmacol Rev*, **1999**, *51*, 159-212. If binding and calcium uptake were mediated by the same receptor, a logical prediction would be that these two responses should display similar structure-activity relations. With regard to DRG neurons expressing native vanilloid receptors, this is clearly not the case: structure-activity analysis of different vanilloid derivatives revealed that the various compounds have distinct potencies for receptor binding and inducing $^{45}Ca^{2+}$-uptake. Szallasi, A. and Blumberg, P.M., *Pain JID - 7508686*, **1996**, *68*, 195-208. One extreme is capsaicin, which evokes calcium influx with an EC50 of about 50 nM but inhibits [^{3}H]RTX binding with a 30-fold lower affinity of 1.8 micromol in our current system. One model to account for the above discrepancies in vanilloid structure-activity relations was that RTX binding and calcium uptake detected two distinct classes of vanilloid receptors. Szallasi, A., Blumberg, P.M., Annicelli, L.L., Krause, J.E., and Cortright, D.N., *Mol Pharmacol*, **1999**, *56*, 581-587; Szallasi, A. and Blumberg, P.M., *Pain JID - 7508686*, **1996**, 68, 195-208. These putative receptors were referred to as R-type (preferentially labeled by RTX) and C-type (displaying a higher potency for capsaicin) vanilloid receptors, respectively. This model was somewhat challenged by the cloning of the vanilloid receptor-1, which was identified that the only receptor for vanilloids, like resiniferatoxin (RTX) or capsaicin. Caterina, M.J., Schumacher, M.A., Tominaga, M., Rosen, T.A., Levine, J.D., and Julius, D.,

Nature, **1997**, *389*, 816-824. Interestingly, the cloned VR1 mediated capsaicin responses are not much different from that of in DRG cells. Szallasi, A., Blumberg, P.M., Annicelli, L.L., Krause, J.E., and Cortright, D.N., *Mol Pharmacol*, **1999**, *56*, 581-587.

Two models were suggested to explain the different behaviors of ligands like capsaicin showing different structure-activity ratios. The first model was based on the assumption that the vanilloid binding site may be within or at the inner face of the cell membrane. Since this idea has been proven, it is possible that the calcium uptake assay may be subject to access constraints due to differences in cell membrane penetration, leading to distinct and independent structure-activity profiles from binding affinities for the compounds. Jung, J., Hwang, S.W., Kwak, J., Lee, S.Y., Kang, C.J., Kim, W.B., Kim, D., and Oh, U., *J Neurosci*, **1999**, *19*, 529-538. According to our model, presented here, a single polypeptide (VR1) could mediate both R-type binding and C-type $^{45}Ca^{2+}$ uptake.

The subcellular localization of VR1 is most likely intracellular, than plasmamembrane in the endogenous systems (DRG) and in the overexpressed systems as well. Ma, Q.P., *Neurosci Lett*, **2002**, *319*, 87-90; Olah, Z., Szabo, T., Karai, L., Hough, C., Fields, R.D., Caudle, R.M., Blumberg, P.M., and Iadarola, M.J., *J Biol Chem*, **2001**, *276*, 11021-11030. The functional consequences of this fact are unknown. However, emerging evidences support the idea, that the VR could play a role in the regulation of the release of Ca^{2+} from the intracellular pools. Liu, M., Liu, M.C., Magoulas, C., Priestley, J.V., and Willmott, N.J., *J Biol Chem*, **2003**, *278*, 5462-5472; Wisnoskey, B.J., Sinkins, W.G., and Schilling, W.P., *Biochem J*, **2003**, (in press). It was also suggested, that the plasma membrane localized VR1 could function as a transient receptor potential (trp) channel, namely it could be activated by the release of Ca^{2+} from the intracellular pools of Ca^{2+}. Liu, M., Liu, M.C., Magoulas, C., Priestley, J.V., and Willmott, N.J., *J Biol Chem*, **2003**, *278*, 5462-5472. Somewhat challenges this idea, that in previous experiments, the treatment of VR1 expressing CHO cells with thapsigargin was able to induce a robust release of the Ca^{2+}, but was not able to induce the influx of the Ca from the extracellular solution nor to induce $^{45}Ca^{2+}$ uptake. Wisnoskey, B.J., Sinkins, W.G., and Schilling, W.P., *Biochem J*, **2003**, (in press); Toth, A., Kedei, N., Szabo, T., Wang, Y., and Blumberg, P.M., *Biochem Biophys Res Commun*, **2002**, *293*, 777-782.

The data presented here suggest that the physiological context of a single protein could be important in the regulation of the functional properties of this polypeptide. The mechanism behind the remarkable specificity of compound **1** to the plasmamembrane

localized VR1 versus intracellular membrane localized VR1 is not clear. The possibilities are, at least, that the solubility of compound **1** in the different membranes is very different. If the membrane-drug interaction is an issue, the case could be, that compound **1** must bind to a component of the plasmamembrane and the two molecular complex could inhibit the VR1. This idea is challenged by the fast kinetics of the inhibition with compound **1**. An alternative explanation could be that the membrane - protein interaction is the reason of the differences. In this case the 3 dimensional structure of the VR1 is somewhat different in plasma or intracellular membranes. Since the importance of the lipophylic C region of capsaicin is well known in the interaction between the VR1 and vanilloids, one could speculate, that the distance for example of the membranes and the vanilloid binding site is affected by the membrane environment. Walpole, C.S., Wrigglesworth, R., Bevan, S., Campbell, E.A., Dray, A., James, I.F., Masdin, K.J., Perkins, M.N., and Winter, J., *J Med Chem*, **1993**, *36*, 2381-2389. If the binding site is not in the optimal distance, then the potency of the inhibitor is different. The third possibility is that the VR1 form a complex with another protein, having restricted localization. The interaction could mask or unmask potential binding sites for compound **1**.

Besides the molecular mechanism of the specificity of compound **1** the results suggest important information about the identity of receptors involved in the ^{3}H-RTX binding inhibition assay (R-type receptor) and in the $^{45}Ca^{2+}$ uptake assay (C-type receptor). Taken together that (i) compound **1** was unable to inhibit the RTX induced release of Ca^{2+} from the intracellular pools; (ii) compound **1** was unable to inhibit the ^{3}H-RTX binding to the membranes of CHO-VR1 cells; (iii) the majority of the VR1 localize in the intracellular membranes; (iv) the dose response for RTX on the induction of release of Ca^{2+} from the intracellular Ca^{2+} pools and on the induction of the Ca^{2+} influx from the extracellular solution is similar (under our circumstances) strongly supports the idea, that the identity of R-type receptor is the intracellular membrane localized VR1. In this case the replacement of ^{3}H-RTX by compound **1** (or other C-type receptor specific vanilloid, like capsaicin) is not detected, because the vast majority of the binding sites (intracellular VR1) are not affected. Assuming that only 1-5% of the VR1 expressed in the plasmamembrane, full replacement of ^{3}H-RTX on the plasmamembrane could cause only 1-5% inhibition of binding, which would be most likely impossible to measure. On the other hand, the identity of the C-type receptors most probably is the plasmamembrane localized VR1 since (i) the relative low amount of these receptors makes it possible to not effect the ^{3}H-RTX binding

experiments significantly; (ii) both the intracellular imaging and the $^{45}Ca^{2+}$ uptake assays are a measure of the Ca^{2+} influx from the extracellular milieu, and the VR1 is directly involved in this procedure; (iii) the Ca^{2+} influx is relatively insensitive from the release of the Ca^{2+} from the extracellular pools.

One of the important practical questions about the different properties of certain compounds and certain assay conditions is the functional consequences of the data. The pharmacological tools to investigate the specific roles of the different types of VR1 receptors were limited, so far. The capsaicin as a C-type specific agonist for example induces much higher elevations of the intracellular Ca^{2+} concentrations via activating of the plasmamembrane localized VR1 than it could cause by activating the release of Ca^{2+} from the intracellular pools. The possible specific effects of the release of Ca^{2+} from the intracellular pools are masked by the robust influx of Ca^{2+}. What is more, it could induce the influx of Ca^{2+} at much lower concentration. In summary, the overall response via C-type receptors could make it impossible to measure the specific effects on the R-type receptor. Compound **1** may be in this case a very useful drug, indeed. Using compound **1** as a potent, specific inhibitor of the C-type receptor, the R-type specific responses could be uniquely addressed using a not particularly specific agonist, like RTX. Another possibility is that the contribution of the R-type receptor to the physiological responses of the whole animal to painful stimuli, or other endogenous activators of the VR1 could be also addressed using compound **1**. One of the other interesting aspects could be the investigation of the role of intracellular VR1 in diseases, where the capsaicin treatment proven to be effective and the development of the disease is slow, like painful diabetic neuropathy or other neuropathies. Spruce, M.C., Potter, J., and Coppini, D.V., *Diabet Med*, **2003**, *20*, 88-98; Attal, N., *Clin J Pain*, **2000**, *16*, S118-S130.

Dosages

The dosage of any compositions of the present invention will vary depending on the symptoms, age and body weight of the patient, the nature and severity of the disorder to be treated or prevented, the route of administration, and the form of the subject composition. Any of the subject formulations may be administered in a single dose or in divided doses. Dosages for the compositions of the present invention may be readily determined by techniques known to those of skill in the art or as taught herein.

In certain embodiments, the dosage of the subject compounds will generally be in the range of about 0.01 ng to about 10 g per kg body weight, specifically in the range of about 1 ng to about 0.1 g per kg, and more specifically in the range of about 100 ng to about 10 mg per kg.

An effective dose or amount, and any possible affects on the timing of administration of the formulation, may need to be identified for any particular composition of the present invention. This may be accomplished by routine experiment as described herein, using one or more groups of animals (preferably at least 5 animals per group), or in human trials if appropriate. The effectiveness of any subject composition and method of treatment or prevention may be assessed by administering the composition and assessing the effect of the administration by measuring one or more applicable indices, and comparing the post-treatment values of these indices to the values of the same indices prior to treatment.

The precise time of administration and amount of any particular subject composition that will yield the most effective treatment in a given patient will depend upon the activity, pharmacokinetics, and bioavailability of a subject composition, physiological condition of the patient (including age, sex, disease type and stage, general physical condition, responsiveness to a given dosage and type of medication), route of administration, and the like. The guidelines presented herein may be used to optimize the treatment, e.g., determining the optimum time and/or amount of administration, which will require no more than routine experimentation consisting of monitoring the subject and adjusting the dosage and/or timing.

While the subject is being treated, the health of the patient may be monitored by measuring one or more of the relevant indices at predetermined times during the treatment period. Treatment, including composition, amounts, times of administration and formulation, may be optimized according to the results of such monitoring. The patient may be periodically reevaluated to determine the extent of improvement by measuring the same parameters. Adjustments to the amount(s) of subject composition administered and possibly to the time of administration may be made based on these reevaluations.

Treatment may be initiated with smaller dosages which are less than the optimum dose of the compound. Thereafter, the dosage may be increased by small increments until the optimum therapeutic effect is attained.

The use of the subject compositions may reduce the required dosage for any individual agent contained in the compositions because the onset and duration of effect of the different agents may be complimentary.

Toxicity and therapeutic efficacy of subject compositions may be determined by standard pharmaceutical procedures in cell cultures or experimental animals, e.g., for determining the LD_{50} and the ED_{50}.

The data obtained from the cell culture assays and animal studies may be used in formulating a range of dosage for use in humans. The dosage of any subject composition lies preferably within a range of circulating concentrations that include the ED_{50} with little or no toxicity. The dosage may vary within this range depending upon the dosage form employed and the route of administration utilized. For compositions of the present invention, the therapeutically effective dose may be estimated initially from cell culture assays.

Formulation

The compositions of the present invention may be administered by various means, depending on their intended use, as is well known in the art. For example, if compositions of the present invention are to be administered orally, they may be formulated as tablets, capsules, granules, powders or syrups. Alternatively, formulations of the present invention may be administered parenterally as injections (intravenous, intramuscular or subcutaneous), drop infusion preparations or suppositories. For application by the ophthalmic mucous membrane route, compositions of the present invention may be formulated as eyedrops or eye ointments. These formulations may be prepared by conventional means, and, if desired, the compositions may be mixed with any conventional additive, such as an excipient, a binder, a disintegrating agent, a lubricant, a corrigent, a solubilizing agent, a suspension aid, an emulsifying agent or a coating agent.

In formulations of the subject invention, wetting agents, emulsifiers and lubricants, such as sodium lauryl sulfate and magnesium stearate, as well as coloring agents, release agents, coating agents, sweetening, flavoring and perfuming agents, preservatives and antioxidants may be present in the formulated agents.

Subject compositions may be suitable for oral, nasal, topical (including buccal and sublingual), rectal, vaginal, aerosol and/or parenteral administration. The formulations may conveniently be presented in unit dosage form and may be prepared by any methods well known in the art of pharmacy. The amount of composition that may be combined with a carrier material to produce a single dose vary depending upon the subject being treated, and the particular mode of administration.

Methods of preparing these formulations include the step of bringing into association compositions of the present invention with the carrier and, optionally, one or more accessory ingredients. In general, the formulations are prepared by uniformly and intimately bringing into association agents with liquid carriers, or finely divided solid carriers, or both, and then, if necessary, shaping the product.

Formulations suitable for oral administration may be in the form of capsules, cachets, pills, tablets, lozenges (using a flavored basis, usually sucrose and acacia or tragacanth), powders, granules, or as a solution or a suspension in an aqueous or non-aqueous liquid, or as an oil-in-water or water-in-oil liquid emulsion, or as an elixir or syrup, or as pastilles (using an inert base, such as gelatin and glycerin, or sucrose and acacia), each containing a predetermined amount of a subject composition thereof as an active ingredient. Compositions of the present invention may also be administered as a bolus, electuary, or paste.

In solid dosage forms for oral administration (capsules, tablets, pills, dragees, powders, granules and the like), the subject composition is 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 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, acetyl alcohol and glycerol monostearate; (8) absorbents, such as kaolin and bentonite clay; (9) lubricants, such a talc, calcium stearate, magnesium stearate, solid polyethylene glycols, sodium lauryl sulfate, and mixtures thereof; and (10) coloring agents. In the case of capsules, tablets and pills, the compositions may also comprise buffering agents. Solid compositions of a similar type

may also be employed as fillers in soft and hard-filled gelatin capsules using such excipients as lactose or milk 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 subject composition moistened with an inert liquid diluent. Tablets, and other solid dosage forms, such as dragees, 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.

Liquid dosage forms for oral administration include pharmaceutically acceptable emulsions, microemulsions, solutions, suspensions, syrups and elixirs. In addition to the subject composition, the liquid dosage forms may contain inert diluents commonly used in the art, such as, for example, water or other solvents, solubilizing agents and emulsifiers, such as ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propylene glycol, 1,3-butylene glycol, 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.

Suspensions, in addition to the subject composition, may contain suspending agents as, for example, ethoxylated isostearyl alcohols, polyoxyethylene sorbitol and sorbitan esters, microcrystalline cellulose, aluminum metahydroxide, bentonite, agar-agar and tragacanth, and mixtures thereof.

Formulations for rectal or vaginal administration may be presented as a suppository, which may be prepared by mixing a subject composition with one or more suitable non-irritating 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 body cavity and release the active agent. Formulations which are suitable for vaginal administration also include pessaries, tampons, creams, gels, pastes, foams or spray formulations containing such carriers as are known in the art to be appropriate.

Dosage forms for transdermal administration of a subject composition includes powders, sprays, ointments, pastes, creams, lotions, gels, solutions, patches and inhalants. The active component may be mixed under sterile conditions with a pharmaceutically acceptable carrier, and with any preservatives, buffers, or propellants which may be required.

The ointments, pastes, creams and gels may contain, in addition to a subject composition, excipients, such as animal and vegetable fats, oils, waxes, paraffins, starch, tragacanth, cellulose derivatives, polyethylene glycols, silicones, bentonites, silicic acid, talc and zinc oxide, or mixtures thereof.

Powders and sprays may contain, in addition to a subject composition, excipients such as lactose, talc, silicic acid, aluminum hydroxide, calcium silicates and polyamide powder, or mixtures of these substances. Sprays may additionally contain customary propellants, such as chlorofluorohydrocarbons and volatile unsubstituted hydrocarbons, such as butane and propane.

Compositions of the present invention may alternatively be administered by aerosol. This is accomplished by preparing an aqueous aerosol, liposomal preparation or solid particles containing the compound. A non-aqueous (e.g., fluorocarbon propellant) suspension could be used. Sonic nebulizers may be used because they minimize exposing the agent to shear, which may result in degradation of the compounds contained in the subject compositions.

Ordinarily, an aqueous aerosol is made by formulating an aqueous solution or suspension of a subject composition together with conventional pharmaceutically acceptable carriers and stabilizers. The carriers and stabilizers vary with the requirements of the particular subject composition, but typically include non-ionic surfactants (Tweens, Pluronics, or polyethylene glycol), innocuous proteins like serum albumin, sorbitan esters, oleic acid, lecithin, amino acids such as glycine, buffers, salts, sugars or sugar alcohols. Aerosols generally are prepared from isotonic solutions.

Pharmaceutical compositions of this invention suitable for parenteral administration comprise a subject composition in combination with one or more pharmaceutically-acceptable sterile isotonic aqueous or non-aqueous 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 formulation isotonic with the blood of the intended recipient or suspending or thickening agents.

Examples of suitable aqueous and non-aqueous carriers which may be employed in the pharmaceutical compositions of the invention include water, ethanol, polyols (such as glycerol, propylene glycol, polyethylene glycol, and the like), and suitable mixtures thereof, vegetable oils, such as olive oil, and injectable organic esters, such as ethyl oleate. Proper fluidity may 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.

Kits

This invention also provides kits for conveniently and effectively implementing the methods of this invention. Such kits comprise any subject composition, and a means for facilitating compliance with methods of this invention. Such kits provide a convenient and effective means for assuring that the subject to be treated takes the appropriate active in the correct dosage in the correct manner. The compliance means of such kits includes any means which facilitates administering the actives according to a method of this invention. Such compliance means include instructions, packaging, and dispensing means, and combinations thereof. Kit components may be packaged for either manual or partially or wholly automated practice of the foregoing methods. In other embodiments involving kits, this invention contemplates a kit including compositions of the present invention, and optionally instructions for their use.

Exemplification

Materials

Resiniferatoxin was from Biomol (Plymouth Meeting, PA, USA); capsaicin, iodo-resiniferatoxin and other chemicals were from Sigma (St. Louis, MO, USA) if not stated otherwise.

Cell culture

The selected stable CHO cell clone expressing VR1 (Tet-Off induced CHO-VR1 cells) were cultured in maintaining media (F12 supplemented with 10% FBS (USA sourced), 25 mM HEPES, pH 7.5, 250 μg/mL geneticin (all from Life Technologies Inc.,

Rockville, MD, USA) and 1 mg/L tetracycline (Calbiochem, La Jolla, CA, USA). For transfections, CHO cells were plated into the wells of 96 well plates (Croning) containing 25 mm round, uncoated glass coverslips at the bottom of the wells. The next day, when the confluency was about 20-30% the cells were transfected with GFP-VR1 plasmid (1 microgram plasmid into each well) using the lipofectamine plus method according to the manufacturer's instructions.

$^{45}Ca^{2+}$ uptake experiments

CHO-VR1 cells were plated in 24-well plates to yield a cell density of 20-40% confluency. The next day, the media was changed to remove the tetracycline and induce VR1 expression. Experiments were done approximately 48 h after induction. For assay of $^{45}Ca^{2+}$ uptake, cells were incubated for 5 min at 37 °C in a total volume of 500 µl of serum-free DMEM (Life Technologies Inc., Rockville, MD, USA) containing 1.8 mM $CaCl_2$ in the presence of 0.25 mg/mL bovine serum albumin (BSA, Sigma, St. Louis, MO, USA), 1 µCi/mL $^{45}Ca^{2+}$ (ICN, Costa Mesa, CA, USA), and increasing concentrations of the compound to be tested. Immediately after the incubation, extracellular $^{45}Ca^{2+}$ was removed by washing the cells three times with cold DPBS (Life Technologies Inc., Rockville, MD, USA) containing 1.8 mM $CaCl_2$. Then, 400 µl RIPA buffer (50 mM Tris-Cl pH 7.4; 150 mM NaCl; 1% Triton X-100; 0.1% SDS; 1% sodium deoxycholate) was added to each well in order to lyse the cells. Plates were shaken slowly for 20 min. Then, 300 µl of cell lysate was transferred from each well into a scintillation vial and radioactivity was determined by scintillation counting. For each data point in each experiment, four wells were assayed. Data from these experiments were analyzed by computer fit to the Hill equation. Each experiment was performed at least three times.

[^{3}H]RTX binding experiments

Binding assay mixtures were set up on ice and contained about $5x10^5$ VR1-transfected CHO cells, 0.25 mg/mL bovine serum albumin (Cohn fraction V, Sigma, St. Louis, MO, USA), [^{3}H]resiniferatoxin (37 mCi/mmol; Perkin Elmer, Boston, MA, USA) and non-radioactive ligands. The final volume was adjusted to 400 µl with the buffer described above. Non-specific binding was defined as binding occurring in the presence of 100 nM non-radioactive RTX (Alexis Corp., San Diego, CA, USA). Binding was analyzed in the presence of a fixed concentration of [^{3}H]RTX (~40 pM) and various concentrations of competing ligands.

The binding was initiated by transferring the assay tubes into a 37 °C water bath and then was terminated following a 60 min incubation period by cooling the assay mixtures on ice. Non-specific binding was reduced by adding 200 µg of bovine glycoprotein fraction VI (ICN, Costa Mesa, CA, USA) to each tube. Membrane-bound RTX was separated from the free and the glycoprotein-bound RTX by pelleting the membranes in a Beckman 12 benchtop centrifuge (15 min; maximal velocity), and the radioactivity was determined by scintillation counting.

Ca^{2+} imaging

CHO-VR1 cells were plated on 25 mm round glass coverslips in maintaining media (F12 supplemented with 10% FBS, 25 mM HEPES, pH 7.5, 250 µg/mL geneticin and 1 mg/L tetracycline). The next day, the media was changed to inducing media (maintaining media without tetracycline but containing 1 mM sodium butyrate) to induce VR1 expression. Experiments were done approximately 24 hours after induction. For the fura2 loading, the cells were transferred to DPBS containing 1 mg/mL BSA and 5 µM fura2-AM (Molecular Probes, Eugene, OR, USA) for 2 hours at room temperature. The cells were kept in maintaining media at room temperature until the measurements, which were carried out in DPBS, were performed. The fluorescence of individual cells was measured with an IntCyt Im2 fluorescence imaging system (Intracellular Imaging Inc., Cincinnati, OH, USA). The cells within a field were illuminated alternately at 340 and 380 nm. Emitted light >510nm was measured. Data were analyzed with the Incyt 4.5 software and further processed with Excel (Microsoft) and GraphPad Prism 2.0 (Graphpad Software Inc.) software.

References

All publications and patents mentioned herein, including those items listed below, are hereby incorporated by reference in their entirety as if each individual publication or patent was specifically and individually incorporated by reference. In case of conflict, the present application, including any definitions herein, will control.

U.S. Patent Nos.: 6,559,159; 6,559,158; 6,548,637; 6,538,120; 6,538,008; 6,534,514; 6,528,271; 6,525,062; 6,512,009; 6,500,927; 6,500,824; 6,476,076; 6,475,494; 6,465,442; 6,455,278; 6,444,440; 6,432,652; 6,419,959; 6,406,908; and 6,395,705.

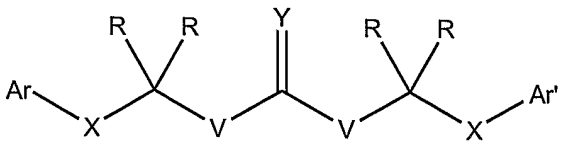
Equivalents

While specific embodiments of the subject invention have been discussed, the above specification is illustrative and not restrictive. Many variations of the invention will become apparent to those skilled in the art upon review of this specification. The full scope of the invention should be determined by reference to the claims, along with their full scope of equivalents, and the specification, along with such variations.

Unless otherwise indicated, all numbers expressing quantities of ingredients, reaction conditions, and so forth used in the specification and claims are to be understood as being modified in all instances by the term "about." Accordingly, unless indicated to the contrary, the numerical parameters set forth in this specification and attached claims are approximations that may vary depending upon the desired properties sought to be obtained by the present invention.

We claim:

1. A compound represented by formula **I**:



I

wherein, independently for each occurrence:

Y is O, S, or $N(R_1)$;

V is O, S, or $N(R_4)$;

X is a bond, O, S, N(R), or $C(R)_2$;

R is H, alkyl, cycloalkyl, aryl, or aralkyl;

R_1 is alkyl, cycloalkyl, aryl, or aralkyl;

R_4 is H, alkyl, cycloalkyl, aryl, or aralkyl;

Ar is a monocyclic or bicyclic aromatic moiety of 5 to 12 atoms, unsubstituted or substituted with one or more R_3;

Ar' is a monocyclic or bicyclic aromatic moiety of 5 to 12 atoms, unsubstituted or substituted with one or more R_3; and

R_3 is alkyl, cycloalkyl, alkenyl, alkynyl, aryl, aralkyl, hydroxy, alkoxy, acetyl, acetyloxy, nitro, cyano, aryloxy, amino, halogen, methanesulfonylamino, $-NHCO_2CH_3$, $-NHCOCH_3$, $-CF_3$, sulfamoyl, or $-OCH_2OCH_3$.

2. The compound of claim 1, wherein Y is S or O.

3. The compound of claim 1, wherein Y is S.

4. The compound of claim 1, wherein V is $N(R_4)$.

5. The compound of claim 1, wherein V is $N(R_4)$; and R_4 is H.

6. The compound of claim 1, wherein X is a bond.

7. The compound of claim 1, wherein R is H or alkyl.

8. The compound of claim 1, wherein Ar represents unsubstituted or substituted phenyl or naphthalenyl.

9. The compound of claim 1, wherein Ar' represents unsubstituted or substituted phenyl or naphthalenyl.

10. The compound of claim 1, wherein Ar represents substituted phenyl.

11. The compound of claim 1, wherein Ar' represents substituted phenyl.

12. The compound of claim 1, wherein Ar represents 4-chlorophenyl.

13. The compound of claim 1, wherein Ar' represents 3-methoxy-4-hydroxy-5-iodophenyl.

14. The compound of claim 1, wherein Y is S; and V is $N(R_4)$.

15. The compound of claim 1, wherein Y is S; V is $N(R_4)$; and R_4 is H.

16. The compound of claim 1, wherein Y is S; V is $N(R_4)$; R_4 is H; and X is a bond.

17. The compound of claim 1, wherein Y is S; V is $N(R_4)$; R_4 is H; X is a bond; and R is H or alkyl.

18. The compound of claim 1, wherein Y is S; V is $N(R_4)$; R_4 is H; X is a bond; R is H or alkyl; Ar represents unsubstituted or substituted phenyl or naphthalenyl; and Ar' represents unsubstituted or substituted phenyl or naphthalenyl.

19. The compound of claim 1, wherein Y is S; V is $N(R_4)$; R_4 is H; X is a bond; and R is H or alkyl; Ar represents unsubstituted or substituted phenyl or naphthalenyl; and Ar' represents 3-methoxy-4-hydroxy-5-iodophenyl.

20. The compound of claim 1, wherein Y is S; V is $N(R_4)$; R_4 is H; X is a bond; and R is H or alkyl; Ar represents substituted phenyl; and Ar' represents 3-methoxy-4-hydroxy-5-iodophenyl.

21. The compound of claim 1, wherein Y is S; V is $N(R_4)$; R_4 is H; X is a bond; and R is H or alkyl; Ar represents 4-chlorophenyl; and Ar' represents 3-methoxy-4-hydroxy-5-iodophenyl.

22. The compound of claim 1, wherein the compound has an IC_{50} less than 1 μM in a $^{45}Ca^{2+}$ uptake assay.

23. The compound of claim 1, wherein the compound has an IC_{50} less than 100 nM in a $^{45}Ca^{2+}$ uptake assay.

24. The compound of claim 1, wherein the compound has an IC_{50} less than 10 nM in a $^{45}Ca^{2+}$ uptake assay.

25. A pharmaceutical composition, comprising a compound of claim 1; and a pharmaceutically acceptable excipient.

26. A method of modulating the activity of a vanilloid receptor in a mammal, comprising administering to the mammal a therapeutically effective amount of a compound of claim 1.

27. The method of claim 26, wherein the mammal is primate, equine, canine or feline.

28. The method of claim 26, wherein the mammal is a human.

29. The method of claim 26, wherein the compound is administered orally.

30. The method of claim 26, wherein the compound is administered intravenously.

31. The method of claim 26, wherein the compound is administered sublingually.

32. The method of claim 26, wherein the compound is administered ocularly.

33. The method of claim 26, wherein the compound is administered transdermally.

34. The method of claim 26, wherein the compound is administered rectally.

35. The method of claim 26, wherein the compound is administered vaginally.

36. The method of claim 26, wherein the compound is administered topically.

37. The method of claim 26, wherein the compound is administered intramuscularly.

38. The method of claim 26, wherein the compound is administered subcutaneously.

39. The method of claim 26, wherein the compound is administered buccally.

40. The method of claim 26, wherein the compound is administered nasally.

41. A method of treating a mammal suffering from pain associated with a malady selected from the group consisting of bladder hyperreflexia, detrusor instability, post-mastectomy pain, mucositis, interstitial cystitis, pharyngitis, pancreatitis, enteritis, cellulitis, postherpetic neuralgia, peripheral neuropathy, arthritis, and bony

fractures, comprising administering to the mammal a therapeutically effective amount of a compound of claim 1.

42. The method of claim 41, wherein the mammal is a primate, equine, canine or feline.

43. The method of claim 41, wherein the mammal is a human.

44. The method of claim 41, wherein the compound is administered orally.

45. The method of claim 41, wherein the compound is administered intravenously.

46. The method of claim 41, wherein the compound is administered sublingually.

47. The method of claim 41, wherein the compound is administered ocularly.

48. The method of claim 41, wherein the compound is administered transdermally.

49. The method of claim 41, wherein the compound is administered rectally.

50. The method of claim 41, wherein the compound is administered vaginally.

51. The method of claim 41, wherein the compound is administered topically.

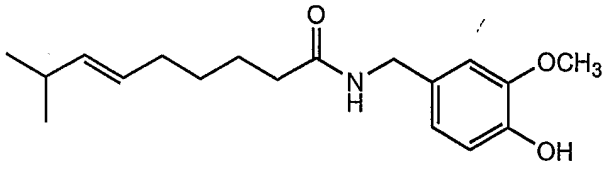
52. The method of claim 41, wherein the compound is administered intramuscularly.

53. The method of claim 41, wherein the compound is administered subcutaneously.

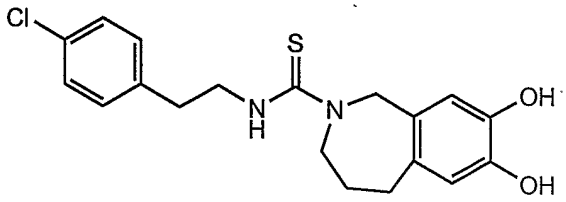
54. The method of claim 41, wherein the compound is administered buccally.

55. The method of claim 41, wherein the compound is administered nasally.

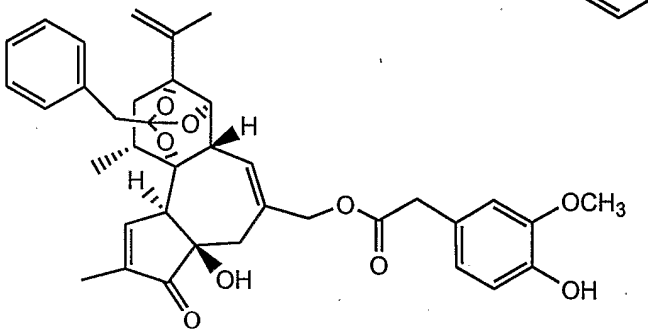
Figure 1



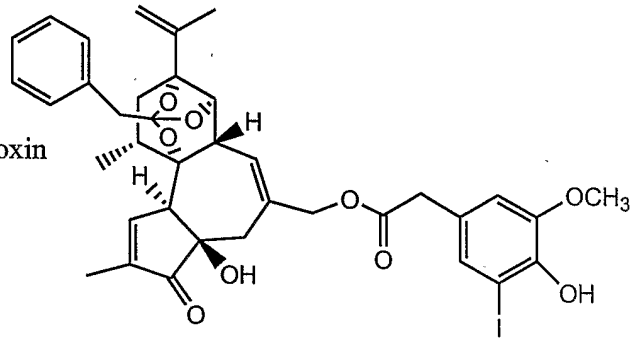
Capsaicin



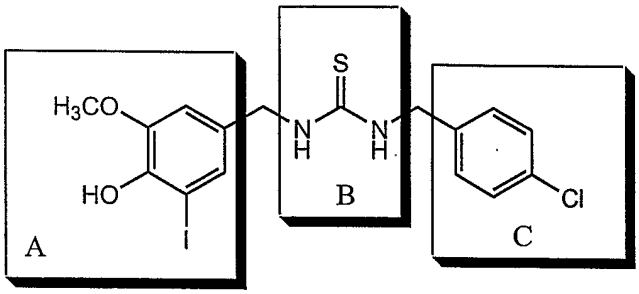
Capsazepine



Resiniferatoxin



5-Iodo-resiniferatoxin



Compound 1