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(54) Title: SUBSTITUTED PYRIMIDINONES



(I)

(57) Abstract: Substituted pyrimidinones are provided, of the Formula (I): wherein variables are as described herein. Such compounds are ligands that may be used to modulate specific receptor activity in vivo or in vitro, and are particularly useful in the treatment of conditions associated with pathological receptor activation in humans, domesticated companion animals and livestock animals. Pharmaceutical compositions and methods for using such compounds to treat such disorders are provided, as are methods for using such ligands for receptor localization studies.

SUBSTITUTED PYRIMIDINONES

RELATED APPLICATIONS

5 This application claims the benefit of U.S. Provisional Patent Application Nos. 60/943,547, filed June 12, 2007, 61/016,429, filed February 11, 2008, and 61/022,432, filed February 22, 2008. The contents of all of these applications are incorporated herein in their entirety.

10 FIELD OF THE INVENTION

 This invention relates generally to substituted pyrimidinones that have useful pharmacological properties. The invention further relates to the use of such compounds for treating conditions related to capsaicin receptor activation, for identifying other agents that bind to capsaicin receptor, and as probes for the detection and localization of capsaicin
15 receptors.

BACKGROUND OF THE INVENTION

 Pain perception, or nociception, is mediated by the peripheral terminals of a group of specialized sensory neurons, termed "nociceptors." A wide variety of physical and chemical
20 stimuli induce activation of such neurons in mammals, leading to recognition of a potentially harmful stimulus. Inappropriate or excessive activation of nociceptors, however, can result in debilitating acute or chronic pain.

 Neuropathic pain involves pain signal transmission in the absence of stimulus, and typically results from damage to the nervous system. In most instances, such pain is thought
25 to occur because of sensitization in the peripheral and central nervous systems following initial damage to the peripheral system (*e.g.*, via direct injury or systemic disease). Neuropathic pain is typically burning, shooting and unrelenting in its intensity and can sometimes be more debilitating than the initial injury or disease process that induced it.

 Existing treatments for neuropathic pain are largely ineffective. Opiates, such as
30 morphine, are potent analgesics, but their usefulness is limited because of adverse side effects, such as physical addictiveness and withdrawal properties, as well as respiratory depression, mood changes, and decreased intestinal motility with concomitant constipation, nausea, vomiting, and alterations in the endocrine and autonomic nervous systems. In addition, neuropathic pain is frequently non-responsive or only partially responsive to

conventional opioid analgesic regimens. Treatments employing the N-methyl-D-aspartate antagonist ketamine or the alpha(2)-adrenergic agonist clonidine can reduce acute or chronic pain, and permit a reduction in opioid consumption, but these agents are often poorly tolerated due to side effects.

5 Topical treatment with capsaicin has been used to treat chronic and acute pain, including neuropathic pain. Capsaicin is a pungent substance derived from the plants of the Solanaceae family (which includes hot chili peppers) and appears to act selectively on the small diameter afferent nerve fibers (A-delta and C fibers) that are believed to mediate pain. The response to capsaicin is characterized by persistent activation of nociceptors in
10 peripheral tissues, followed by eventual desensitization of peripheral nociceptors to one or more stimuli. From studies in animals, capsaicin appears to trigger C fiber membrane depolarization by opening cation selective channels for calcium and sodium.

Similar responses are also evoked by structural analogues of capsaicin that share a common vanilloid moiety. One such analogue is resiniferatoxin (RTX), a natural product of
15 *Euphorbia* plants. The term vanilloid receptor (VR) was coined to describe the neuronal membrane recognition site for capsaicin and such related irritant compounds. The capsaicin response is competitively inhibited (and thereby antagonized) by another capsaicin analog, capsazepine, and is also inhibited by the non-selective cation channel blocker ruthenium red, which binds to VR with no more than moderate affinity (typically with a K_i value of no lower
20 than 140 μM).

Rat and human vanilloid receptors have been cloned from dorsal root ganglion cells. The first type of vanilloid receptor to be identified is known as vanilloid receptor type 1 (VR1, also known as TRPV1), and the terms "VR1" and "capsaicin receptor" are used interchangeably herein to refer to rat and/or human receptors of this type, as well as
25 mammalian homologues. The role of VR1 in pain sensation has been confirmed using mice lacking this receptor, which exhibit no vanilloid-evoked pain behavior and impaired responses to heat and inflammation. VR1 is a nonselective cation channel with a threshold for opening that is lowered in response to elevated temperatures, low pH, and capsaicin receptor agonists. Opening of the capsaicin receptor channel is generally followed by the
30 release of inflammatory peptides from neurons expressing the receptor and other nearby neurons, increasing the pain response. After initial activation by capsaicin, the capsaicin receptor undergoes a rapid desensitization via phosphorylation by cAMP-dependent protein kinase.

Because of their ability to desensitize nociceptors in peripheral tissues, VR1 agonist
35 vanilloid compounds have been used as topical anesthetics. However, agonist application

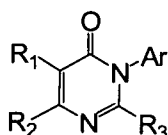
may itself cause burning pain, which limits this therapeutic use. Recently, it has been reported that VR1 antagonists, including certain nonvanilloid compounds, are also useful for the treatment of pain (*see, e.g.*, PCT International Application Publication Numbers WO 05/049613, WO 06/100520, WO 06/120481 and WO 06/122200).

5 Thus, compounds that interact with VR1, but do not elicit the initial painful sensation of VR1 agonist vanilloid compounds, are desirable for the treatment of chronic and acute pain, including neuropathic pain, as well as other conditions that are responsive to capsaicin receptor modulation. The present invention fulfills this need, and provides further related advantages.

10

SUMMARY OF THE INVENTION

The present invention provides substituted pyrimidinones of Formula I:



Formula I

as well as pharmaceutically acceptable salts of such compounds. Within Formula I:

Ar is 6- to 10-membered aryl (*e.g.*, phenyl) or a 5- to 10-membered heteroaryl, (*e.g.*, pyridyl)

15 that is optionally substituted and is preferably substituted with from 1 to 3 substituents independently chosen from halogen, cyano, amino, nitro, C₁-C₆alkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, C₁-C₆haloalkyl, C₁-C₆hydroxyalkyl, C₁-C₆alkoxy, C₁-C₆haloalkoxy, (C₃-C₇cycloalkyl)C₀-C₄alkyl, and mono- or di-(C₁-C₆alkyl)amino;

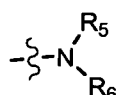
R₁ is:

20 (i) hydrogen, halogen, hydroxy, amino or cyano; or
 (ii) C₁-C₆alkyl, C₁-C₆alkoxy, mono- or di-(C₁-C₆alkyl)amino, (C₃-C₇cycloalkyl)C₀-C₄alkyl, phenyl or 5- or 6-membered heteroaryl, each of which is optionally substituted and each of which is substituted with from 0 to 4 substituents independently chosen from R₇;

25 R₂ is:

(i) hydrogen, hydroxy, halogen or cyano;
 (ii) C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆alkoxy, C₂-C₆alkyl ether, (C₃-C₇cycloalkyl)C₀-C₄alkyl, or phenyl, each of which is optionally substituted and each of which is preferably substituted with from 0 to 4 substituents independently chosen from R₇; or

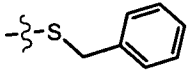
30 (iii) a group of the formula:



wherein R_5 and R_6 are independently chosen from hydrogen, C_1 - C_6 alkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, $(C_3$ - C_7 cycloalkyl) C_0 - C_4 alkyl, C_1 - C_6 alkanoyl, C_1 - C_6 alkylsulfonyl and (4- to 7-membered heterocycle) C_0 - C_4 alkyl, each of which is optionally substituted and each of which is preferably substituted with from 0 to 2 substituents independently chosen from R_7 ; or R_5 and R_6 are taken together to form a 4- to 7-membered heterocycle that is substituted with from 0 to 2 substituents independently chosen from R_7 ; and

R_3 is:

- (i) $(C_3$ - C_7 cycloalkyl) C_0 - C_4 alkyl that is substituted with from 0 to 4 substituents (e.g., from 1 to 4 substituents) independently chosen from C_1 - C_6 alkyl, C_1 - C_6 haloalkyl and substituents that are taken together to form a fused C_3 - C_7 cycloalkyl or a C_1 - C_3 alkylene bridge;
- (ii) C_1 - C_6 haloalkyl, C_1 - C_6 alkoxy, C_1 - C_6 haloalkoxy, C_1 - C_6 alkylthio, C_1 - C_6 haloalkylthio or mono- or di- $(C_1$ - C_6 alkyl)amino, each of which is substituted with from 0 to 4 substituents independently chosen from R_7 , phenyl and 5- or 6-membered heteroaryl, which phenyl and heteroaryl are substituted with from 0 to 4 substituents independently chosen from R_7 ,

such that R_3 is not unsubstituted benzylthio (i.e., ); or

- (iii) phenoxy that is substituted with from 0 to 4 substituents independently chosen from R_7 ; and

each R_7 is independently chosen from halogen, hydroxy, cyano, amino, nitro, oxo, C_1 - C_6 alkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, C_1 - C_6 haloalkyl, C_1 - C_6 hydroxyalkyl, C_1 - C_6 alkoxy, C_1 - C_6 haloalkoxy, $(C_3$ - C_7 cycloalkyl) C_0 - C_4 alkyl, and mono- or di- $(C_1$ - C_6 alkyl)amino.

Within certain aspects, compounds of Formula I are VR1 modulators and exhibit a K_i of no greater than 1 micromolar, 500 nanomolar, 100 nanomolar, 50 nanomolar, 10 nanomolar or 1 nanomolar in a capsaicin receptor binding assay and/or have an EC_{50} or IC_{50} value of no greater than 1 micromolar, 500 nanomolar, 100 nanomolar, 50 nanomolar, 10 nanomolar or 1 nanomolar in an *in vitro* assay for determination of capsaicin receptor agonist or antagonist activity. In certain embodiments, such VR1 modulators are VR1 antagonists and exhibit no detectable agonist activity in an *in vitro* assay of capsaicin receptor activation (e.g., the assay provided in Example 6, herein) at a concentration equal to the IC_{50} , 10 times the IC_{50} or 100 times the IC_{50} .

Within certain aspects, compounds provided herein are labeled with a detectable marker (e.g., radiolabeled or fluorescein conjugated).

The present invention further provides, within other aspects, pharmaceutical compositions comprising at least one substituted pyrimidinone in combination with a physiologically acceptable carrier or excipient.

5 Within further aspects, methods are provided for reducing calcium conductance of a cellular capsaicin receptor, comprising contacting a cell (*e.g.*, neuronal, such as cells of the central nervous system or peripheral ganglia, urothelial or lung) that expresses a capsaicin receptor with at least one VR1 modulator as described herein. Such contact may occur *in vivo* or *in vitro* and is generally performed using a concentration of VR1 modulator that is sufficient to alter the binding of vanilloid ligand to VR1 *in vitro* (using the assay provided in
10 Example 5) and/or VR1-mediated signal transduction (using an assay provided in Example 6).

Methods are further provided for inhibiting binding of vanilloid ligand to a capsaicin receptor. Within certain aspects, the inhibition takes place *in vitro*. Such methods comprise contacting a capsaicin receptor with at least one VR1 modulator as described herein, under conditions and in an amount or concentration sufficient to detectably inhibit vanilloid ligand
15 binding to the capsaicin receptor. Within other aspects, the capsaicin receptor is in a patient. Such methods comprise contacting cells expressing a capsaicin receptor in a patient with at least one VR1 modulator as described herein in an amount or concentration that would be sufficient to detectably inhibit vanilloid ligand binding to cells expressing a cloned capsaicin receptor *in vitro*.

20 The present invention further provides methods for treating a condition responsive to capsaicin receptor modulation in a patient, comprising administering to the patient a therapeutically effective amount of at least one VR1 modulator as described herein.

Within other aspects, methods are provided for treating pain in a patient, comprising administering to a patient suffering from (or at risk for) pain a therapeutically effective
25 amount of at least one VR1 modulator as described herein.

Methods are further provided for treating itch, urinary incontinence, overactive bladder, menopause symptoms, cough and/or hiccup in a patient, comprising administering to a patient suffering from (or at risk for) one or more of the foregoing conditions a therapeutically effective amount of at least one VR1 modulator as described herein.

30 The present invention further provides methods for promoting weight loss in an obese patient, comprising administering to an obese patient a therapeutically effective amount of at least one VR1 modulator as described herein.

Methods are further provided for identifying an agent that binds to capsaicin receptor, comprising: (a) contacting capsaicin receptor with a labeled compound as described herein
35 under conditions that permit binding of the compound to capsaicin receptor, thereby

generating bound, labeled compound; (b) detecting a signal that corresponds to the amount of bound, labeled compound in the absence of test agent; (c) contacting the bound, labeled compound with a test agent; (d) detecting a signal that corresponds to the amount of bound labeled compound in the presence of test agent; and (e) detecting a decrease in signal detected in step (d), as compared to the signal detected in step (b).

Within further aspects, the present invention provides methods for determining the presence or absence of capsaicin receptor in a sample, comprising: (a) contacting a sample with a compound as described herein under conditions that permit binding of the compound to capsaicin receptor; and (b) detecting a signal indicative of a level of the compound bound to capsaicin receptor.

The present invention also provides packaged pharmaceutical preparations, comprising: (a) a pharmaceutical composition as described herein in a container; and (b) instructions for using the composition to treat one or more conditions responsive to capsaicin receptor modulation, such as pain, itch, urinary incontinence, overactive bladder, cough, hiccup and/or obesity.

In yet another aspect, the present invention provides methods for preparing the compounds disclosed herein, including the intermediates.

These and other aspects of the invention will become apparent upon reference to the following detailed description.

20

DETAILED DESCRIPTION

As noted above, the present invention provides substituted pyrimidinones. Such compounds may be used *in vitro* or *in vivo*, to modulate capsaicin receptor activity in a variety of contexts.

25 TERMINOLOGY

Compounds are generally described herein using standard nomenclature. For compounds having asymmetric centers, it should be understood that (unless otherwise specified) all of the optical isomers and mixtures thereof are encompassed. In addition, compounds with carbon-carbon double bonds may occur in Z- and E- forms, with all isomeric forms of the compounds being included in the present invention unless otherwise specified. Where a compound exists in various tautomeric forms, a recited compound is not limited to any one specific tautomer, but rather is intended to encompass all tautomeric forms. Certain compounds are described herein using a general formula that includes variables (*e.g.*, R₁, Ar). Unless otherwise specified, each variable within such a formula is defined independently of

any other variable, and any variable that occurs more than one time in a formula is defined independently at each occurrence.

The phrase "substituted pyrimidinones," as used herein, encompasses all compounds of Formula I, as well as compounds of other Formulas provided herein (including any enantiomers, racemates and stereoisomers) and pharmaceutically acceptable salts thereof. In certain embodiments, substituted pyrimidinones provided herein are isolated so as to be substantially free of residual organic solvent (*i.e.*, any such solvent in the preparation is present in an amount that is at or below the limit set for that solvent by the International Council on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH)).

A "pharmaceutically acceptable salt" of a compound recited herein is an acid or base salt that is suitable for use in contact with the tissues of human beings or animals without excessive toxicity or carcinogenicity, and preferably without irritation, allergic response, or other problem or complication. Such salts include mineral and organic acid salts of basic residues such as amines, as well as alkali or organic salts of acidic residues such as carboxylic acids. Specific pharmaceutically acceptable anions for use in salt formation include, but are not limited to, acetate, 2-acetoxybenzoate, ascorbate, benzoate, bicarbonate, bromide, calcium edetate, carbonate, chloride, citrate, dihydrochloride, diphosphate, ditartrate, edetate, estolate (ethylsuccinate), formate, fumarate, gluceptate, gluconate, glutamate, glycolate, glycollylarsanilate, hexylresorcinate, hydrabamine, hydrobromide, hydrochloride, hydroiodide, hydroxymaleate, hydroxynaphthoate, iodide, isethionate, lactate, lactobionate, malate, maleate, mandelate, methylbromide, methylnitrate, methylsulfate, mucate, napsylate, nitrate, pamoate, pantothenate, phenylacetate, phosphate, polygalacturonate, propionate, salicylate, stearate, subacetate, succinate, sulfamate, sulfanilate, sulfate, sulfonates including besylate (benzenesulfonate), camsylate (camphorsulfonate), edisylate (ethane-1,2-disulfonate), esylate (ethanesulfonate) 2-hydroxyethylsulfonate, mesylate (methanesulfonate), triflate (trifluoromethanesulfonate) and tosylate (*p*-toluenesulfonate), tannate, tartrate, teoclate and triethiodide. Similarly, pharmaceutically acceptable cations for use in salt formation include, but are not limited to ammonium, benzathine, chlorprocaine, choline, diethanolamine, ethylenediamine, meglumine, procaine, and metals such as aluminum, calcium, lithium, magnesium, potassium, sodium and zinc. Those of ordinary skill in the art will recognize further pharmaceutically acceptable salts for the compounds provided herein. In general, a pharmaceutically acceptable acid or base salt can be synthesized from a parent compound that contains a basic or acidic moiety by any conventional chemical method. Briefly, such salts can be prepared by reacting the free acid or base forms of these compounds

with a stoichiometric amount of the appropriate base or acid in water or in an organic solvent, or in a mixture of the two; generally, the use of nonaqueous media, such as ether, ethyl acetate, ethanol, methanol, isopropanol or acetonitrile, is preferred.

It will be apparent that compounds and salts thereof provided herein may, but need not, be formulated as a hydrate, and that such hydrates are encompassed by the formulas, names and structures recited herein. In addition, the various non-hydrate solvates, non-covalent complexes, crystal forms and polymorphs of the compounds provided herein are within the scope of the present invention. Also provided herein are prodrugs of the compounds of the recited Formulas. A "prodrug" is a compound that may not fully satisfy the structural requirements of the compounds provided herein, but is modified *in vivo*, following administration to a patient, to produce a compound a formula provided herein. For example, a prodrug may be an acylated derivative of a compound as provided herein. Prodrugs include compounds wherein hydroxy, amine or sulfhydryl groups are bonded to any group that, when administered to a mammalian subject, cleaves to form a free hydroxy, amino, or sulfhydryl group, respectively. Examples of prodrugs include, but are not limited to, acetate, formate and benzoate derivatives of alcohol and amine functional groups within the compounds provided herein. Prodrugs of the compounds provided herein may be prepared by modifying functional groups present in the compounds in such a way that the modifications are cleaved *in vivo* to yield the parent compounds.

As used herein, the term "alkyl" refers to a straight or branched chain saturated aliphatic hydrocarbon. Alkyl groups include, for example, groups having from 1 to 6 carbon atoms (C₁-C₆alkyl) and from 1 to 4 carbon atoms (C₁-C₄alkyl), such as methyl, ethyl, propyl, isopropyl, n-butyl, *sec*-butyl, *tert*-butyl, pentyl, 2-pentyl, isopentyl, neopentyl, hexyl, 2-hexyl, 3-hexyl and 3-methylpentyl. In some instances, a substituent of an alkyl group is specifically indicated. For example, "hydroxyalkyl" refers to an alkyl group substituted with at least one hydroxy substituent.

"Alkylene" refers to a divalent alkyl group, as defined above. C₁-C₂alkylene is methylene or ethylene; C₀-C₄alkylene is a single covalent bond or an alkylene group having 1, 2, 3 or carbon atoms; C₀-C₂alkylene is a single covalent bond or an alkylene group having 1 or 2 carbon atoms.

"Alkenyl" refers to a straight or branched chain alkene group, which comprises at least one unsaturated carbon-carbon double bond. Alkenyl groups include, for example, C₂-C₆alkenyl, which has from 2 to 6 carbon atoms, such as ethenyl, allyl or isopropenyl. "Alkynyl" refers to straight or branched chain alkyne groups, which have one or more

unsaturated carbon-carbon bonds, at least one of which is a triple bond. Alkynyl groups include, for example, C₂-C₆alkynyl, which has from 2 to 6 carbon atoms.

A "cycloalkyl" is a group that comprises one or more saturated and/or partially saturated rings in which all ring members are carbon, such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, and partially saturated variants of the foregoing, such as cyclohexenyl. Cycloalkyl groups do not comprise an aromatic ring or a heterocyclic ring. Certain cycloalkyl groups are C₃-C₇cycloalkyl, in which the cycloalkyl group contains a single ring having from 3 to 7 ring members, all of which are carbon. A "(C₃-C₇cycloalkyl)C₀-C₄alkyl" is a C₃-C₇cycloalkyl group linked via a single covalent bond or a C₁-C₄alkylene group.

The term "oxo" is used herein to refer to an oxygen substituent of a carbon atom that results in the formation of a carbonyl group (C=O). An oxo group that is a substituent of a nonaromatic carbon atom results in a conversion of -CH₂- to -C(=O)-. An oxo group that is a substituent of an aromatic carbon atom results in a conversion of -CH- to -C(=O)- and may result in a loss of aromaticity.

By "alkoxy," as used herein, is meant an alkyl group as described above attached via an oxygen bridge. Alkoxy groups include C₁-C₆alkoxy and C₁-C₄alkoxy groups, which have from 1 to 6 or from 1 to 4 carbon atoms, respectively. Methoxy, ethoxy, propoxy, isopropoxy, n-butoxy, *sec*-butoxy, *tert*-butoxy, n-pentoxy, 2-pentoxy, 3-pentoxy, isopentoxy, neopentoxy, hexoxy, 2-hexoxy, 3-hexoxy, and 3-methylpentoxy are representative alkoxy groups. Similarly, "alkylthio" refers to an alkyl group as described above attached via a sulfur bridge.

The term "alkanoyl" refers to an acyl group (*e.g.*, -(C=O)-alkyl), in which carbon atoms are in a linear or branched alkyl arrangement and where attachment is through the carbon of the keto group. Alkanoyl groups have the indicated number of carbon atoms, with the carbon of the keto group being included in the numbered carbon atoms. For example a C₂alkanoyl group is an acetyl group having the formula -(C=O)CH₃. Alkanoyl groups include, for example, C₁-C₆alkanoyl and C₁-C₄alkanoyl groups, which have from 1 to 6 or from 1 to 4 carbon atoms, respectively. "C₁alkanoyl" refers to -(C=O)H.

"Alkyl ether" refers to a linear or branched ether substituent (*i.e.*, an alkyl group that is substituted with an alkoxy group). Alkyl ether groups include, for example, C₂-C₆alkyl ether groups, which have 2 to 6 carbon atoms. A C₂ alkyl ether has the structure -CH₂-O-CH₃.

"Alkylamino" refers to a secondary or tertiary amine that has the general structure -NH-alkyl or -N(alkyl)(alkyl), wherein each alkyl is selected independently from alkyl, cycloalkyl and (cycloalkyl)alkyl groups. Such groups include, for example, mono- and di-

(C₁-C₆alkyl)amino groups, in which each C₁-C₆alkyl may be the same or different. It will be apparent that the definition of "alkyl" as used in the term "alkylamino" differs from the definition of "alkyl" used for all other alkyl-containing groups, in the inclusion of cycloalkyl and (cycloalkyl)alkyl groups (*e.g.*, (C₃-C₆cycloalkyl)C₀-C₃alkyl).

5 "Alkylsulfonyl" refers to groups of the formula -(SO₂)-alkyl, in which the sulfur atom is the point of attachment. Alkylsulfonyl groups include, for example, C₁-C₆alkylsulfonyl groups, which have from 1 to 6 carbon atoms.

The term "halogen" refers to fluorine, chlorine, bromine or iodine.

10 A "haloalkyl" is an alkyl group that is substituted with 1 or more independently chosen halogens (*e.g.*, "C₁-C₆haloalkyl" groups have from 1 to 6 carbon atoms). Examples of haloalkyl groups include, but are not limited to, mono-, di- or tri-fluoromethyl; mono-, di- or tri-chloromethyl; mono-, di-, tri-, tetra- or penta-fluoroethyl; mono-, di-, tri-, tetra- or penta-chloroethyl; and 1,2,2,2-tetrafluoro-1-trifluoromethyl-ethyl. Typical haloalkyl groups are trifluoromethyl and difluoromethyl. The term "haloalkoxy" refers to a haloalkyl group as
15 defined above that is linked via an oxygen bridge. The term "haloalkylthio" refers to a haloalkyl group as defined above that is linked via a sulfur bridge.

"Aryl" refers to a cyclic moiety (*e.g.*, a monocycle or a fused bicyclic group) in which all ring members are carbon and at least one ring is aromatic. Aryl groups include, for example, phenyl and groups with fused rings such as naphthyl, fluorenyl, indanyl and 1,2,3,4-
20 tetrahydro-naphthyl.

A "heterocycle" is a group that comprises at least one heterocyclic ring (*i.e.*, a ring in which one or more ring atoms are heteroatoms independently chosen from O, S and N, with the remaining ring atoms being carbon). Additional rings, if present, may be heterocyclic or carbocyclic. Typically, a heterocyclic ring comprises 1, 2, 3 or 4 heteroatoms; within certain
25 embodiments each heterocyclic ring has 1 or 2 heteroatoms per ring. Each heterocyclic ring generally contains from 3 to 8 ring members (rings having from 4 or 5 to 7 ring members are recited in certain embodiments). Certain heterocycles comprise a sulfur atom as a ring member; in certain embodiments, the sulfur atom is oxidized to SO or SO₂. Heterocycles may be optionally substituted with a variety of substituents, as indicated. Unless otherwise
30 specified, a heterocycle may be a heterocycloalkyl group (*i.e.*, each ring is saturated or partially saturated) or a heteroaryl group (*i.e.*, an aromatic group in which at least one aromatic ring comprises at least one heteroatom selected from N, O and S), and may be linked via any ring atom, provided that a stable compound results. A "(4- to 7-membered heterocycle)C₀-C₄alkyl" is a heterocyclic ring containing from 4 to 7 ring members that is
35 linked via a single covalent bond (C₀) or a C₁-C₄alkylene moiety. Representative 4- to 7-

membered heterocycles include, for example, heterocycloalkyl moieties such as piperazine, piperidine, morpholine, thiomorpholine, pyrrolidine and imidazolidine, as well as 5- and 6-membered heteroaryls such as imidazole, furan, furazan, isothiazole, isoxazole, oxadiazole, oxazole, pyrazine, pyrazole, pyridazine, pyridine, pyrimidine, tetrazole, thiazole and thiophene.

A "substituent," as used herein, refers to a molecular moiety that is covalently bonded to an atom within a molecule of interest. For example, a ring substituent may be a moiety such as a halogen, alkyl group, haloalkyl group or other group that is covalently bonded to an atom (preferably a carbon or nitrogen atom) that is a ring member. Substituents of aromatic groups are generally covalently bonded to a ring carbon atom. The term "substitution" refers to replacing a hydrogen atom in a molecular structure with a substituent, such that the valence on the designated atom is not exceeded, and such that a chemically stable compound (*i.e.*, a compound that can be isolated, characterized, and tested for biological activity) results from the substitution.

Groups that are "optionally substituted" are unsubstituted or are substituted by other than hydrogen at one or more available positions, typically 1, 2, 3, 4 or 5 positions, by one or more suitable groups (which may be the same or different). Optional substitution is also indicated by the phrase "substituted with from 0 to X substituents," where X is the maximum number of possible substituents. Certain optionally substituted groups are substituted with from 0 to 2, 3 or 4 independently selected substituents (*i.e.*, are unsubstituted or substituted with up to the recited maximum number of substituents). Other optionally substituted groups are substituted with at least one substituent (*e.g.*, substituted with from 1 to 2, 3 or 4 independently selected substituents).

The terms "VR1" and "capsaicin receptor" are used interchangeably herein to refer to a type 1 vanilloid receptor. Unless otherwise specified, these terms encompass both rat and human VR1 receptors (*e.g.*, GenBank Accession Numbers AF327067, AJ277028 and NM_018727; sequences of certain human VR1 cDNAs and the encoded amino acid sequences are provided in U.S. Patent No. 6,482,611), as well as homologues thereof found in other species.

A "VR1 modulator," also referred to herein as a "modulator," is a compound that modulates VR1 activation and/or VR1-mediated signal transduction. VR1 modulators specifically provided herein are compounds of Formula I and pharmaceutically acceptable salts, hydrates and esters thereof. Certain preferred VR1 modulators are not vanilloids. A VR1 modulator may be a VR1 agonist or antagonist. Certain modulators bind to VR1 with a K_i that is less than 1 micromolar, preferably less than 500 nanomolar, 100 nanomolar, 10

nanomolar or 1 nanomolar. A representative assay for determining K_i at VR1 is provided in Example 5, herein.

A modulator is considered an "antagonist" if it detectably inhibits vanilloid ligand binding to VR1 and/or VR1-mediated signal transduction (using, for example, the representative assay provided in Example 6); in general, such an antagonist inhibits VR1 activation with a IC_{50} value of less than 1 micromolar, preferably less than 500 nanomolar, and more preferably less than 100 nanomolar, 10 nanomolar or 1 nanomolar within the assay provided in Example 6. VR1 antagonists include neutral antagonists and inverse agonists.

An "inverse agonist" of VR1 is a compound that reduces the activity of VR1 below its basal activity level in the absence of added vanilloid ligand. Inverse agonists of VR1 may also inhibit the activity of vanilloid ligand at VR1 and/or binding of vanilloid ligand to VR1. The basal activity of VR1, as well as the reduction in VR1 activity due to the presence of VR1 antagonist, may be determined from a calcium mobilization assay, such as the assay of Example 6.

A "neutral antagonist" of VR1 is a compound that inhibits the activity of vanilloid ligand at VR1, but does not significantly change the basal activity of the receptor (*i.e.*, within a calcium mobilization assay as described in Example 6 performed in the absence of vanilloid ligand, VR1 activity is reduced by no more than 10%, preferably by no more than 5%, and more preferably by no more than 2%; most preferably, there is no detectable reduction in activity). Neutral antagonists of VR1 may inhibit the binding of vanilloid ligand to VR1.

As used herein a "capsaicin receptor agonist" or "VR1 agonist" is a compound that elevates the activity of the receptor above the basal activity level of the receptor (*i.e.*, enhances VR1 activation and/or VR1-mediated signal transduction). Capsaicin receptor agonist activity may be identified using the representative assay provided in Example 6. In general, such an agonist has an EC_{50} value of less than 1 micromolar, preferably less than 500 nanomolar, and more preferably less than 100 nanomolar or 10 nanomolar within the assay provided in Example 6.

A "vanilloid" is any compound that comprises a phenyl ring with two oxygen atoms bound to adjacent ring carbon atoms (one of which carbon atom is located *para* to the point of attachment of a third moiety that is bound to the phenyl ring). Capsaicin is a representative vanilloid. A "vanilloid ligand" is a vanilloid that binds to VR1 with a K_i (determined as described herein) that is no greater than 10 μ M. Vanilloid ligand agonists include capsaicin, olvanil, N-arachidonoyl-dopamine and resiniferatoxin (RTX). Vanilloid ligand antagonists include capsazepine and iodo-resiniferatoxin.

A "therapeutically effective amount" (or dose) is an amount that, upon administration to a patient, results in a discernible patient benefit (*e.g.*, provides detectable relief from at least one condition being treated). Such relief may be detected using any appropriate criteria, including alleviation of one or more symptoms such as pain. A therapeutically effective amount or dose generally results in a concentration of compound in a body fluid (such as blood, plasma, serum, CSF, synovial fluid, lymph, cellular interstitial fluid, tears or urine) that is sufficient to alter the binding of vanilloid ligand to VR1 *in vitro* (using the assay provided in Example 5) and/or VR1-mediated signal transduction (using an assay provided in Example 6). It will be apparent that the discernible patient benefit may be apparent after administration of a single dose, or may become apparent following repeated administration of the therapeutically effective dose according to a predetermined regimen, depending upon the indication for which the compound is administered.

By "statistically significant," as used herein, is meant results varying from control at the $p < 0.1$ level of significance as measured using a standard parametric assay of statistical significance such as a student's T test.

A "patient" is any individual treated with a compound provided herein. Patients include humans, as well as other animals such as companion animals (*e.g.*, dogs and cats) and livestock. Patients may be experiencing one or more symptoms of a condition responsive to capsaicin receptor modulation (*e.g.*, pain, exposure to vanilloid ligand, itch, urinary incontinence, overactive bladder, respiratory disorders, cough and/or hiccup), or may be free of such symptom(s) (*i.e.*, treatment may be prophylactic in a patient considered at risk for the development of such symptoms).

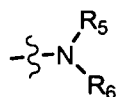
SUBSTITUTED PYRIMIDINONES

As noted above, the present invention provides substituted pyrimidinones of Formula I. Within certain aspects, such compounds are VR1 modulators that may be used in a variety of contexts, including in the treatment of pain (*e.g.*, neuropathic or peripheral nerve-mediated pain); exposure to capsaicin; exposure to acid, heat, light, tear gas, air pollutants (such as, for example, tobacco smoke), infectious agents (including viruses, bacteria and yeast), pepper spray or related agents; respiratory conditions such as asthma or chronic obstructive pulmonary disease; itch; urinary incontinence or overactive bladder; cough or hiccup; menopause symptoms and/or obesity. Such compounds may also be used within *in vitro* assays (*e.g.*, assays for receptor activity), as probes for detection and localization of VR1 and as standards in ligand binding and VR1-mediated signal transduction assays.

Ar is, in certain embodiments, phenyl or a 6-membered heteroaryl, each of which is optionally substituted as described above. In certain compounds, Ar is phenyl or pyridyl, each of which is substituted with from 1 to 3 substituents independently chosen from halogen, cyano, nitro and C₁-C₆alkyl.

5 The variable R₁, in certain substituted pyrimidinones, is hydrogen, halogen, cyano, C₁-C₄alkyl, (C₃-C₅cycloalkyl)C₀-C₂alkyl, or phenyl that is unsubstituted or substituted with from 1 to 3 substituents independently chosen from halogen, cyano, oxo, C₁-C₄alkyl, C₁-C₄haloalkyl, C₁-C₄alkoxy and C₁-C₄haloalkoxy. In certain such compounds, R₁ is hydrogen, cyano, halogen, C₁-C₄alkyl or C₁-C₄alkanoyl. In further such compounds, R₁ is bromo,
10 chloro, fluoro, iodo, methyl or ethyl.

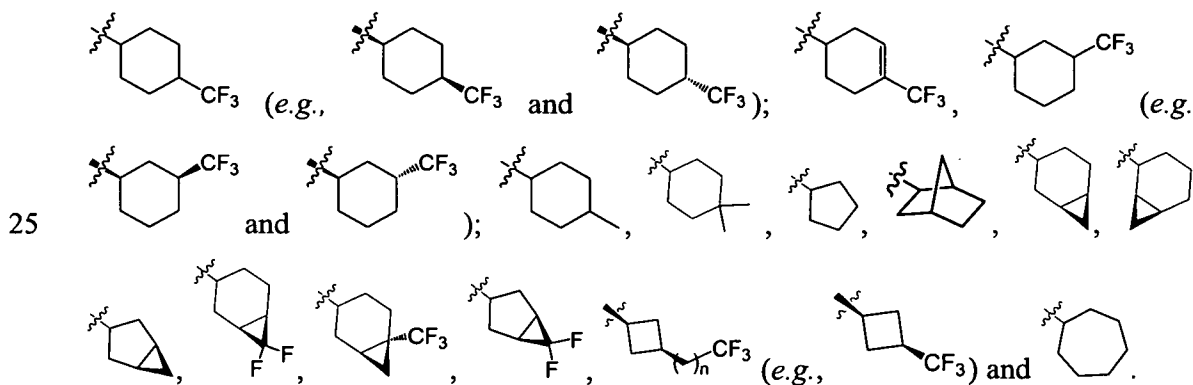
In certain embodiments, R₂ is C₁-C₆alkyl; C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₂-C₆alkyl ether or C₁-C₆haloalkyl; or a group of the formula:



wherein R₅ and R₆ are independently chosen from hydrogen, C₁-C₆alkyl, (C₃-C₇cycloalkyl)C₀-C₄alkyl, C₁-C₆alkanoyl, and C₁-C₆alkylsulfonyl, each of which is substituted
15 with from 0 to 2 substituents independently chosen from R₇, such that at least one of R₅ and R₆ is not hydrogen; or R₅ and R₆ are taken together to form a 4- to 7-membered heterocycloalkyl that is substituted with from 0 to 2 substituents independently chosen from R₇. It will be apparent that when R₂ is hydroxy, Formula I encompasses the tautomeric
20 structure.

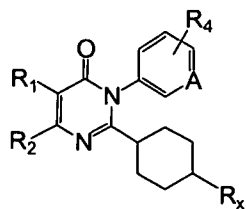
In certain embodiments, R₃ is C₅-C₇cycloalkyl that is substituted with from 1 to 2 substituents independently chosen from C₁-C₄alkyl, halogen and C₁-C₄haloalkyl.

Representative R₃ groups include, for example:

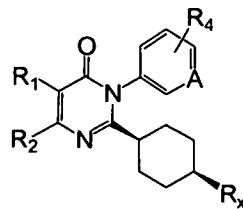


wherein n is an integer ranging from 0 to 5.

Certain substituted pyrimidinones further satisfy Formula II or Formula III:



Formula II



Formula III

in which:

A is CH or N;

R_4 represents from 0 to 3 substituents independently chosen from halogen, cyano, amino, nitro, C_1 - C_6 alkyl, C_1 - C_6 haloalkyl, C_1 - C_6 hydroxyalkyl, C_1 - C_6 alkoxy and C_1 - C_6 haloalkoxy; and

R_x is C_1 - C_4 alkyl or C_1 - C_4 haloalkyl.

It will be apparent that Formula I encompasses both cis and trans isomers, and Formula III specifically recites the cis isomer. Representative R_x moieties include, for example, methyl, ethyl, isopropyl, t-butyl, difluoromethyl and trifluoromethyl.

Representative compounds provided herein include, but are not limited to, those specifically described in Examples 2 and 3. It will be apparent that the specific compounds recited herein are representative only, and are not intended to limit the scope of the present invention. Further, as noted above, all compounds of the present invention may be present as a free acid or base, or as a pharmaceutically acceptable salt. In addition, other forms such as hydrates and prodrugs of such compounds are specifically contemplated by the present invention.

Within certain aspects of the present invention, substituted pyrimidinones provided herein detectably alter (modulate) VR1 activity, as determined using an *in vitro* VR1 functional assay such as a calcium mobilization assay. As an initial screen for such activity, a VR1 ligand binding assay may be used. References herein to a "VR1 ligand binding assay" are intended to refer to a standard *in vitro* receptor binding assay such as that provided in Example 5, and a "calcium mobilization assay" (also referred to herein as a "signal transduction assay") may be performed as described in Example 6. Briefly, to assess binding to VR1, a competition assay may be performed in which a VR1 preparation is incubated with labeled (*e.g.*, ^{125}I or ^3H) compound that binds to VR1 (*e.g.*, a capsaicin receptor agonist such as RTX) and unlabeled test compound. Within the assays provided herein, the VR1 used is preferably mammalian VR1, more preferably human or rat VR1. The receptor may be recombinantly expressed or naturally expressed. The VR1 preparation may be, for example, a membrane preparation from HEK293 or CHO cells that recombinantly express human VR1. Incubation with a compound that detectably modulates vanilloid ligand binding to VR1

results in a decrease or increase in the amount of label bound to the VR1 preparation, relative to the amount of label bound in the absence of the compound. This decrease or increase may be used to determine the K_i at VR1 as described herein. In general, compounds that decrease the amount of label bound to the VR1 preparation within such an assay are preferred.

5 Certain VR1 modulators provided herein detectably modulate VR1 activity at nanomolar (*i.e.*, submicromolar) concentrations, at subnanomolar concentrations, or at concentrations below 100 picomolar, 20 picomolar, 10 picomolar or 5 picomolar.

As noted above, compounds that are VR1 antagonists are preferred within certain embodiments. IC_{50} values for such compounds may be determined using a standard *in vitro*
10 VR1-mediated calcium mobilization assay, as provided in Example 6. Briefly, cells expressing capsaicin receptor are contacted with a compound of interest and with an indicator of intracellular calcium concentration (*e.g.*, a membrane permeable calcium sensitivity dye such as Fluo-3 or Fura-2 (Molecular Probes, Eugene, OR), each of which produce a fluorescent signal when bound to Ca^{++}). Such contact is preferably carried out by one or more
15 incubations of the cells in buffer or culture medium comprising either or both of the compound and the indicator in solution. Contact is maintained for an amount of time sufficient to allow the dye to enter the cells (*e.g.*, 1-2 hours). Cells are washed or filtered to remove excess dye and are then contacted with a vanilloid receptor agonist (*e.g.*, capsaicin, RTX or olvanil), typically at a concentration equal to the EC_{50} concentration, and a
20 fluorescence response is measured. When agonist-contacted cells are contacted with a compound that is a VR1 antagonist the fluorescence response is generally reduced by at least 20%, preferably at least 50% and more preferably at least 80%, as compared to cells that are contacted with the agonist in the absence of test compound. The IC_{50} for VR1 antagonists provided herein is preferably less than 1 micromolar, less than 100 nM, less than 10 nM or
25 less than 1 nM. In certain embodiments, VR1 antagonists provided herein exhibit no detectable agonist activity in an *in vitro* assay of capsaicin receptor agonism at a concentration of compound equal to the IC_{50} . Certain such antagonists exhibit no detectable agonist activity in an *in vitro* assay of capsaicin receptor agonism at a concentration of compound that is 100-fold higher than the IC_{50} .

30 In other embodiments, compounds that are capsaicin receptor agonists are preferred. Capsaicin receptor agonist activity may generally be determined as described in Example 6. When cells are contacted with 1 micromolar of a compound that is a VR1 agonist, the fluorescence response is generally increased by an amount that is at least 30% of the increase observed when cells are contacted with 100 nM capsaicin. The EC_{50} for VR1 agonists
35 provided herein is preferably less than 1 micromolar, less than 100 nM or less than 10 nM.

VR1 modulating activity may also, or alternatively, be assessed using a cultured dorsal root ganglion assay as provided in Example 7 and/or an *in vivo* pain relief assay as provided in Example 8. VR1 modulators provided herein preferably have a statistically significant specific effect on VR1 activity within one or more functional assays provided herein.

5 Within certain embodiments, VR1 modulators provided herein do not substantially modulate ligand binding to other cell surface receptors, such as EGF receptor tyrosine kinase or the nicotinic acetylcholine receptor. In other words, such modulators do not substantially inhibit activity of a cell surface receptor such as the human epidermal growth factor (EGF) receptor tyrosine kinase or the nicotinic acetylcholine receptor (*e.g.*, the IC₅₀ or IC₄₀ at such a
10 receptor is preferably greater than 1 micromolar, and most preferably greater than 10 micromolar). Preferably, a modulator does not detectably inhibit EGF receptor activity or nicotinic acetylcholine receptor activity at a concentration of 0.5 micromolar, 1 micromolar or more preferably 10 micromolar. Assays for determining cell surface receptor activity are commercially available, and include the tyrosine kinase assay kits available from Panvera
15 (Madison, WI).

 In certain embodiments, preferred VR1 modulators are non-sedating. In other words, a dose of VR1 modulator that is twice the minimum dose sufficient to provide analgesia in an animal model for determining pain relief (such as a model provided in Example 8, herein) causes only transient (*i.e.*, lasting for no more than ½ the time that pain relief lasts) or
20 preferably no statistically significant sedation in an animal model assay of sedation (using the method described by Fitzgerald et al. (1988) *Toxicology* 49(2-3):433-9). Preferably, a dose that is five times the minimum dose sufficient to provide analgesia does not produce statistically significant sedation. More preferably, a VR1 modulator provided herein does not produce sedation at intravenous doses of less than 25 mg/kg (preferably less than 10 mg/kg)
25 or at oral doses of less than 140 mg/kg (preferably less than 50 mg/kg, more preferably less than 30 mg/kg).

 If desired, compounds provided herein may be evaluated for certain pharmacological properties including, but not limited to, oral bioavailability (preferred compounds are orally bioavailable to an extent allowing for therapeutically effective concentrations of the
30 compound to be achieved at oral doses of less than 140 mg/kg, preferably less than 50 mg/kg, more preferably less than 30 mg/kg, even more preferably less than 10 mg/kg, still more preferably less than 1 mg/kg and most preferably less than 0.1 mg/kg), toxicity (a preferred compound is nontoxic when a therapeutically effective amount is administered to a subject), side effects (a preferred compound produces side effects comparable to placebo when a
35 therapeutically effective amount of the compound is administered to a subject), serum protein

binding and *in vitro* and *in vivo* half-life (a preferred compound exhibits an *in vivo* half-life allowing for Q.I.D. dosing, preferably T.I.D. dosing, more preferably B.I.D. dosing, and most preferably once-a-day dosing). In addition, differential penetration of the blood brain barrier may be desirable for VR1 modulators used to treat pain by modulating CNS VR1 activity such that total daily oral doses as described above provide such modulation to a therapeutically effective extent, while low brain levels of VR1 modulators used to treat peripheral nerve mediated pain may be preferred (*i.e.*, such doses do not provide brain (*e.g.*, CSF) levels of the compound sufficient to significantly modulate VR1 activity). Routine assays that are well known in the art may be used to assess these properties, and identify superior compounds for a particular use. For example, assays used to predict bioavailability include transport across human intestinal cell monolayers, including Caco-2 cell monolayers. Penetration of the blood brain barrier of a compound in humans may be predicted from the brain levels of the compound in laboratory animals given the compound (*e.g.*, intravenously). Serum protein binding may be predicted from albumin binding assays. Compound half-life is inversely proportional to the frequency of dosage of a compound. *In vitro* half-lives of compounds may be predicted from assays of microsomal half-life as described, for example, within Example 7 of U.S. Patent Application Publication Number 2005/0070547.

As noted above, preferred compounds provided herein are nontoxic. In general, the term "nontoxic" shall be understood in a relative sense and is intended to refer to any substance that has been approved by the United States Food and Drug Administration ("FDA") for administration to mammals (preferably humans) or, in keeping with established criteria, is susceptible to approval by the FDA for administration to mammals (preferably humans). In addition, a highly preferred nontoxic compound generally satisfies one or more of the following criteria: (1) does not substantially inhibit cellular ATP production; (2) does not significantly prolong heart QT intervals; (3) does not cause substantial liver enlargement, or (4) does not cause substantial release of liver enzymes.

As used herein, a compound that does not substantially inhibit cellular ATP production is a compound that satisfies the criteria set forth in Example 8 of U.S. Patent Application Publication Number 2005/0070547. In other words, cells treated as described therein with 100 μ M of such a compound exhibit ATP levels that are at least 50% of the ATP levels detected in untreated cells. In more highly preferred embodiments, such cells exhibit ATP levels that are at least 80% of the ATP levels detected in untreated cells.

A compound that does not significantly prolong heart QT intervals is a compound that does not result in a statistically significant prolongation of heart QT intervals (as determined by electrocardiography) in guinea pigs, minipigs or dogs upon administration of a dose that

yields a serum concentration equal to the EC₅₀ or IC₅₀ for the compound. In certain preferred embodiments, a dose of 0.01, 0.05, 0.1, 0.5, 1, 5, 10, 40 or 50 mg/kg administered parenterally or orally does not result in a statistically significant prolongation of heart QT intervals.

5 A compound does not cause substantial liver enlargement if daily treatment of laboratory rodents (*e.g.*, mice or rats) for 5-10 days with a dose that yields a serum concentration equal to the EC₅₀ or IC₅₀ for the compound results in an increase in liver to body weight ratio that is no more than 100% over matched controls. In more highly preferred
10 embodiments, such doses do not cause liver enlargement of more than 75% or 50% over matched controls. If non-rodent mammals (*e.g.*, dogs) are used, such doses should not result in an increase of liver to body weight ratio of more than 50%, preferably not more than 25%, and more preferably not more than 10% over matched untreated controls. Preferred doses within such assays include 0.01, 0.05, 0.1, 0.5, 1, 5, 10, 40 or 50 mg/kg administered parenterally or orally.

15 Similarly, a compound does not promote substantial release of liver enzymes if administration of twice the minimum dose that yields a serum concentration equal to the EC₅₀ or IC₅₀ at VR1 for the compound does not elevate serum levels of ALT, LDH or AST in laboratory animals (*e.g.*, rodents) by more than 100% over matched mock-treated controls. In more highly preferred embodiments, such doses do not elevate such serum levels by more
20 than 75% or 50% over matched controls. Alternatively, a compound does not promote substantial release of liver enzymes if, in an *in vitro* hepatocyte assay, concentrations (in culture media or other such solutions that are contacted and incubated with hepatocytes *in vitro*) that are equal to the EC₅₀ or IC₅₀ for the compound do not cause detectable release of any of such liver enzymes into culture medium above baseline levels seen in media from
25 matched mock-treated control cells. In more highly preferred embodiments, there is no detectable release of any of such liver enzymes into culture medium above baseline levels when such compound concentrations are five-fold, and preferably ten-fold the EC₅₀ or IC₅₀ for the compound.

 In other embodiments, certain preferred compounds do not inhibit or induce
30 microsomal cytochrome P450 enzyme activities, such as CYP1A2 activity, CYP2A6 activity, CYP2C9 activity, CYP2C19 activity, CYP2D6 activity, CYP2E1 activity or CYP3A4 activity at a concentration equal to the EC₅₀ or IC₅₀ at VR1 for the compound.

 Certain preferred compounds are not clastogenic (*e.g.*, as determined using a mouse erythrocyte precursor cell micronucleus assay, an Ames micronucleus assay, a spiral
35 micronucleus assay or the like) at a concentration equal the EC₅₀ or IC₅₀ for the compound.

In other embodiments, certain preferred compounds do not induce sister chromatid exchange (*e.g.*, in Chinese hamster ovary cells) at such concentrations.

For detection purposes, as discussed in more detail below, VR1 modulators provided herein may be isotopically-labeled or radiolabeled. For example, compounds may have one or more atoms replaced by an atom of the same element having an atomic mass or mass number different from the atomic mass or mass number usually found in nature. Examples of isotopes that can be present in the compounds provided herein include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorous, fluorine and chlorine, such as ^2H , ^3H , ^{11}C , ^{13}C , ^{14}C , ^{15}N , ^{18}O , ^{17}O , ^{31}P , ^{32}P , ^{35}S , ^{18}F and ^{36}Cl . In addition, substitution with heavy isotopes such as deuterium (*i.e.*, ^2H) can afford certain therapeutic advantages resulting from greater metabolic stability, for example increased in vivo half-life or reduced dosage requirements and, hence, may be preferred in some circumstances.

PREPARATION OF SUBSTITUTED PYRIMIDINONES

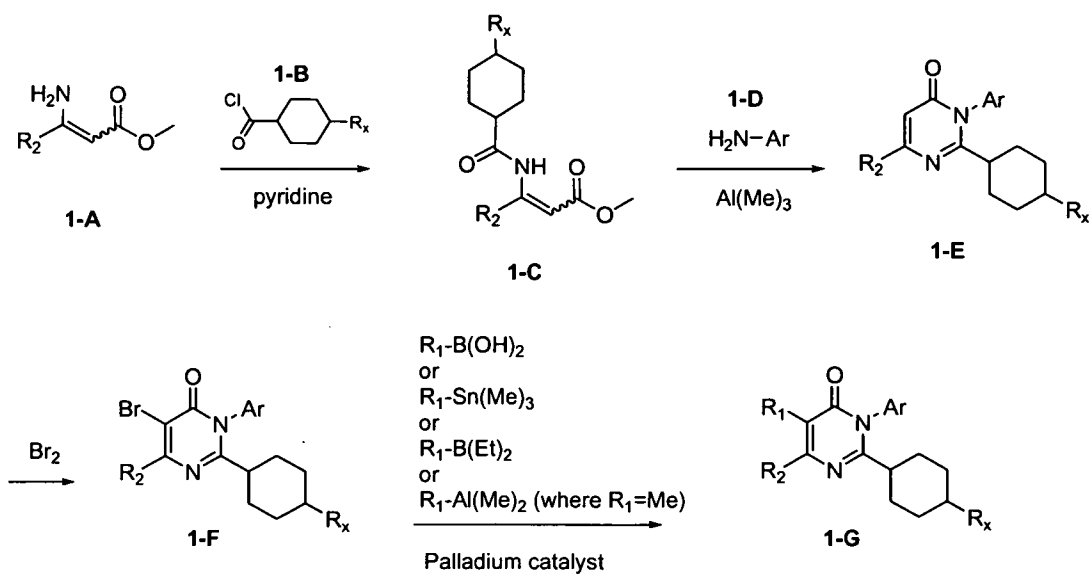
Substituted pyrimidinones may generally be prepared using standard synthetic methods. Starting materials are commercially available from suppliers such as Sigma-Aldrich Corp. (St. Louis, MO), or may be synthesized from commercially available precursors using established protocols. By way of example, a synthetic route similar to that shown in any of the following Schemes may be used, together with synthetic methods known in the art of synthetic organic chemistry. Each variable in the following schemes refers to any group consistent with the description of the compounds provided herein.

Certain abbreviations used in the following Schemes and elsewhere herein include:

δ	chemical shift
DCE	dichloroethane
DCM	dichloromethane
Dess Martin	1,1,1-Tris(acetyloxy)-1,1-dihydro-1,2-benziodoxol-3(1H)-one
DMF	N,N-dimethylformamide
DMSO	dimethylsulfoxide
DPPA	diphenyl phosphoryl azide
EtOAc	ethyl acetate
EtOH	ethanol
h	hour(s)
^1H NMR	proton nuclear magnetic resonance
HPLC	high pressure liquid chromatography
Hz	hertz
Me	methyl

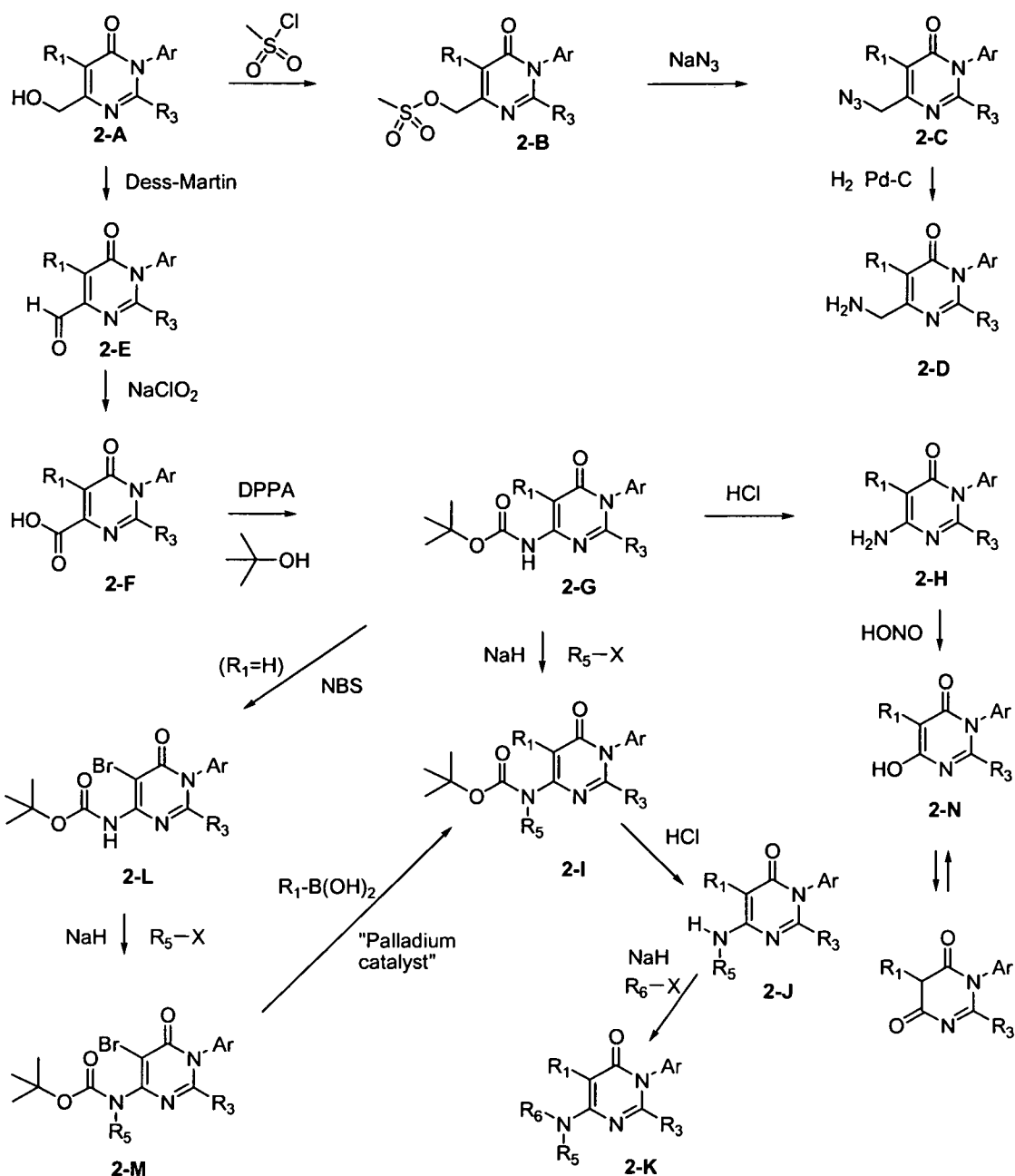
	min	minute(s)
	MS	mass spectrometry
	(M+1)	mass + 1
	NCS	N-chlorosuccinimide
5	NIS	N-iodosuccinimide
	Pd(PPh ₃) ₄	tetrakis(triphenylphosphine) palladium (0)
	Rochelle's Salt	potassium sodium tartrate
	RT	room temperature
	Selectfluor™	1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis-
10	(tetrafluoroborate)	
	TFA	trifluoroacetic acid
	THF	tetrahydrofuran
	TLC	thin layer chromatography

Scheme 1



15

Scheme 2



In certain embodiments, a compound provided herein may contain one or more asymmetric carbon atoms, so that the compound can exist in different stereoisomeric forms. Such forms can be, for example, racemates or optically active forms. As noted above, all stereoisomers are encompassed by the present invention. Nonetheless, it may be desirable to obtain single enantiomers (*i.e.*, optically active forms). Standard methods for preparing single enantiomers include asymmetric synthesis and resolution of the racemates. Resolution of the racemates can be accomplished, for example, by conventional methods such as crystallization

in the presence of a resolving agent, or chromatography using, for example a chiral HPLC column.

Compounds may be radiolabeled by carrying out their synthesis using precursors comprising at least one atom that is a radioisotope. Each radioisotope is preferably carbon (e.g., ^{14}C), hydrogen (e.g., ^3H), sulfur (e.g., ^{35}S), or iodine (e.g., ^{125}I). Tritium labeled compounds may also be prepared catalytically via platinum-catalyzed exchange in tritiated acetic acid, acid-catalyzed exchange in tritiated trifluoroacetic acid, or heterogeneous-catalyzed exchange with tritium gas using the compound as substrate. In addition, certain precursors may be subjected to tritium-halogen exchange with tritium gas, tritium gas reduction of unsaturated bonds, or reduction using sodium borotritide, as appropriate. Preparation of radiolabeled compounds may be conveniently performed by a radioisotope supplier specializing in custom synthesis of radiolabeled probe compounds.

PHARMACEUTICAL COMPOSITIONS

The present invention also provides pharmaceutical compositions comprising one or more compounds provided herein, together with at least one physiologically acceptable carrier or excipient. Pharmaceutical compositions may comprise, for example, one or more of water, buffers (e.g., neutral buffered saline or phosphate buffered saline), ethanol, mineral oil, vegetable oil, dimethylsulfoxide, carbohydrates (e.g., glucose, mannose, sucrose or dextrans), mannitol, proteins, adjuvants, polypeptides or amino acids such as glycine, antioxidants, chelating agents such as EDTA or glutathione and/or preservatives. In addition, other active ingredients may (but need not) be included in the pharmaceutical compositions provided herein.

Pharmaceutical compositions may be formulated for any appropriate manner of administration, including, for example, topical, oral, nasal, rectal or parenteral administration. The term parenteral as used herein includes subcutaneous, intradermal, intravascular (e.g., intravenous), intramuscular, spinal, intracranial, intrathecal and intraperitoneal injection, as well as any similar injection or infusion technique. In certain embodiments, compositions suitable for oral use are preferred. Such compositions include, for example, tablets, troches, lozenges, aqueous or oily suspensions, dispersible powders or granules, emulsion, hard or soft capsules, or syrups or elixirs. Within yet other embodiments, pharmaceutical compositions may be formulated as a lyophilizate. Formulation for topical administration may be preferred for certain conditions (e.g., in the treatment of skin conditions such as burns or itch). Formulation for direct administration into the bladder (intravesicular administration) may be preferred for treatment of urinary incontinence and overactive bladder.

Compositions intended for oral use may further comprise one or more components such as sweetening agents, flavoring agents, coloring agents and/or preserving agents in order to provide appealing and palatable preparations. Tablets contain the active ingredient in admixture with physiologically acceptable excipients that are suitable for the manufacture of tablets. Such excipients include, for example, inert diluents (*e.g.*, calcium carbonate, sodium carbonate, lactose, calcium phosphate or sodium phosphate), granulating and disintegrating agents (*e.g.*, corn starch or alginic acid), binding agents (*e.g.*, starch, gelatin or acacia) and lubricating agents (*e.g.*, magnesium stearate, stearic acid or talc). Tablets may be formed using standard techniques, including dry granulation, direct compression and wet granulation. The tablets may be uncoated or they may be coated by known techniques.

Formulations for oral use may also be presented as hard gelatin capsules wherein the active ingredient is mixed with an inert solid diluent (*e.g.*, calcium carbonate, calcium phosphate or kaolin), or as soft gelatin capsules wherein the active ingredient is mixed with water or an oil medium (*e.g.*, peanut oil, liquid paraffin or olive oil).

Aqueous suspensions contain the active material(s) in admixture with suitable excipients, such as suspending agents (*e.g.*, sodium carboxymethylcellulose, methylcellulose, hydropropylmethylcellulose, sodium alginate, polyvinylpyrrolidone, gum tragacanth and gum acacia); and dispersing or wetting agents (*e.g.*, naturally-occurring phosphatides such as lecithin, condensation products of an alkylene oxide with fatty acids such as polyoxyethylene stearate, condensation products of ethylene oxide with long chain aliphatic alcohols such as heptadecaethyleneoxycetanol, condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol such as polyoxyethylene sorbitol monooleate, or condensation products of ethylene oxide with partial esters derived from fatty acids and hexitol anhydrides such as polyethylene sorbitan monooleate). Aqueous suspensions may also comprise one or more preservatives, such as ethyl or n-propyl p-hydroxybenzoate, one or more coloring agents, one or more flavoring agents, and/or one or more sweetening agents, such as sucrose or saccharin.

Oily suspensions may be formulated by suspending the active ingredient(s) in a vegetable oil (*e.g.*, arachis oil, olive oil, sesame oil or coconut oil) or in a mineral oil such as liquid paraffin. The oily suspensions may contain a thickening agent such as beeswax, hard paraffin or cetyl alcohol. Sweetening agents such as those set forth above, and/or flavoring agents may be added to provide palatable oral preparations. Such suspensions may be preserved by the addition of an anti-oxidant such as ascorbic acid.

Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water provide the active ingredient in admixture with a dispersing or wetting

agent, a suspending agent and one or more preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified by those already mentioned above. Additional excipients, such as sweetening, flavoring and coloring agents, may also be present.

Pharmaceutical compositions may also be formulated as oil-in-water emulsions. The oily phase may be a vegetable oil (*e.g.*, olive oil or arachis oil), a mineral oil (*e.g.*, liquid paraffin) or a mixture thereof. Suitable emulsifying agents include naturally-occurring gums (*e.g.*, gum acacia or gum tragacanth), naturally-occurring phosphatides (*e.g.*, soy bean lecithin, and esters or partial esters derived from fatty acids and hexitol), anhydrides (*e.g.*, sorbitan monooleate) and condensation products of partial esters derived from fatty acids and hexitol with ethylene oxide (*e.g.*, polyoxyethylene sorbitan monooleate). An emulsion may also comprise one or more sweetening and/or flavoring agents.

Syrups and elixirs may be formulated with sweetening agents, such as glycerol, propylene glycol, sorbitol or sucrose. Such formulations may also comprise one or more demulcents, preservatives, flavoring agents and/or coloring agents.

Formulations for topical administration typically comprise a topical vehicle combined with active agent(s), with or without additional optional components. Suitable topical vehicles and additional components are well known in the art, and it will be apparent that the choice of a vehicle will depend on the particular physical form and mode of delivery. Topical vehicles include water; organic solvents such as alcohols (*e.g.*, ethanol or isopropyl alcohol) or glycerin; glycols (*e.g.*, butylene, isoprene or propylene glycol); aliphatic alcohols (*e.g.*, lanolin); mixtures of water and organic solvents and mixtures of organic solvents such as alcohol and glycerin; lipid-based materials such as fatty acids, acylglycerols (including oils, such as mineral oil, and fats of natural or synthetic origin), phosphoglycerides, sphingolipids and waxes; protein-based materials such as collagen and gelatin; silicone-based materials (both non-volatile and volatile); and hydrocarbon-based materials such as microsponges and polymer matrices. A composition may further include one or more components adapted to improve the stability or effectiveness of the applied formulation, such as stabilizing agents, suspending agents, emulsifying agents, viscosity adjusters, gelling agents, preservatives, antioxidants, skin penetration enhancers, moisturizers and sustained release materials. Examples of such components are described in Martindale--The Extra Pharmacopoeia (Pharmaceutical Press, London 1993) and *Remington: The Science and Practice of Pharmacy*, 21st ed., Lippincott Williams & Wilkins, Philadelphia, PA (2005). Formulations may comprise microcapsules, such as hydroxymethylcellulose or gelatin-microcapsules, liposomes, albumin microspheres, microemulsions, nanoparticles or nanocapsules.

A topical formulation may be prepared in any of a variety of physical forms including, for example, solids, pastes, creams, foams, lotions, gels, powders, aqueous liquids and emulsions. The physical appearance and viscosity of such pharmaceutically acceptable forms can be governed by the presence and amount of emulsifier(s) and viscosity adjuster(s) present in the formulation. Solids are generally firm and non-pourable and commonly are formulated as bars or sticks, or in particulate form; solids can be opaque or transparent, and optionally can contain solvents, emulsifiers, moisturizers, emollients, fragrances, dyes/colorants, preservatives and other active ingredients that increase or enhance the efficacy of the final product. Creams and lotions are often similar to one another, differing mainly in their viscosity; both lotions and creams may be opaque, translucent or clear and often contain emulsifiers, solvents, and viscosity adjusting agents, as well as moisturizers, emollients, fragrances, dyes/colorants, preservatives and other active ingredients that increase or enhance the efficacy of the final product. Gels can be prepared with a range of viscosities, from thick or high viscosity to thin or low viscosity. These formulations, like those of lotions and creams, may also contain solvents, emulsifiers, moisturizers, emollients, fragrances, dyes/colorants, preservatives and other active ingredients that increase or enhance the efficacy of the final product. Liquids are thinner than creams, lotions, or gels and often do not contain emulsifiers. Liquid topical products often contain solvents, emulsifiers, moisturizers, emollients, fragrances, dyes/colorants, preservatives and other active ingredients that increase or enhance the efficacy of the final product.

Suitable emulsifiers for use in topical formulations include, but are not limited to, ionic emulsifiers, cetearyl alcohol, non-ionic emulsifiers like polyoxyethylene oleyl ether, PEG-40 stearate, cetareth-12, cetareth-20, cetareth-30, cetareth alcohol, PEG-100 stearate and glyceryl stearate. Suitable viscosity adjusting agents include, but are not limited to, protective colloids or non-ionic gums such as hydroxyethylcellulose, xanthan gum, magnesium aluminum silicate, silica, microcrystalline wax, beeswax, paraffin, and cetyl palmitate. A gel composition may be formed by the addition of a gelling agent such as chitosan, methyl cellulose, ethyl cellulose, polyvinyl alcohol, polyquaterniums, hydroxyethylcellulose, hydroxypropylcellulose, hydroxypropylmethylcellulose, carbomer or ammoniated glycyrrhizinate. Suitable surfactants include, but are not limited to, nonionic, amphoteric, ionic and anionic surfactants. For example, one or more of dimethicone copolyol, polysorbate 20, polysorbate 40, polysorbate 60, polysorbate 80, lauramide DEA, cocamide DEA, and cocamide MEA, oleyl betaine, cocamidopropyl phosphatidyl PG-dimonium chloride, and ammonium laureth sulfate may be used within topical formulations. Suitable preservatives include, but are not limited to, antimicrobials such as methylparaben,

propylparaben, sorbic acid, benzoic acid, and formaldehyde, as well as physical stabilizers and antioxidants such as vitamin E, sodium ascorbate/ascorbic acid and propyl gallate. Suitable moisturizers include, but are not limited to, lactic acid and other hydroxy acids and their salts, glycerin, propylene glycol, and butylene glycol. Suitable emollients include lanolin alcohol, lanolin, lanolin derivatives, cholesterol, petrolatum, isostearyl neopentanoate and mineral oils. Suitable fragrances and colors include, but are not limited to, FD&C Red No. 40 and FD&C Yellow No. 5. Other suitable additional ingredients that may be included a topical formulation include, but are not limited to, abrasives, absorbents, anti-caking agents, anti-foaming agents, anti-static agents, astringents (*e.g.*, witch hazel, alcohol and herbal extracts such as chamomile extract), binders/excipients, buffering agents, chelating agents, film forming agents, conditioning agents, propellants, opacifying agents, pH adjusters and protectants.

An example of a suitable topical vehicle for formulation of a gel is: hydroxypropylcellulose (2.1%); 70/30 isopropyl alcohol/water (90.9%); propylene glycol (5.1%); and Polysorbate 80 (1.9%). An example of a suitable topical vehicle for formulation as a foam is: cetyl alcohol (1.1%); stearyl alcohol (0.5%); Quaternium 52 (1.0%); propylene glycol (2.0%); Ethanol 95 PGF3 (61.05%); deionized water (30.05%); P75 hydrocarbon propellant (4.30%). All percents are by weight.

Typical modes of delivery for topical compositions include application using the fingers; application using a physical applicator such as a cloth, tissue, swab, stick or brush; spraying (including mist, aerosol or foam spraying); dropper application; sprinkling; soaking; and rinsing.

A pharmaceutical composition may be prepared as a sterile injectible aqueous or oleaginous suspension. The compound(s) provided herein, depending on the vehicle and concentration used, can either be suspended or dissolved in the vehicle. Such a composition may be formulated according to the known art using suitable dispersing, wetting agents and/or suspending agents such as those mentioned above. Among the acceptable vehicles and solvents that may be employed are water, 1,3-butanediol, Ringer's solution and isotonic sodium chloride solution. In addition, sterile, fixed oils may be employed as a solvent or suspending medium. For this purpose any bland fixed oil may be employed, including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid find use in the preparation of injectible compositions, and adjuvants such as local anesthetics, preservatives and/or buffering agents can be dissolved in the vehicle.

Pharmaceutical compositions may also be formulated as suppositories (*e.g.*, for rectal administration). Such compositions can be prepared by mixing the drug with a suitable non-

irritating excipient that is solid at ordinary temperatures but liquid at the rectal temperature and will therefore melt in the rectum to release the drug. Suitable excipients include, for example, cocoa butter and polyethylene glycols.

5 Compositions for inhalation typically can be provided in the form of a solution, suspension or emulsion that can be administered as a dry powder or in the form of an aerosol using a conventional propellant (*e.g.*, dichlorodifluoromethane or trichlorofluoromethane).

Pharmaceutical compositions may be formulated for release at a pre-determined rate. Instantaneous release may be achieved, for example, via sublingual administration (*i.e.*, administration by mouth in such a way that the active ingredient(s) are rapidly absorbed via
10 the blood vessels under the tongue rather than via the digestive tract). Controlled release formulations (*i.e.*, formulations such as a capsule, tablet or coated tablet that slows and/or delays release of active ingredient(s) following administration) may be administered by, for example, oral, rectal or subcutaneous implantation, or by implantation at a target site. In general, a controlled release formulation comprises a matrix and/or coating that delays
15 disintegration and absorption in the gastrointestinal tract (or implantation site) and thereby provides a delayed action or a sustained action over a longer period. One type of controlled-release formulation is a sustained-release formulation, in which at least one active ingredient is continuously released over a period of time at a constant rate. Preferably, the therapeutic agent is released at such a rate that blood (*e.g.*, plasma) concentrations are maintained within
20 the therapeutic range, but below toxic levels, over a period of time that is at least 4 hours, preferably at least 8 hours, and more preferably at least 12 hours. Such formulations may generally be prepared using well known technology and administered by, for example, oral, rectal or subcutaneous implantation, or by implantation at the desired target site. Carriers for use within such formulations are biocompatible, and may also be biodegradable; preferably
25 the formulation provides a relatively constant level of modulator release. The amount of modulator contained within a sustained release formulation depends upon, for example, the site of implantation, the rate and expected duration of release and the nature of the condition to be treated or prevented.

Controlled release may be achieved by combining the active ingredient(s) with a
30 matrix material that itself alters release rate and/or through the use of a controlled-release coating. The release rate can be varied using methods well known in the art, including (a) varying the thickness or composition of coating, (b) altering the amount or manner of addition of plasticizer in a coating, (c) including additional ingredients, such as release-modifying agents, (d) altering the composition, particle size or particle shape of the matrix, and (e)
35 providing one or more passageways through the coating. The amount of modulator contained

within a sustained release formulation depends upon, for example, the method of administration (*e.g.*, the site of implantation), the rate and expected duration of release and the nature of the condition to be treated or prevented.

The matrix material, which itself may or may not serve a controlled-release function, is generally any material that supports the active ingredient(s). For example, a time delay material such as glyceryl monostearate or glyceryl distearate may be employed. Active ingredient(s) may be combined with matrix material prior to formation of the dosage form (*e.g.*, a tablet). Alternatively, or in addition, active ingredient(s) may be coated on the surface of a particle, granule, sphere, microsphere, bead or pellet that comprises the matrix material. Such coating may be achieved by conventional means, such as by dissolving the active ingredient(s) in water or other suitable solvent and spraying. Optionally, additional ingredients are added prior to coating (*e.g.*, to assist binding of the active ingredient(s) to the matrix material or to color the solution). The matrix may then be coated with a barrier agent prior to application of controlled-release coating. Multiple coated matrix units may, if desired, be encapsulated to generate the final dosage form.

In certain embodiments, a controlled release is achieved through the use of a controlled release coating (*i.e.*, a coating that permits release of active ingredient(s) at a controlled rate in aqueous medium). The controlled release coating should be a strong, continuous film that is smooth, capable of supporting pigments and other additives, non-toxic, inert and tack-free. Coatings that regulate release of the modulator include pH-independent coatings, pH-dependent coatings (which may be used to release modulator in the stomach) and enteric coatings (which allow the formulation to pass intact through the stomach and into the small intestine, where the coating dissolves and the contents are absorbed by the body). It will be apparent that multiple coatings may be employed (*e.g.*, to allow release of a portion of the dose in the stomach and a portion further along the gastrointestinal tract). For example, a portion of active ingredient(s) may be coated over an enteric coating, and thereby released in the stomach, while the remainder of active ingredient(s) in the matrix core is protected by the enteric coating and released further down the GI tract. pH dependent coatings include, for example, shellac, cellulose acetate phthalate, polyvinyl acetate phthalate, hydroxypropylmethylcellulose phthalate, methacrylic acid ester copolymers and zein.

In certain embodiments, the coating is a hydrophobic material, preferably used in an amount effective to slow the hydration of the gelling agent following administration. Suitable hydrophobic materials include alkyl celluloses (*e.g.*, ethylcellulose or carboxymethylcellulose), cellulose ethers, cellulose esters, acrylic polymers (*e.g.*, poly(acrylic acid), poly(methacrylic acid), acrylic acid and methacrylic acid copolymers, methyl

methacrylate copolymers, ethoxy ethyl methacrylates, cyanoethyl methacrylate, methacrylic acid alkamide copolymer, poly(methyl methacrylate), polyacrylamide, ammonio methacrylate copolymers, aminoalkyl methacrylate copolymer, poly(methacrylic acid anhydride) and glycidyl methacrylate copolymers) and mixtures of the foregoing. Representative aqueous
5 dispersions of ethylcellulose include, for example, AQUACOAT® (FMC Corp., Philadelphia, PA) and SURELEASE® (Colorcon, Inc., West Point, PA), both of which can be applied to the substrate according to the manufacturer's instructions. Representative acrylic polymers include, for example, the various EUDRAGIT® (Rohm America, Piscataway, NJ) polymers, which may be used singly or in combination depending on the desired release profile,
10 according to the manufacturer's instructions.

The physical properties of coatings that comprise an aqueous dispersion of a hydrophobic material may be improved by the addition of one or more plasticizers. Suitable plasticizers for alkyl celluloses include, for example, dibutyl sebacate, diethyl phthalate, triethyl citrate, tributyl citrate and triacetin. Suitable plasticizers for acrylic polymers include,
15 for example, citric acid esters such as triethyl citrate and tributyl citrate, dibutyl phthalate, polyethylene glycols, propylene glycol, diethyl phthalate, castor oil and triacetin.

Controlled-release coatings are generally applied using conventional techniques, such as by spraying in the form of an aqueous dispersion. If desired, the coating may comprise pores or channels or to facilitate release of active ingredient. Pores and channels may be
20 generated by well known methods, including the addition of organic or inorganic material that is dissolved, extracted or leached from the coating in the environment of use. Certain such pore-forming materials include hydrophilic polymers, such as hydroxyalkylcelluloses (*e.g.*, hydroxypropylmethylcellulose), cellulose ethers, synthetic water-soluble polymers (*e.g.*, polyvinylpyrrolidone, cross-linked polyvinylpyrrolidone and polyethylene oxide), water-
25 soluble polydextrose, saccharides and polysaccharides and alkali metal salts. Alternatively, or in addition, a controlled release coating may include one or more orifices, which may be formed by methods such as those described in US Patent Nos. 3,845,770; 4,034,758; 4,077,407; 4,088,864; 4,783,337 and 5,071,607. Controlled-release may also be achieved through the use of transdermal patches, using conventional technology (*see, e.g.*, US Patent
30 No. 4,668,232).

Further examples of controlled release formulations, and components thereof, may be found, for example, in US Patent Nos. 4,572,833; 4,587,117; 4,606,909; 4,610,870; 4,684,516; 4,777,049; 4,994,276; 4,996,058; 5,128,143; 5,202,128; 5,376,384; 5,384,133; 5,445,829; 5,510,119; 5,618,560; 5,643,604; 5,891,474; 5,958,456; 6,039,980; 6,143,353;
35 6,126,969; 6,156,342; 6,197,347; 6,387,394; 6,399,096; 6,437,000; 6,447,796; 6,475,493;

6,491,950; 6,524,615; 6,838,094; 6,905,709; 6,923,984; 6,923,988; and 6,911,217; each of which is hereby incorporated by reference for its teaching of the preparation of controlled release dosage forms.

5 In addition to or together with the above modes of administration, a compound provided herein may be conveniently added to food or drinking water (*e.g.*, for administration to non-human animals including companion animals (such as dogs and cats) and livestock). Animal feed and drinking water compositions may be formulated so that the animal takes in an appropriate quantity of the composition along with its diet. It may also be convenient to present the composition as a premix for addition to feed or drinking water.

10 Compounds are generally administered in a therapeutically effective amount. Preferred systemic doses are no higher than 50 mg per kilogram of body weight per day (*e.g.*, ranging from about 0.001 mg to about 50 mg per kilogram of body weight per day), with oral doses generally being about 5-20 fold higher than intravenous doses (*e.g.*, ranging from 0.01 to 40 mg per kilogram of body weight per day).

15 The amount of active ingredient that may be combined with the carrier materials to produce a single dosage unit will vary depending, for example, upon the patient being treated, the particular mode of administration and any other co-administered drugs. Dosage units generally contain between from about 10 μ g to about 500 mg of active ingredient. Optimal dosages may be established using routine testing, and procedures that are well known in the art.

20 Pharmaceutical compositions may be packaged for treating conditions responsive to VR1 modulation (*e.g.*, treatment of exposure to vanilloid ligand or other irritant, pain, itch, obesity or urinary incontinence). Packaged pharmaceutical compositions generally include (i) a container holding a pharmaceutical composition that comprises at least one VR1 modulator as described herein and (ii) instructions (*e.g.*, labeling or a package insert) indicating that the contained composition is to be used for treating a condition responsive to VR1 modulation in the patient.

METHODS OF USE

30 VR1 modulators provided herein may be used to alter activity and/or activation of capsaicin receptors in a variety of contexts, both *in vitro* and *in vivo*. Within certain aspects, VR1 antagonists may be used to inhibit the binding of vanilloid ligand agonist (such as capsaicin and/or RTX) to capsaicin receptor *in vitro* or *in vivo*. In general, such methods comprise the step of contacting a capsaicin receptor with one or more VR1 modulators provided herein, in the presence of vanilloid ligand in aqueous solution and under conditions otherwise suitable for binding of the ligand to capsaicin receptor. The VR1 modulator(s) are

generally present at a concentration that is sufficient to alter the binding of vanilloid ligand to VR1 *in vitro* (using the assay provided in Example 5) and/or VR1-mediated signal transduction (using an assay provided in Example 6). The capsaicin receptor may be present in solution or suspension (*e.g.*, in an isolated membrane or cell preparation), or in a cultured or isolated cell. Within certain embodiments, the capsaicin receptor is expressed by a neuronal cell present in a patient, and the aqueous solution is a body fluid. Preferably, one or more VR1 modulators are administered to an animal in an amount such that the VR1 modulator is present in at least one body fluid of the animal at a therapeutically effective concentration that is 5 micromolar or less; preferably 1 micromolar or less; more preferably 100 nanomolar or less. For example, such compounds may be administered at a therapeutically effective dose that is less than 20 mg/kg body weight, preferably less than 5 mg/kg and, in some instances, less than 1 mg/kg.

Also provided herein are methods for modulating, preferably reducing, the signal-transducing activity (*i.e.*, the calcium conductance) of a cellular capsaicin receptor. Such modulation may be achieved by contacting a capsaicin receptor (either *in vitro* or *in vivo*) with one or more VR1 modulators provided herein under conditions suitable for binding of the modulator(s) to the receptor. The VR1 modulator(s) are generally present at a concentration that is sufficient to alter the binding of vanilloid ligand to VR1 *in vitro* and/or VR1-mediated signal transduction as described herein. The receptor may be present in solution or suspension, in a cultured or isolated cell preparation or in a cell within a patient. For example, the cell may be a neuronal cell that is contacted *in vivo* in an animal. Alternatively, the cell may be an epithelial cell, such as a urinary bladder epithelial cell (urothelial cell) or an airway epithelial cell that is contacted *in vivo* in an animal. Modulation of signal transducing activity may be assessed by detecting an effect on calcium ion conductance (also referred to as calcium mobilization or flux). Modulation of signal transducing activity may alternatively be assessed by detecting an alteration of a symptom (*e.g.*, pain, burning sensation, broncho-constriction, inflammation, cough, hiccup, itch, urinary incontinence or overactive bladder) of a patient being treated with one or more VR1 modulators provided herein.

VR1 modulator(s) provided herein are preferably administered to a patient (*e.g.*, a human) orally or topically, and are present within at least one body fluid of the animal while modulating VR1 signal-transducing activity. Preferred VR1 modulators for use in such methods modulate VR1 signal-transducing activity *in vitro* at a concentration of 1 nanomolar or less, preferably 100 picomolar or less, more preferably 20 picomolar or less, and *in vivo* at

a concentration of 1 micromolar or less, 500 nanomolar or less, or 100 nanomolar or less in a body fluid such as blood.

The present invention further provides methods for treating conditions responsive to VR1 modulation. Within the context of the present invention, the term "treatment" encompasses both disease-modifying treatment and symptomatic treatment, either of which may be prophylactic (*i.e.*, before the onset of symptoms, in order to prevent, delay or reduce the severity of symptoms) or therapeutic (*i.e.*, after the onset of symptoms, in order to reduce the severity and/or duration of symptoms). A condition is "responsive to VR1 modulation" if it is characterized by inappropriate activity of a capsaicin receptor, regardless of the amount of vanilloid ligand present locally, and/or if modulation of capsaicin receptor activity results in alleviation of the condition or a symptom thereof. Such conditions include, for example, symptoms resulting from exposure to VR1-activating stimuli, pain, respiratory disorders (such as cough, asthma, chronic obstructive pulmonary disease, chronic bronchitis, cystic fibrosis and rhinitis, including allergic rhinitis, such as seasonal and perennial rhinitis, and non-allergic rhinitis), depression, itch, urinary incontinence, overactive bladder, diabetes and prediabetic conditions (*e.g.*, insulin resistance or glucose tolerance), hiccup and obesity, as described in more detail below. Such conditions may be diagnosed and monitored using criteria that have been established in the art. Patients may include humans, domesticated companion animals and livestock, with dosages as described above.

Treatment regimens may vary depending on the compound used and the particular condition to be treated; however, for treatment of most disorders, a frequency of administration of 4 times daily or less is preferred. In general, a dosage regimen of 2 times daily is more preferred, with once a day dosing particularly preferred. For the treatment of acute pain, a single dose that rapidly reaches effective concentrations is desirable. It will be understood, however, that the specific dose level and treatment regimen for any particular patient will depend upon a variety of factors including the activity of the specific compound employed, the age, body weight, general health, sex, diet, time of administration, route of administration, and rate of excretion, drug combination and the severity of the particular disease undergoing therapy. In general, the use of the minimum dose sufficient to provide effective therapy is preferred. Patients may generally be monitored for therapeutic effectiveness using medical or veterinary criteria suitable for the condition being treated or prevented.

Patients experiencing symptoms resulting from exposure to capsaicin receptor-activating stimuli include individuals with burns caused by heat, light, tear gas or acid and those whose mucous membranes are exposed (*e.g.*, via ingestion, inhalation or eye contact) to

capsaicin (*e.g.*, from hot peppers or in pepper spray) or a related irritant such as acid, tear gas, infectious agent(s) or air pollutant(s). The resulting symptoms (which may be treated using VR1 modulators, especially antagonists, provided herein) may include, for example, pain, broncho-constriction and inflammation.

5 Pain that may be treated using the VR1 modulators provided herein may be chronic or acute and includes, but is not limited to, peripheral nerve-mediated pain (especially neuropathic pain). Compounds provided herein may be used in the treatment of, for example, postmastectomy pain syndrome, stump pain, phantom limb pain, oral neuropathic pain, toothache (dental pain), denture pain, postherpetic neuralgia, diabetic neuropathy, 10 chemotherapy-induced neuropathy, reflex sympathetic dystrophy, trigeminal neuralgia, osteoarthritis, rheumatoid arthritis, fibromyalgia, Guillain-Barre syndrome, meralgia paresthetica, burning-mouth syndrome and/or pain associated with nerve and root damage, including as pain associated with peripheral nerve disorders (*e.g.*, nerve entrapment and brachial plexus avulsions, amputation, peripheral neuropathies including bilateral peripheral 15 neuropathy, tic douloureux, atypical facial pain, nerve root damage, and arachnoiditis). Additional neuropathic pain conditions include causalgia (reflex sympathetic dystrophy - RSD, secondary to injury of a peripheral nerve), neuritis (including, for example, sciatic neuritis, peripheral neuritis, polyneuritis, optic neuritis, postfebrile neuritis, migrating neuritis, segmental neuritis and Gombault's neuritis), neuronitis, neuralgias (*e.g.*, those mentioned 20 above, cervicobrachial neuralgia, cranial neuralgia, geniculate neuralgia, glossopharyngeal neuralgia, migranous neuralgia, idiopathic neuralgia, intercostals neuralgia, mammary neuralgia, mandibular joint neuralgia, Morton's neuralgia, nasociliary neuralgia, occipital neuralgia, red neuralgia, Sluder's neuralgia, splenopalatine neuralgia, supraorbital neuralgia and vidian neuralgia), surgery-related pain, musculoskeletal pain, myofascial pain syndromes, 25 AIDS-related neuropathy, MS-related neuropathy, central nervous system pain (*e.g.*, pain due to brain stem damage, sciatica, and ankylosing spondylitis), and spinal pain, including spinal cord injury-related pain. Headache, including headaches involving peripheral nerve activity may also be treated as described herein. Such pain includes, for example, such as sinus, cluster (*i.e.*, migranous neuralgia) and tension headaches, migraine, temporomandibular pain 30 and maxillary sinus pain. For example, migraine headaches may be prevented by administration of a compound provided herein as soon as a pre-migrainous aura is experienced by the patient. Further conditions that can be treated as described herein include Charcot's pains, intestinal gas pains, ear pain, heart pain, muscle pain, eye pain, orofacial pain (*e.g.*, odontalgia), abdominal pain, gynaecological pain (*e.g.*, menstrual pain, dysmenorrhoea, 35 pain associated with cystitis, labor pain, chronic pelvic pain, chronic proctitis and

endometriosis), acute and chronic back pain (*e.g.*, lower back pain), gout, scar pain, hemorrhoidal pain, dyspeptic pains, angina, nerve root pain, "non-painful" neuropathies, complex regional pain syndrome, homotopic pain and heterotopic pain – including pain associated with carcinoma, often referred to as cancer pain (*e.g.*, in patients with bone cancer),
5 pain (and inflammation) associated with venom exposure (*e.g.*, due to snake bite, spider bite, or insect sting) and trauma associated pain (*e.g.*, post-surgical pain, episiotomy pain, pain from cuts, musculoskeletal pain, bruises and broken bones, and burn pain, especially primary hyperalgesia associated therewith). Additional pain conditions that may be treated as described herein include pain associated with respiratory disorders as described above,
10 autoimmune diseases, immunodeficiency disorders, hot flashes, inflammatory bowel disease, gastroesophageal reflux disease (GERD), irritable bowel syndrome and/or inflammatory bowel disease.

Within certain aspects, VR1 modulators provided herein may be used for the treatment of mechanical pain. As used herein, the term "mechanical pain" refers to pain other than
15 headache pain that is not neuropathic or a result of exposure to heat, cold or external chemical stimuli. Mechanical pain includes physical trauma (other than thermal or chemical burns or other irritating and/or painful exposures to noxious chemicals) such as post-surgical pain and pain from cuts, bruises and broken bones; toothache; denture pain; nerve root pain; osteoarthritis; rheumatoid arthritis; fibromyalgia; meralgia paresthetica; back pain; cancer-associated pain; angina; carpal tunnel syndrome; and pain resulting from bone fracture, labor,
20 hemorrhoids, intestinal gas, dyspepsia, and menstruation.

Itching conditions that may be treated include psoriatic pruritus, itch due to hemodialysis, aquagenic pruritus, and itching associated with vulvar vestibulitis, contact dermatitis, insect bites and skin allergies. Urinary tract conditions that may be treated as
25 described herein include urinary incontinence (including overflow incontinence, urge incontinence and stress incontinence), as well as overactive or unstable bladder conditions (including bladder detrusor hyper-reflexia, detrusor hyper-reflexia of spinal origin and bladder hypersensitivity). In certain such treatment methods, VR1 modulator is administered via a catheter or similar device, resulting in direct injection of VR1 modulator into the bladder.
30 Compounds provided herein may also be used as anti-tussive agents (to prevent, relieve or suppress coughing, including cough induced by medications such as ACE inhibitors) and for the treatment of hiccup, for the treatment of menopause symptoms such as hot flashes, and to promote weight loss in an obese patient.

Within other aspects, VR1 modulators provided herein may be used within
35 combination therapy for the treatment of conditions involving pain and/or inflammatory

components. Such conditions include, for example, autoimmune disorders and pathologic autoimmune responses known to have an inflammatory component including, but not limited to, arthritis (especially rheumatoid arthritis), psoriasis, Crohn's disease, lupus erythematosus, irritable bowel syndrome, tissue graft rejection, and hyperacute rejection of transplanted organs. Other such conditions include trauma (*e.g.*, injury to the head or spinal cord), cardio- and cerebro-vascular disease and certain infectious diseases.

Within such combination therapy, a VR1 modulator is administered to a patient along with an analgesic and/or anti-inflammatory agent. The VR1 modulator and analgesic and/or anti-inflammatory agent may be present in the same pharmaceutical composition, or may be administered separately in either order. Anti-inflammatory agents include, for example, non-steroidal anti-inflammatory drugs (NSAIDs), non-specific and cyclooxygenase-2 (COX-2) specific cyclooxygenase enzyme inhibitors, gold compounds, corticosteroids, methotrexate, tumor necrosis factor (TNF) receptor antagonists, anti-TNF alpha antibodies, anti-C5 antibodies, and interleukin-1 (IL-1) receptor antagonists. Examples of NSAIDs include, but are not limited to ibuprofen, flurbiprofen, naproxen or naproxen sodium, diclofenac, combinations of diclofenac sodium and misoprostol, sulindac, oxaprozin, diflunisal, piroxicam, indomethacin, etodolac, fenoprofen calcium, ketoprofen, sodium nabumetone, sulfasalazine, tolmetin sodium, and hydroxychloroquine. One class of NSAIDs consists of compounds that inhibit cyclooxygenase (COX) enzymes; such compounds include celecoxib and rofecoxib. NSAIDs further include salicylates such as acetylsalicylic acid or aspirin, sodium salicylate, choline and magnesium salicylates, and salsalate, as well as corticosteroids such as cortisone, dexamethasone, methylprednisolone, prednisolone, prednisolone sodium phosphate, and prednisone. Further anti-inflammatory agents include meloxicam, etoricoxib, parecoxib, valdecoxib and tilicoxib.

Suitable dosages for VR1 modulator within a combination therapy are generally as described above. Dosages and methods of administration of anti-inflammatory agents can be found, for example, in the manufacturer's instructions in the *Physician's Desk Reference*. In certain embodiments, the combination administration of a VR1 modulator with an anti-inflammatory agent results in a reduction of the dosage of the anti-inflammatory agent required to produce a therapeutic effect (*i.e.*, a decrease in the minimum therapeutically effective amount). Thus, preferably, the dosage of anti-inflammatory agent in a combination or combination treatment method is less than the maximum dose advised by the manufacturer for administration of the anti-inflammatory agent without combination administration of a VR1 antagonist. More preferably this dosage is less than $\frac{3}{4}$, even more preferably less than $\frac{1}{2}$, and highly preferably, less than $\frac{1}{4}$ of the maximum dose, while most preferably the dose is

less than 10% of the maximum dose advised by the manufacturer for administration of the anti-inflammatory agent(s) when administered without combination administration of a VR1 antagonist. It will be apparent that the dosage amount of VR1 antagonist component of the combination needed to achieve the desired effect may similarly be affected by the dosage amount and potency of the anti-inflammatory agent component of the combination.

In certain preferred embodiments, the combination administration of a VR1 modulator with an anti-inflammatory agent is accomplished by packaging one or more VR1 modulators and one or more anti-inflammatory agents in the same package, either in separate containers within the package or in the same contained as a mixture of one or more VR1 antagonists and one or more anti-inflammatory agents. Preferred mixtures are formulated for oral administration (*e.g.*, as pills, capsules, tablets or the like). In certain embodiments, the package comprises a label bearing indicia indicating that the one or more VR1 modulators and one or more anti-inflammatory agents are to be taken together for the treatment of an inflammatory pain condition.

Within further aspects, VR1 modulators provided herein may be used in combination with one or more additional pain relief medications. Certain such medications are also anti-inflammatory agents, and are listed above. Other such medications are analgesic agents, including narcotic agents which typically act at one or more opioid receptor subtypes (*e.g.*, μ , κ and/or δ), preferably as agonists or partial agonists. Such agents include opiates, opiate derivatives and opioids, as well as pharmaceutically acceptable salts and hydrates thereof. Specific examples of narcotic analgesics include, within preferred embodiments, alfentanil, alphaprodine, anileridine, bezitramide, buprenorphine, butorphanol, codeine, diacetyldihydromorphine, diacetylmorphine, dihydrocodeine, diphenoxylate, ethylmorphine, fentanyl, heroin, hydrocodone, hydromorphone, isomethadone, levomethorphan, levorphanol, meperidine, metazocine, methadone, methorphan, metopon, morphine, nalbuphine, opium extracts, opium fluid extracts, powdered opium, granulated opium, raw opium, tincture of opium, oxycodone, oxymorphone, paregoric, pentazocine, pethidine, phenazocine, piminodine, propoxyphene, racemethorphan, racemorphan, sulfentanyl, thebaine and pharmaceutically acceptable salts and hydrates of the foregoing agents.

Other examples of narcotic analgesic agents include acetorphine, acetyldihydrocodeine, acetylmethadol, allylprodine, alpracetalmethadol, alphameprodine, alphamethadol, benzethidine, benzylmorphine, betacetylmethadol, betameprodine, betamethadol, betaprodine, clonitazene, codeine methylbromide, codeine-N-oxide, cyprenorphine, desomorphine, dextromoramide, diampromide, diethylthiambutene, dihydromorphine, dimenoxadol, dimepheptanol, dimethylthiamubutene, dioxaphetyl butyrate,

dipipanone, drotebanol, ethanol, ethylmethylthiambutene, etonitazene, etorphine, etoxeridine, furethidine, hydromorphenol, hydroxypethidine, ketobemidone, levomoramide, levophenacymorphan, methylidesorphine, methyldihydromorphine, morpheridine, morphine methylpromide, morphine methylsulfonate, morphine-N-oxide, myrophin, naloxone, 5 naltrexone, nicocodeine, nicomorphine, noracymethadol, norlevorphanol, normethadone, normorphine, norpiperone, pentazocaine, phenadoxone, phenampromide, phenomorphan, phenoperidine, piritramide, pholcodine, proheptazone, properidine, propiran, racemoramide, thebacon, trimeperidine and the pharmaceutically acceptable salts and hydrates thereof.

Further specific representative analgesic agents include, for example acetaminophen 10 (paracetamol); aspirin and other NSAIDs described above; NR2B antagonists; bradykinin antagonists; anti-migraine agents; anticonvulsants such as oxcarbazepine and carbamazepine; antidepressants (such as TCAs, SSRIs, SNRIs, substance P antagonists, etc.); spinal blocks; pentazocine/naloxone; meperidine; levorphanol; buprenorphine; hydromorphone; fentanyl; sufentanyl; oxycodone; oxycodone/acetaminophen, nalbuphine and oxymorphone. Still 15 further analgesic agents include CB2-receptor agonists, such as AM1241, capsaicin receptor antagonists and compounds that bind to the $\alpha 2\delta$ subunit of voltage-gated calcium channels, such as gabapentin and pregabalin.

Representative anti-migraine agents for use in combination with a VR1 modulator provided herein include CGRP antagonists, ergotamines and 5-HT₁ agonists, such as 20 sumatriptan, naratriptan, zolmatriptan and rizatriptan.

Within still further aspects, modulators provided herein may be used, for example, in the treatment of pulmonary disorders such as asthma, in combination with one or more beta(2)-adrenergic receptor agonists or leukotriene receptor antagonists (*e.g.*, agents that inhibits the cysteinyl leukotriene CysLT₁ receptor). CysLT₁ antagonists include montelukast, 25 zafirlukast, and pranlukast.

For the treatment or prevention of cough, a VR1 modulator as provided herein may be used in combination with other medication designed to treat this condition, such as antibiotics, anti-inflammatory agents, cystinyl leukotrienes, histamine antagonists, corticosteroids, opioids, NMDA antagonists, proton pump inhibitors, nociceptin, neurokinin (NK1, NK2 and 30 NK3) and bradykinin (BK1 and BK2) receptor antagonists, cannabinoids, blockers of Na⁺-dependent channels and large conductance Ca⁺²-dependent K⁺-channel activators. Specific agents include dexbrompheniramine plus pseudoephedrine, loratadine, oxymetazoline, ipratropium, albuterol, beclomethasone, morphine, codeine, pholcodeine and dextromethorphan.

The present invention further provides combination therapy for the treatment of urinary incontinence. Within such aspects, a VR1 modulator provided herein may be used in combination with other medication designed to treat this condition, such as estrogen replacement therapy, progesterone congeners, electrical stimulation, calcium channel
5 blockers, antispasmodic agents, cholinergic antagonists, antimuscarinic drugs, tricyclic antidepressants, SNRIs, beta adrenoceptor agonists, phosphodiesterase inhibitors, potassium channel openers, nociceptin/orphanin FQ (OP4) agonists, neurokinin (NK1 and NK2) antagonists, P2X3 antagonists, musculotrophic drugs and sacral neuromodulation. Specific agents include oxybutinin, emepronium, tolterodine, flavoxate, flurbiprofen, tolterodine,
10 dicyclomine, propiverine, propantheline, dicyclomine, imipramine, doxepin, duloxetine, 1-deamino-8-D-arginine vasopressin, muscarinic receptor antagonists such as tolterodine and anticholinergic agents such as oxybutynin.

Suitable dosages for VR1 modulator within such combination therapy are generally as described above. Dosages and methods of administration of other pain relief medications can
15 be found, for example, in the manufacturer's instructions in the *Physician's Desk Reference*. In certain embodiments, the combination administration of a VR1 modulator with one or more additional pain medications results in a reduction of the dosage of each therapeutic agent required to produce a therapeutic effect (*e.g.*, the dosage of one or both agent may less than $\frac{3}{4}$, less than $\frac{1}{2}$, less than $\frac{1}{4}$ or less than 10% of the maximum dose listed above or
20 advised by the manufacturer).

For use in combination therapy, pharmaceutical compositions as described above may further comprise one or more additional medications as described above. In certain such compositions, the additional medication is an analgesic. Also provided herein are packaged pharmaceutical preparations comprising one or more VR1 modulators and one or more
25 additional medications (*e.g.*, analgesics) in the same package. Such packaged pharmaceutical preparations generally include (i) a container holding a pharmaceutical composition that comprises at least one VR1 modulator as described herein; (ii) a container holding a pharmaceutical composition that comprises at least one additional medication (such as a pain relief and/or anti-inflammatory medication) as described above and (iii) instructions (*e.g.*,
30 labeling or a package insert) indicating that the compositions are to be used simultaneously, separately or sequentially for treating or preventing a condition responsive to VR1 modulation in the patient (such as a condition in which pain and/or inflammation predominates).

Compounds that are VR1 agonists may further be used, for example, in crowd control (as a substitute for tear gas) or personal protection (*e.g.*, in a spray formulation) or as
35 pharmaceutical agents for the treatment of pain, itch, urinary incontinence or overactive

bladder via capsaicin receptor desensitization. In general, compounds for use in crowd control or personal protection are formulated and used according to conventional tear gas or pepper spray technology.

Within separate aspects, the present invention provides a variety of non-pharmaceutical *in vitro* and *in vivo* uses for the compounds provided herein. For example, such compounds may be labeled and used as probes for the detection and localization of capsaicin receptor (in samples such as cell preparations or tissue sections, preparations or fractions thereof). In addition, compounds provided herein that comprise a suitable reactive group (such as an aryl carbonyl, nitro or azide group) may be used in photoaffinity labeling studies of receptor binding sites. In addition, compounds provided herein may be used as positive controls in assays for receptor activity, as standards for determining the ability of a candidate agent to bind to capsaicin receptor, or as radiotracers for positron emission tomography (PET) imaging or for single photon emission computerized tomography (SPECT). Such methods can be used to characterize capsaicin receptors in living subjects. For example, a VR1 modulator may be labeled using any of a variety of well known techniques (*e.g.*, radiolabeled with a radionuclide such as tritium, as described herein), and incubated with a sample for a suitable incubation time (*e.g.*, determined by first assaying a time course of binding). Following incubation, unbound compound is removed (*e.g.*, by washing), and bound compound detected using any method suitable for the label employed (*e.g.*, autoradiography or scintillation counting for radiolabeled compounds; spectroscopic methods may be used to detect luminescent groups and fluorescent groups). As a control, a matched sample containing labeled compound and a greater (*e.g.*, 10-fold greater) amount of unlabeled compound may be processed in the same manner. A greater amount of detectable label remaining in the test sample than in the control indicates the presence of capsaicin receptor in the sample. Detection assays, including receptor autoradiography (receptor mapping) of capsaicin receptor in cultured cells or tissue samples may be performed as described by Kuhar in sections 8.1.1 to 8.1.9 of *Current Protocols in Pharmacology* (1998) John Wiley & Sons, New York.

Compounds provided herein may also be used within a variety of well known cell separation methods. For example, modulators may be linked to the interior surface of a tissue culture plate or other support, for use as affinity ligands for immobilizing and thereby isolating, capsaicin receptors (*e.g.*, isolating receptor-expressing cells) *in vitro*. Within one preferred embodiment, a modulator linked to a fluorescent marker, such as fluorescein, is contacted with the cells, which are then analyzed (or isolated) by fluorescence activated cell sorting (FACS).

VR1 modulators provided herein may further be used within assays for the identification of other agents that bind to capsaicin receptor. In general, such assays are standard competition binding assays, in which bound, labeled VR1 modulator is displaced by a test compound. Briefly, such assays are performed by: (a) contacting capsaicin receptor with a radiolabeled VR1 modulator as described herein, under conditions that permit binding of the VR1 modulator to capsaicin receptor, thereby generating bound, labeled VR1 modulator; (b) detecting a signal that corresponds to the amount of bound, labeled VR1 modulator in the absence of test agent; (c) contacting the bound, labeled VR1 modulator with a test agent; (d) detecting a signal that corresponds to the amount of bound labeled VR1 modulator in the presence of test agent; and (e) detecting a decrease in signal detected in step (d), as compared to the signal detected in step (b).

The following Examples are offered by way of illustration and not by way of limitation. Unless otherwise specified all reagents and solvent are of standard commercial grade and are used without further purification. Using routine modifications, the starting materials may be varied and additional steps employed to produce other compounds provided herein.

EXAMPLES

Mass spectroscopy data in the following Examples is Electrospray MS, obtained in positive ion mode using a Micromass Time-of-Flight LCT (Waters Corp.; Milford, MA), equipped with a Waters 600 pump (Waters Corp.; Milford, MA), Waters 996 photodiode array detector (Waters Corp.; Milford, MA), and a Gilson 215 autosampler (Gilson, Inc.; Middleton, WI). MassLynx™ (Waters Corp.; Milford, MA) version 4.0 software with OpenLynx Global Server™, OpenLynx™ and AutoLynx™ processing is used for data collection and analysis. MS conditions are as follows: capillary voltage = 3.5 kV; cone voltage = 30 V, desolvation and source temperature = 350°C and 120°C, respectively; mass range = 181-750 with a scan time of 0.22 seconds and an interscan delay of 0.05 seconds.

Sample volume of 1 microliter is injected onto a 50x4.6mm Chromolith SpeedROD RP-18e column (Merck KGaA, Darmstadt, Germany), and eluted using a 2-phase linear gradient at a flow rate of 6 ml/min. Sample is detected using total absorbance count over the 220-340nm UV range. The elution conditions are: Mobile Phase A - 95% water, 5% MeOH with 0.05% TFA; Mobile Phase B - 5% water, 95% MeOH with 0.025% TFA. The following gradient is used: 0-0.5 min 10-100%B, hold at 100%B to 1.2 min, return to 10%B at 1.21 min. Inject to inject cycle is 2.15 min.

The determined molecular weight (MS) is provided as M+1, with retention times (R_T) given in minutes. The IC₅₀ determined as described in Example 6 is 1 micromolar or less for compounds 1-10, 12-16 and 18-20.

EXAMPLE 1

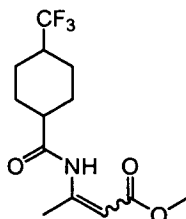
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Preparation of Representative Substituted Pyrimidinones

This Example illustrates the preparation of substituted pyrimidinones.

A. 3-(4-Chlorophenyl)-6-methyl-2-[cis-4-(trifluoromethyl)cyclohexyl]pyrimidin-4(3H)-one (Compound 1)

1. *Methyl 3-(4-(trifluoromethyl)cyclohexanecarboxamido)but-2-enoate*

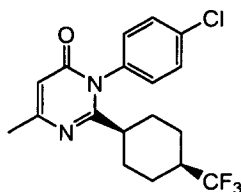


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To a solution of methyl 3-aminocrotonate (1.38 g, 12.0 mmol) in pyridine (10 mL) and CHCl₃ (30 mL) add 4-(trifluoromethyl)cyclohexanecarbonyl chloride (2.14 g, 10 mmol). Heat the mixture to reflux for overnight, cool to RT, concentrate, and partition between EtOAc and water. Wash the organic layer with 6 M HCl, H₂O and brine. Dry over Na₂SO₄, concentrate under vacuum. Purify using flash chromatography (25% ethyl acetate/hexanes eluent) to give the title compound.

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2. *3-(4-Chlorophenyl)-6-methyl-2-[cis-4-(trifluoromethyl)cyclohexyl]pyrimidin-4(3H)-one (cmpd 1)*

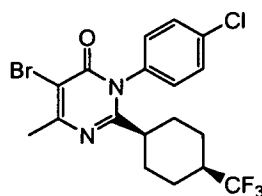


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To a solution of 4-chloroaniline (1.83 g, 14.3 mmol) in DCE (30 mL) under nitrogen add trimethylaluminum (2 M in hexane, 7.2 mL, 14.3 mmol). Stir the mixture at RT for 30 min and add a solution of methyl 3-(4-(trifluoromethyl)-cyclohexanecarboxamido)but-2-enoate (2.8 g, 9.55 mmol) in DCE (10 mL). Stir the mixture at 90°C for overnight, cool to RT, quench with saturated Rochelle's salt, and extract with EtOAc. Dry over Na₂SO₄, and concentrate under vacuum. Purify using flash chromatography (25% ethyl acetate/hexanes eluent) to give the title compound. MS (M+1) = 371.06; R_T = 1.25 min.

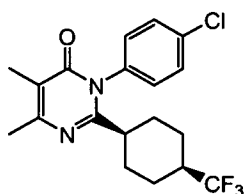
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B. 5-Bromo-3-(4-chlorophenyl)-6-methyl-2-[cis-4-(trifluoromethyl)cyclohexyl]-pyrimidin-4(3H)-one (Compound 2)



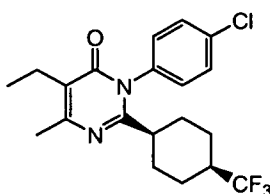
To a solution of 3-(4-chlorophenyl)-6-methyl-2-[cis-4-(trifluoromethyl)-
 5 cyclohexyl]pyrimidin-4(3H)-one (2.5 g, 6.71 mmol) in HOAc (30 mL) add Br₂ (2.2 g, 13.48 mmol). Stir the mixture at RT for overnight, dilute with H₂O, and collect the solid. Purify using flash chromatography (10% ethyl acetate/hexanes eluent) to give the title compound. MS (M+1) = 451.07; R_T = 1.35 min.

C. 3-(4-Chlorophenyl)-5,6-dimethyl-2-[cis-4-(trifluoromethyl)cyclohexyl]pyrimidin-4(3H)-
 10 one (Compound 3)



To a de-gassed mixture of 5-bromo-3-(4-chlorophenyl)-6-methyl-2-[cis-4-(trifluoromethyl)cyclohexyl]pyrimidin-4(3H)-one (100 mg, 0.22 mmol) and trimethylaluminum (2 M in hexane, 0.33 mL, 0.66 mmol) in THF (6 mL) under nitrogen add
 15 Pd(PPh₃)₄ (27 mg, 0.022 mmol). Stir the mixture at 80°C for overnight, cool to RT, quench with saturated Rochelle's salt, and extract with EtOAc. Dry over Na₂SO₄, concentrate under vacuum. Purify using preparative TLC plates (1000 micron/ 15% ethyl acetate/hexanes eluent) to give the title compound. MS (M+1) = 385.20; R_T = 1.35 min.

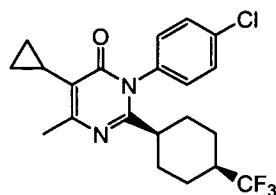
D. 3-(4-Chlorophenyl)-5-ethyl-6-methyl-2-[cis-4-(trifluoromethyl)cyclohexyl]pyrimidin-
 20 4(3H)-one (Compound 4)



To a de-gassed mixture of 5-bromo-3-(4-chlorophenyl)-6-methyl-2-[cis-4-(trifluoromethyl)cyclohexyl]pyrimidin-4(3H)-one (100 mg, 0.22 mmol), BEt₃ (1 M in Hexane, 0.67 mL, 0.67 mmol), and 2 M K₃PO₄ (0.33 mL, 0.67 mmol), in toluene (5 mL) add

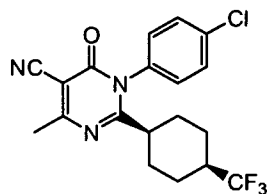
Pd(PPh₃)₄ (26 mg, 0.022 mmol). Heat the reaction for 16 h at 100°C. Cool the reaction, concentrate, and partition between EtOAc and water. Dry over Na₂SO₄ and concentrate under vacuum. Purify using preparative TLC plates (1000 micron/ 25% ethyl acetate/hexanes eluent) to give the title compound. MS (M+1) = 399.22; R_T = 1.37 min.

5 E. 3-(4-Chlorophenyl)-5-cyclopropyl-6-methyl-2-[cis-4-(trifluoromethyl)cyclohexyl]-pyrimidin-4(3H)-one (Compound 5)



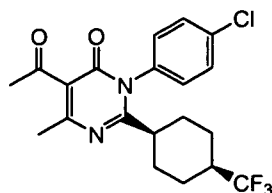
To a de-gassed mixture of 5-bromo-3-(4-chlorophenyl)-6-methyl-2-[cis-4-(trifluoromethyl)cyclohexyl]pyrimidin-4(3H)-one (100 mg, 0.22 mmol), cyclopropylboronic acid (38 mg, 0.44 mmol), K₃PO₄ (170 mg, 0.80 mmol), and tricyclohexylphosphine (6 mg, 0.022mmol) in toluene-water (4 mL/0.2 mL) add Pd(OAc)₂ (3 mg, 0.011 mmol). Heat the mixture for 16 h at 100°C. Cool the reaction, concentrate, and partition between EtOAc and water. Dry over Na₂SO₄ and concentrate under vacuum. Purify using preparative TLC plates (1000 micron/ 25% ethyl acetate/hexanes eluent) to give the title compound. MS (M+1) = 411.21; R_T = 1.38 min.

15 F. 1-(4-Chlorophenyl)-4-methyl-6-oxo-2-[cis-4-(trifluoromethyl)cyclohexyl]-1,6-dihydropyrimidine-5-carbonitrile (Compound 6)



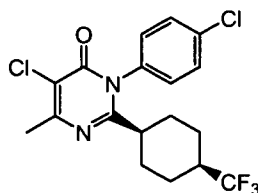
To a de-gassed mixture of 5-bromo-3-(4-chlorophenyl)-6-methyl-2-[cis-4-(trifluoromethyl)cyclohexyl]pyrimidin-4(3H)-one (100 mg, 0.22 mmol) and Zn(CN)₂ (16 mg, 0.13 mmol) in DMF (5 mL) add Pd(PPh₃)₄ (26 mg, 0.022 mmol). Heat the reaction for 16 h at 100°C. Cool the reaction, concentrate, and partition between EtOAc and water. Dry over Na₂SO₄ and concentrate under vacuum. Purify using preparative TLC plates (1000 micron/ 25% ethyl acetate/hexanes eluent) to give the title compound. MS (M+1) = 396.19; R_T = 1.3 min.

G. 5-Acetyl-3-(4-chlorophenyl)-6-methyl-2-[cis-4-(trifluoromethyl)cyclohexyl]-pyrimidin-4(3H)-one (Compound 7)



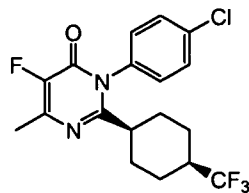
To a de-gassed mixture of 5-bromo-3-(4-chlorophenyl)-6-methyl-2-[cis-4-(trifluoromethyl)cyclohexyl]pyrimidin-4(3H)-one (100 mg, 0.22 mmol) and tributyl(1-ethoxyvinyl)tin (97 mg, 0.27 mmol) in toluene (5 mL) add Pd(PPh₃)₄ (26 mg, 0.022 mmol). Heat the reaction for 16 h at 120°C. Cool the reaction, concentrate, partition between EtOAc and water, and wash with saturated KF solution. Dry over Na₂SO₄ and concentrate under vacuum. Add MeOH (20 mL) and 3 M HCl (4 mL) and stir the mixture at RT for 30 minutes. Concentrate under vacuum and partition between EtOAc and saturated NaHCO₃. Dry over Na₂SO₄ and concentrate under vacuum. Purify using preparative TLC plates (1000 micron/15% ethyl acetate/hexanes eluent) to give the title compound. MS (M+1) = 413.12; R_T = 1.31 min.

H. 5-Chloro-3-(4-chlorophenyl)-6-methyl-2-[cis-4-(trifluoromethyl)cyclohexyl]-pyrimidin-4(3H)-one (Compound 8)



To a solution of 3-(4-chlorophenyl)-6-methyl-2-[cis-4-(trifluoromethyl)cyclohexyl]pyrimidin-4(3H)-one (100 mg, 0.22 mmol) in HOAc (10 mL) add NCS (43 mg, 0.32 mmol). Heat the reaction for 2 h at 75°C. Cool the reaction, dilute with H₂O, and collect the solid. Purify using preparative TLC plates (1000 micron 10% ethyl acetate/hexanes eluent) to give the title compound. MS (M+1) = 405.19; R_T = 1.35 min.

I. 3-(4-Chlorophenyl)-5-fluoro-6-methyl-2-[cis-4-(trifluoromethyl)cyclohexyl]pyrimidin-4(3H)-one (Compound 9)

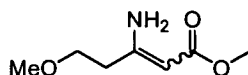


To a solution of 3-(4-chlorophenyl)-6-methyl-2-[cis-4-(trifluoromethyl)-cyclohexyl]pyrimidin-4(3H)-one (100 mg, 0.22 mmol) in acetonitrile (10 mL) add SELECTFLUOR™ (234 mg, 0.66 mmol). Heat the reaction for 16 h at 110°C in a sealed tube. Cool the reaction mixture, dilute with H₂O, extract with EtOAc. Dry over Na₂SO₄ and concentrate under vacuum. Purify using preparative TLC plates (1000 micron 25% ethyl acetate/hexanes eluent) to give the title compound. MS (M+1) = 389.20; R_T = 1.32 min.

J. 3-(4-Chlorophenyl)-6-(2-hydroxyethyl)-2-[cis-4-(trifluoromethyl)cyclohexyl]-pyrimidin-4(3H)-one (Compound 10)

1. *Methyl 3-amino-5-methoxypent-2-enoate*

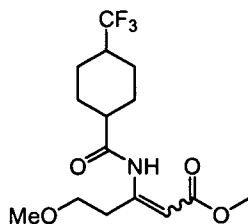
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To a solution of 5-methoxy 3-oxovaleric acid methyl ester (2.0 g, 12.5 mmol) in MeOH (40 mL) add NH₄OAc (3.85 g, 50 mmol). Heat the mixture for 16 h at 50°C in sealed tube. Cool to RT; add 2.0 eq. of NH₃-H₂O, dilute with H₂O, and extract with ether. Dry over Na₂SO₄ and concentrate under vacuum to give the title compound.

15

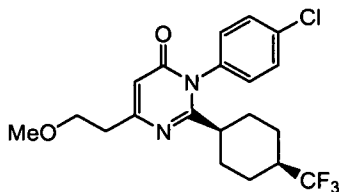
2. *Methyl 5-methoxy-3-(4-(trifluoromethyl)cyclohexancarboxamido)pent-2-enoate*



This compound is prepared essentially according to the procedure described in Example 1 A.

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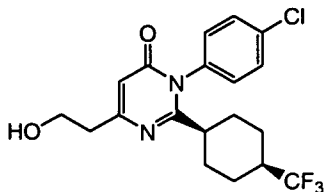
3. *3-(4-Chlorophenyl)-6-(2-methoxyethyl)-2-[cis-4-(trifluoromethyl)cyclohexyl]-pyrimidin-4(3H)-one*



This compound is prepared essentially according to the procedure described in Example 1 A. MS (M+1) = 415.22; R_T = 1.17 min.

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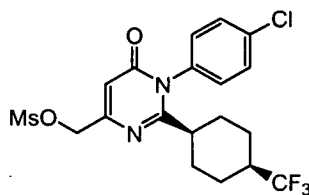
4. *3-(4-Chlorophenyl)-6-(2-hydroxyethyl)-2-[cis-4-(trifluoromethyl)cyclohexyl]-pyrimidin-4(3H)-one (cmpd 10)*



To a cooled solution (-78°C) of 3-(4-chlorophenyl)-6-(2-methoxyethyl)-2-[cis-4-(trifluoromethyl)cyclohexyl]-pyrimidin-4(3H)-one (46 mg, 0.11 mmol) in DCE (10 mL) under nitrogen add BBr₃ (1 M in DCM, 0.22 mL, 0.22 mmol). Bring the reaction mixture to
 5 RT and stir at RT for 1 h. Quench with saturated NaHCO₃, separate the organic layer, dry over Na₂SO₄, and concentrate under vacuum. Purify using preparative TLC plates (1000 micron 25% ethyl acetate/hexanes eluent) to give the title compound. MS (M+1) = 401.20; R_T = 1.15 min.

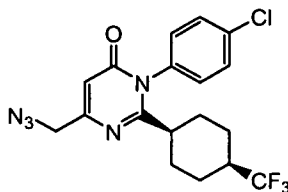
K. 6-(Aminomethyl)-3-(4-chlorophenyl)-2-[cis-4-(trifluoromethyl)cyclohexyl]pyrimidin-
 10 4(3H)-one (Compound 11)

1. *{1-(4-Chlorophenyl)-6-oxo-2-[cis-4-(trifluoromethyl)cyclohexyl]-1,6-dihydropyrimidin-4-ylmethyl} methane sulfonate*



To a cool solution (0°C) of 3-(4-chlorophenyl)-6-(hydroxymethyl)-2-[cis-4-(trifluoromethyl)cyclohexyl]pyrimidin-4(3H)-one (prepared essentially according to the
 15 procedure described in Example 1 J; 200 mg, 0.52 mmol) in DCM (10 mL) add methanesulfonyl chloride (48 μL, 0.62 mmol) and TEA (144 μL, 1.03 mmol). Stir the mixture at RT for 1 h; dilute with DCM, and wash with H₂O and brine. Dry over MgSO₄ and concentrate under vacuum to give the title compound.

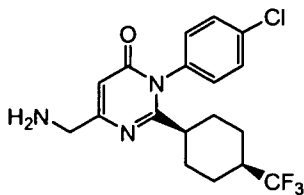
- 20 2. *6-(Azidomethyl)-3-(4-chlorophenyl)-2-[cis-4-(trifluoromethyl)cyclohexyl]-pyrimidin-4(3H)-one*



To a solution of {1-(4-chlorophenyl)-6-oxo-2-[cis-4-(trifluoromethyl)cyclohexyl]-1,6-dihydropyrimidin-4-ylmethyl} methane sulfonate (480 mg, 1.03 mmol) in DMSO (10 mL)

add NaN₃ (134 mg, 2.06 mmol). Heat the mixture for 2 h at 50°C. Cool to RT; dilute with H₂O, and extract with EtOAc. Dry over Na₂SO₄ and concentrate under vacuum. Purify using preparative TLC plates (1000 micron 25% EtOAc/hexanes eluent) to give the title compound.

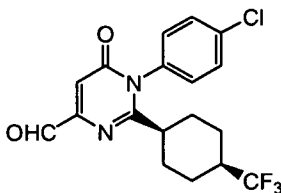
3. *6-(Aminomethyl)-3-(4-chlorophenyl)-2-[cis-4-(trifluoromethyl)cyclohexyl]-pyrimidin-4(3H)-one (cmpd 11)*



To a solution of 6-(azidomethyl)-3-(4-chlorophenyl)-2-[cis-4-(trifluoromethyl)-cyclohexyl]-pyrimidin-4(3H)-one (100 mg, 0.26 mmol) in 8 M NH₃-MeOH (40 mL) add 10% Pd-C (100 mg). Hydrogenate at 45 psi for 3 h. Filter and concentrate. Purify using preparative TLC plates (1000 micron 5% MeOH/DCM eluent) to give the title compound. MS (M+1) = 386.23; R_T = 1.18 min.

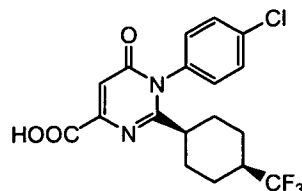
L. 6-Amino-3-(4-chlorophenyl)-2-[cis-4-(trifluoromethyl)cyclohexyl]pyrimidin-4(3H)-one hydrochloride (Compound 12)

1. *1-(4-chlorophenyl)-6-oxo-2-[cis-4-(trifluoromethyl)cyclohexyl]-1,6-dihydropyrimidine-4-carbaldehyde*



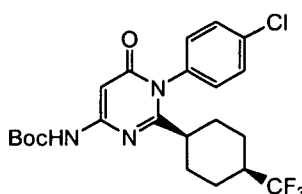
To a cool solution (0°C) of 3-(4-chlorophenyl)-6-(hydroxymethyl)-2-[cis-4-(trifluoromethyl)cyclohexyl]pyrimidin-4(3H)-one (prepared essentially according to the procedure described in Example 1 J; 500 mg, 1.29 mmol) in DCM (30 mL) add Dess-Martin periodinane (1,1,1-Tris(acetyloxy)-1,1-dihydro-1,2-benziodoxol-3(1H)-one) (1.1 g, 2.6 mmol). Stir the mixture at RT for 24 h. Quench with saturated Na₂S₂O₃ and wash with sat NaHCO₃. Dry over Na₂SO₄ and concentrate under vacuum. Purify with flash column (25% ethyl acetate/hexanes eluent) to give the title compound.

2. *1-(4-chlorophenyl)-6-oxo-2-[cis-4-(trifluoromethyl)cyclohexyl]-1,6-dihydropyrimidine-4-carboxylic acid*



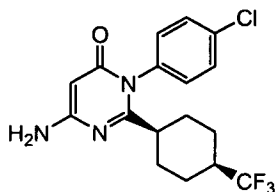
To a solution of 1-(4-chlorophenyl)-6-oxo-2-[cis-4-(trifluoromethyl)cyclohexyl]-1,6-dihydropyrimidine-4-carbaldehyde (385 mg, 1.0 mmol) in THF-*tert*-BuOH (8 mL/24 mL) add 2-methyl-2-butene (8 mL) and a solution of NaClO₂ and KH₂PO₄ in H₂O (8 mL). Stir the mixture at RT for 16 h. Concentrate and extract with DCM. Dry over MgSO₄ and concentrate under vacuum to give the title compound.

3. *tert*-Butyl {1-(4-chlorophenyl)-6-oxo-2-[cis-4-(trifluoromethyl)cyclohexyl]-1,6-dihydropyrimidin-4-yl}carbamate



Reflux a mixture of 1-(4-chlorophenyl)-6-oxo-2-[cis-4-(trifluoromethyl)cyclohexyl]-1,6-dihydropyrimidine-4-carboxylic acid (750 mg, 1.87 mmol), DPPA (524 μL, 2.43 mmol), and TEA (339 μL, 2.43 mmol) in *tert*-BuOH (20 mL) for 16h. Cool to RT and concentrate under vacuum. Purify using flash column (15% ethyl acetate/hexanes eluent) to give the title compound.

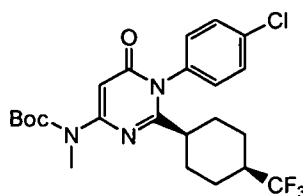
4. 6-Amino-3-(4-chlorophenyl)-2-[cis-4-(trifluoromethyl)cyclohexyl]pyrimidin-4(3H)-one hydrochloride (compd 12)



Stir a mixture of *tert*-butyl {1-(4-chlorophenyl)-6-oxo-2-[cis-4-(trifluoromethyl)cyclohexyl]-1,6-dihydropyrimidin-4-yl}carbamate (140 mg, 0.30 mmol) in 4M HCl-dioxane (8 mL) at 50°C for 30 min. Concentrate and collect the solid from ether to give the title compound. MS (M+1) = 372.10; R_T = 1.45 min.

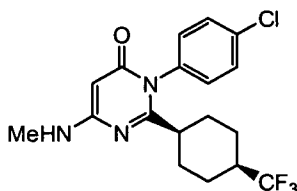
M. 3-(4-Chlorophenyl)-6-(methylamino)-2-[cis-4-(trifluoromethyl)cyclohexyl]pyrimidin-4(3H)-one hydrochloride (Compound 13)

1. *tert*-Butyl {1-(4-chlorophenyl)-6-oxo-2-[cis-4-(trifluoromethyl)cyclohexyl]-1,6-dihydropyrimidin-4-yl}methylcarbamate



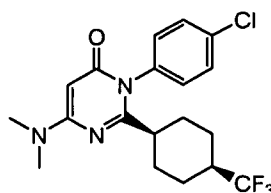
To a cool solution (0°C) of *tert*-butyl {1-(4-chlorophenyl)-6-oxo-2-[cis-4-(trifluoromethyl)cyclohexyl]-1,6-dihydropyrimidin-4-yl}carbamate (200 mg, 0.42 mmol) in THF (15 mL) add NaH (60%, 20 mg, 0.51 mmol). Stir 30 min at 0°C. Add MeI (34 μL, 0.55 mmol). Slowly warm the mixture to RT and stir for 4 h at RT. Dilute with H₂O, and extract with DCM. Dry over Na₂SO₄ and concentrate under vacuum. Purify using preparative TLC plates (1000 micron 25% ethyl acetate/hexanes eluent) to give the title compound.

2. 3-(4-Chlorophenyl)-6-(methylamino)-2-[cis-4-(trifluoromethyl)cyclohexyl]-pyrimidin-4(3H)-one hydrochloride (compd 13)



Stir the mixture of *tert*-butyl {1-(4-chlorophenyl)-6-oxo-2-[cis-4-(trifluoromethyl)cyclohexyl]-1,6-dihydropyrimidin-4-yl}methylcarbamate (140 mg, 0.29 mmol) in 4M HCl-dioxane (10 mL) at 50°C for 30 min. Concentrate and collect the solid from ether to give the title compound. MS (M+1) = 386.14; R_T = 1.24 min.

N. 3-(4-chlorophenyl)-6-(dimethylamino)-2-[cis-4-(trifluoromethyl)cyclohexyl]-pyrimidin-4(3H)-one (Compound 14)

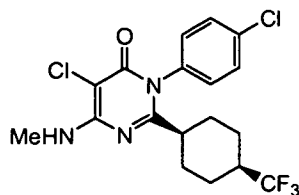


To a cool solution (0°C) of 3-(4-chlorophenyl)-6-(methylamino)-2-[cis-4-(trifluoromethyl)cyclohexyl]-pyrimidin-4(3H)-one (63 mg, 0.16 mmol) in THF (5 mL) add NaH (60%, 8 mg, 0.20 mmol). Stir 30 min at 0°C. Add MeI (13 μL, 0.21 mmol). Slowly warm the mixture to RT and stir for 16 h at RT. Dilute with H₂O, and extract with DCM. Dry over Na₂SO₄ and concentrate under vacuum. Purify using preparative TLC plates (1000

micron 10% ethyl acetate/hexanes eluent) to give the title compound. MS (M+1) = 400.19;

R_T = 1.29 min.

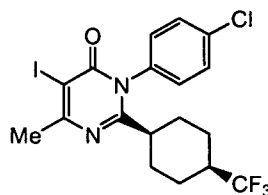
O. 5-Chloro-3-(4-chlorophenyl)-6-(methylamino)-2-[cis-4-(trifluoromethyl)cyclohexyl]-pyrimidin-4(3H)-one (Compound 15)



5

To a solution of 3-(4-chlorophenyl)-6-(methylamino)-2-[cis-4-(trifluoromethyl)-cyclohexyl]pyrimidin-4(3H)-one hydrochloride (50 mg, 0.13 mmol) in HOAc (4 mL) add NCS (21 mg, 0.16 mmol). Stir the reaction for 2 h at RT, dilute with H₂O, extract with EtOAc, and wash with H₂O. Dry over Na₂SO₄ and concentrate under vacuum. Purify using
10 preparative TLC plates (1000 micron 35% ethyl acetate/hexanes eluent) to give the title compound. MS (M+1) = 420.11; R_T = 1.33 min.

P. 3-(4-chlorophenyl)-5-iodo-6-methyl-2-[cis-4-(trifluoromethyl)cyclohexyl]pyrimidin-4(3H)-one (Compound 16)



15

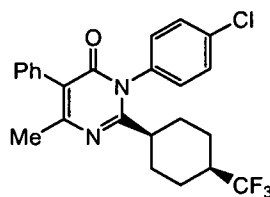
Add NIS (1.46 g, 6.5 mmol) to a solution of 3-(4-chlorophenyl)-6-methyl-2-[cis-4-(trifluoromethyl)cyclohexyl]pyrimidin-4(3H)-one (1.0 g, 2.7 mmol) in acetic acid. Allow the reaction to stir for 72 h. Add water and stir the mixture to form a brown precipitate. Purification by column chromatography on silica gel (hexanes: ethyl acetate 95:5) provides the title compound as a white solid. MS (M+1) = 497.11; R_T = 1.38 min.

EXAMPLE 2

Synthesis of Additional Representative Substituted Pyrimidinones

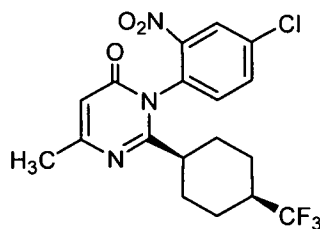
This Example illustrates the synthesis of additional representative substituted pyrimidinones.

5 A. 3-(4-chlorophenyl)-6-methyl-5-phenyl-2-[cis-4-(trifluoromethyl)cyclohexyl]pyrimidin-4(3H)-one (Compound 17)



Combine 3-(4-chlorophenyl)-5-iodo-6-methyl-2-[cis-4-(trifluoromethyl)cyclohexyl]pyrimidin-4(3H)-one (0.1g, 0.22 mmol), phenyl boronic acid (0.035 g, 0.29 mmol), aqueous K₃PO₄ (2M, 0.22 mL) and dioxane (5 mL) and de-gas the solution for 10 min. Add Pd(PPh₃)₄ (8 mg, 0.007 mmol) and heat the mixture overnight (16 h) at 80°C. After cooling to RT, evaporate the volatiles and partition the residue between H₂O and CH₂Cl₂. Separate the layers, dry the organics (Na₂SO₄), filter and concentrate. Purify by preparative TLC (hexanes: ethyl acetate 90:10) to provide the title compound as a white solid. ¹HNMR (300 MHz, CDCl₃) δ 7.49 (d, 2H, *J* = 8.7 Hz), 7.41-7.31 (m, 5H), 7.17 (d, 2H, *J* = 8.4), 2.56 (m, 1H), 2.26 (s, 3H), 2.19-2.13 (m, 3H), 2.04-1.97 (m, 2H), 1.58-1.51 (m, 4H). MS (M+1) = 447.14; R_T = 1.4 min.

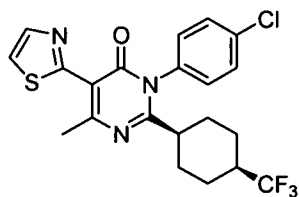
15 B. 3-(4-chloro-2-nitrophenyl)-6-methyl-2-[cis-4-(trifluoromethyl)cyclohexyl]pyrimidin-4(3H)-one (Compound 18)



20 Dissolve 3-(4-Chlorophenyl)-6-methyl-2-[cis-4-(trifluoromethyl)cyclohexyl]pyrimidin-4(3H)-one (0.5g, 1.3 mmol) in cold H₂SO₄ (2 mL) and sonicate for 10 min to promote dissolution. Add 90% nitric acid (0.08 mL) dropwise at 0 °C and stir the reaction while warming to RT for 3 h. Add ice to the reaction, followed by cautious addition of diethyl ether while stirring to form a yellow precipitate. Collect the precipitate by filtration and wash with diethyl ether to provide the title compound as a light yellow solid. ¹HNMR (300 MHz, CDCl₃) δ 7.79 (d, 1H, *J* = 2.7 Hz), 7.73 (d, 2H, *J* = 8.4 Hz),

7.41-7.37 7.38 (dd, 2H, $J = 8.4, 2.4$ Hz), 6.26 (s, 1H), 2.47 (m, 1H), 2.31 (s, 3H), 2.14-2.09 (m, 3H), 1.98-1.88 (m, 2H), 1.59-1.53 (m, 4H). MS (M+1) = 416.19; $R_T = 1.3$ min.

C. 3-(4-chlorophenyl)-6-methyl-5-(1,3-thiazol-2-yl)-2-[cis-4-(trifluoromethyl)cyclohexyl]pyrimidin-4(3H)-one (Compound 19)



5

Combine

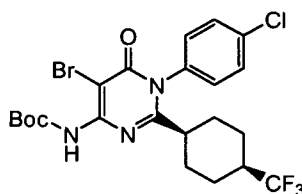
3-(4-chlorophenyl)-5-iodo-6-methyl-2-[cis-4-

(trifluoromethyl)cyclohexyl]pyrimidin-4(3H)-one (70 mg, 0.16 mmol), 2-(tributylstannyl)thiazole (75 mg, 0.20 mmol) and toluene (5 mL) and degas the solution for 10 min. Add Pd(PPh₃)₄ (18 mg, 0.02 mmol). Heat the mixture overnight (16 h) at 110 °C. After cooling to RT, add aqueous KF and stir the reaction for 15 min. Separate the layers and extract the aqueous layer with EtOAc (2 X 10 mL). Combine the organics, wash with KF (aq) then H₂O, dry (Na₂SO₄), filter and concentrate. Purification by preparative TLC (CH₂Cl₂: MeOH 95:5) provides the title compound as a white solid. MS (M+1) = 454.09; $R_T = 0.64$ min.

10

15 D. 3-(4-Chlorophenyl)- 5-methyl 6-(methylamino)-2-[cis-4-(trifluoromethyl)cyclohexyl]-pyrimidin-4(3H)-one (Compound 20)

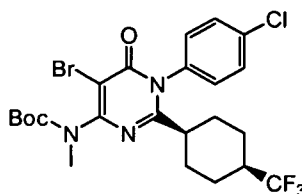
1. tert-Butyl {5-bromo-1-(4-chlorophenyl)-6-oxo-2-[cis-4-(trifluoromethyl)-cyclohexyl]-1,6-dihydropyrimidin-4-yl} carbamate



20 To a solution of *tert*-butyl {1-(4-chlorophenyl)-6-oxo-2-[cis-4-(trifluoromethyl)-cyclohexyl]-1,6-dihydropyrimidin-4-yl} carbamate (300 mg, 0.64 mmol) in acetic acid (10 mL) add N-bromosuccinimide (136 mg, 0.76 mmol). Stir the reaction for 16 h at RT, dilute with H₂O, extract with EtOAc, and wash with H₂O. Dry over Na₂SO₄ and concentrate under vacuum. Purify using silica gel flash chromatography (25% ethyl acetate/hexanes eluent) to

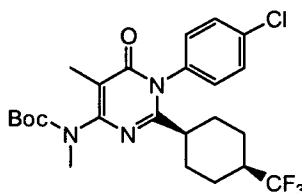
25 give the title compound.

2. *tert-Butyl 5-bromo-1-(4-chlorophenyl)-6-oxo-2-[cis-4-(trifluoromethyl)-cyclohexyl]-1,6-dihydropyrimidin-4-yl(methyl) carbamate*



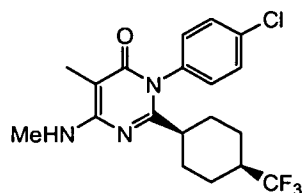
To a cold solution (0 °C) of *tert*-butyl {5-bromo-1-(4-chlorophenyl)-6-oxo-2-[cis-4-(trifluoromethyl)cyclohexyl]-1,6-dihydropyrimidin-4-yl} carbamate (41 mg, 0.074 mmol) in THF (10 mL) add NaH (60%, 4 mg, 0.09 mmol). Stir 30 min at 0°C. Add MeI (6 μL, 0.1 mmol). Slowly warm the mixture to RT and stir for 16 h at RT. Dilute with H₂O, and extract with DCM. Dry over Na₂SO₄ and concentrate under vacuum. Purify using preparative silica gel TLC plates (1000 micron 20% ethyl acetate/hexanes eluent) to give the title compound.

10 3. *tert-Butyl {1-(4-chlorophenyl)-5-methyl-6-oxo-2-[cis-4-(trifluoromethyl)-cyclohexyl]-1,6-dihydropyrimidin-4-yl(methyl) carbamate*



To a de-gassed mixture of *tert*-butyl 5-bromo-1-(4-chlorophenyl)-6-oxo-2-[cis-4-(trifluoromethyl)-cyclohexyl]-1,6-dihydropyrimidin-4-yl(methyl) carbamate (140 mg, 0.25 mmol), methyl boronic acid (152 mg, 2.54 mmol) and K₃PO₄ (2M in water, 318 μL, 0.64 mmol) in dioxane (10 mL) under nitrogen add Pd(PPh₃)₄ (29 mg, 0.025 mmol). Stir the mixture at 110°C in a sealed tube for 16 h, cool to RT, concentrate, and partition between water and EtOAc. Dry over Na₂SO₄, concentrate under vacuum. Purify using preparative silica gel TLC plates (1000 micron/ 25% ethyl acetate/hexanes eluent) to give the title compound.

20 4. *3-(4-Chlorophenyl)-5-methyl 6-(methylamino)-2-[cis-4-(trifluoromethyl)-cyclohexyl]-pyrimidin-4(3H)-one*

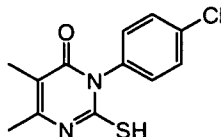


Stir a mixture of *tert*-butyl {1-(4-chlorophenyl)-5-methyl-6-oxo-2-[cis-4-(trifluoromethyl)cyclohexyl]-1,6-dihydropyrimidin-4-yl(methyl) carbamate (60 mg, 0.12

mmol) in 4M HCl-dioxane (6 mL) at 50°C for 30 min. Concentrate and partition between water and EtOAc. Dry over Na₂SO₄, and concentrate under vacuum to give the title compound.

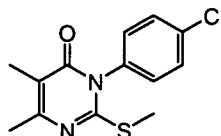
E. 2-(3-(trifluoromethyl)benzylamino)-3-(4-chlorophenyl)-5,6-dimethylpyrimidin-4(3H)-one
5 (Compound 21)

1. *3-(4-chlorophenyl)-2-mercapto-5,6-dimethylpyrimidin-4(3H)-one*



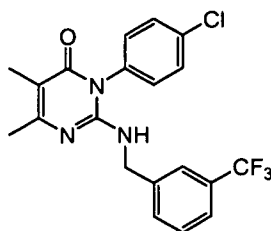
Ethyl 2-methyl-3-oxobutanoate (5 g) is adsorbed onto 8g of bentonite and then ammonium hydroxide solution (12 mL) is added. The resulting mixture is allowed to stand at
10 RT for two days. The mixture is diluted with DCM and the entire mixture is filtered through celite and concentrated to give the crude, ethyl 3-amino-2-methylbut-2-enoate (2.63 g). This crude material is mixed with 4-chlorophenyl isothiocyanate (3.1g) and pyridine (45 mL) and heated for 16 h at 45°C. The solvent is removed under reduced pressure and the residue triturated with a 1:1 mixture of ethyl acetate and hexanes. The title compound is collected as
15 a white solid via suction filtration.

2. *3-(4-chlorophenyl)-5,6-dimethyl-2-(methylthio)pyrimidin-4(3H)-one*



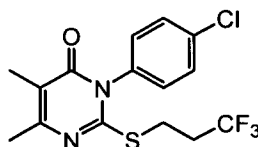
A solution of 3-(4-chlorophenyl)-2-mercapto-5,6-dimethylpyrimidin-4(3H)-one (800 mg) and K₂CO₃ (828 mg) in acetonitrile (30 mL) is treated with 1.2 equivalents of methyl
20 iodide (225 microliters). The mixture is heated at 70°C for 16 h and then the solvent is removed under reduced pressure. The residue is partitioned between EtOAc and water, and the combined organic layers are dried (Na₂SO₄) and concentrated under reduced pressure. The crude product is purified using silica gel column chromatography eluting with hexanes:ethyl acetate (4:1) to yield the title compound as a solid.

3. 2-(3-(trifluoromethyl)benzylamino)-3-(4-chlorophenyl)-5,6-dimethylpyrimidin-4(3H)-one



A solution of 3-(4-chlorophenyl)-5,6-dimethyl-2-(methylthio)pyrimidin-4(3H)-one (105 mg) in DCM (8 mL) is treated with meta-chloroperbenzoic acid (109 mg) and stirred at RT for 2 h. The mixture is washed with saturated aqueous sodium bicarbonate solution, dried (Na₂SO₄) and concentrated under reduced pressure to provide crude sulfoxide which is used in the next step without further purification. The crude intermediate is dissolved in dimethyl sulfoxide and 2 equivalents of CsF are added followed by 1.2 equivalents of meta-trifluoromethyl-benzylamine. The mixture is heated at 80°C until thin layer chromatography indicates the starting material is consumed. The reaction mixture is partitioned between EtOAc and water and the organic layer is dried (Na₂SO₄) and concentrated under reduced pressure. The crude product is purified using preparative thin layer chromatography eluting with EtOAc/ hexanes (1:1). ¹H NMR (CDCl₃): δ 7.53-7.41(m, 6H), 7.19(m, 2H), 4.58(d, 2H), 4.35(b, 1H), 2.23(s, 3H), 1.98(s, 3H).

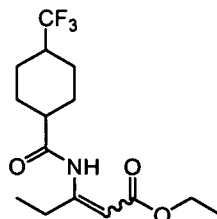
F. 3-(4-chlorophenyl)-5,6-dimethyl-2-(3,3,3-trifluoropropylthio)pyrimidin-4(3H)-one (Compound 22)



A solution of 3-(4-chlorophenyl)-2-mercapto-5,6-dimethylpyrimidin-4(3H)-one (102 mg) and potassium carbonate (106 mg) in acetonitrile is treated with 1.2 equivalents of 3-bromo-1,1,1-trifluoropropane and stirred at RT for 17 h. The solvent is removed under reduced pressure and the mixture partitioned between EtOAc and water. The EtOAc layer is dried (Na₂SO₄) and concentrated under reduced pressure. The residue is purified via preparative thin layer chromatography eluting with hexanes/EtOAc (4:1) to give the title compound. ¹H NMR (CDCl₃): δ 7.48(d, 2H), 7.17(d, 2H), 3.18(m, 2H), 2.50(m, 2H), 2.31(s, 3H), 2.04(s, 3H).

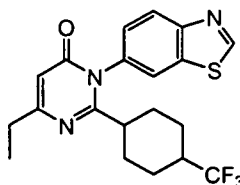
G. 3-(benzo[d]thiazol-6-yl)-5-chloro-6-ethyl-2-(4-(trifluoromethyl)cyclohexyl)pyrimidin-4(3H)-one (Compound 23)

1. ethyl 3-(4-(trifluoromethyl)cyclohexanecarboxamido)pent-2-enoate



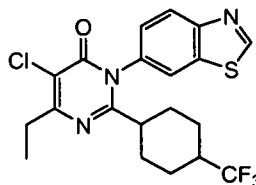
5 This compound is prepared by reacting ethyl 3-aminopent-2-enoate with 4-(trifluoromethyl)cyclohexanecarbonyl chloride using procedures analogous to those described above.

2. 3-(benzo[d]thiazol-6-yl)-6-ethyl-2-(4-(trifluoromethyl)cyclohexyl)pyrimidin-4(3H)-one



10 This compound is prepared by reacting ethyl 3-(4-(trifluoromethyl)cyclohexanecarboxamido)pent-2-enoate with 6-amino-benzothiazole using procedures analogous to those described above.

3. 3-(benzo[d]thiazol-6-yl)-5-chloro-6-ethyl-2-(4-(trifluoromethyl)cyclohexyl)pyrimidin-4(3H)-one



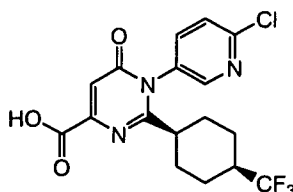
15 A solution of 3-(benzo[d]thiazol-6-yl)-6-ethyl-2-(4-(trifluoromethyl)cyclohexyl)pyrimidin-4(3H)-one (250 mg) in acetic acid is treated with N-chlorosuccinimide (82 mg) and stirred for 1 h. The reaction mixture is heated at 110°C for 2 h and another quantity of N-chlorosuccinimide (40 mg) is added. After an additional 1.5 h, the solvent is removed under reduced pressure and the residue is partitioned between EtOAc and saturated sodium bicarbonate solution. The organic layer is dried (Na₂SO₄), concentrated under reduced pressure and then purified using preparative thin layer chromatography (hexanes/EtOAc [2:1]). Both the cis- and trans-isomers are isolated. ¹H NMR of cis/trans-

20

mixture (CDCl₃): δ 9.13(s, 1H), 8.28(d, 1H), 7.82(s, 1H), 7.34(d, 1H), 2.85(q, 2H), 2.59(m, 1H), 2.16-1.49(m, 9H), 1.31(t, 3H).

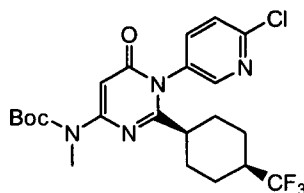
5 H. 5-(5-chloro-4-(methylamino)-6-oxo-2-(cis-4-(trifluoromethyl)cyclohexyl)pyrimidin-1(6H)-yl)picolinonitrile (Compound 24)

1. *1-(6-chloropyridin-3-yl)-6-oxo-2-(cis-4-(trifluoromethyl)cyclohexyl)-1,6-dihydropyrimidine-4-carboxylic acid*



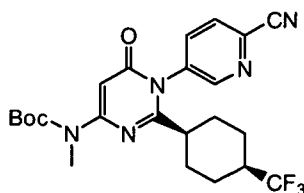
10 This carboxylic acid is prepared essentially as described above for the preparation of 1-(4-chlorophenyl)-6-oxo-2-[cis-4-(trifluoromethyl)cyclohexyl]-1,6-dihydropyrimidine-4-carboxylic acid.

2. *tert-butyl 1-(6-chloropyridin-3-yl)-6-oxo-2-(cis-4-(trifluoromethyl)cyclohexyl)-1,6-dihydropyrimidin-4-yl(methyl)carbamate*



15 This compound is prepared from the above carboxylic acid utilizing procedures analogous to those already given for *tert*-butyl {1-(4-chlorophenyl)-6-oxo-2-[cis-4-(trifluoromethyl)cyclohexyl]-1,6-dihydropyrimidin-4-yl} methylcarbamate.

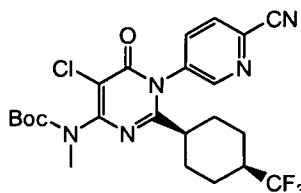
3. *tert-butyl 1-(6-cyanopyridin-3-yl)-6-oxo-2-(cis-4-(trifluoromethyl)cyclohexyl)-1,6-dihydropyrimidin-4-yl(methyl)carbamate*



20 A solution of *tert*-butyl 1-(6-chloropyridin-3-yl)-6-oxo-2-((1*s*,4*s*)-4-(trifluoromethyl)cyclohexyl)-1,6-dihydropyrimidin-4-yl(methyl)carbamate (250 mg, 0.513 mmol), Zn(CN)₂ (36 mg, 0.308 mmol), and bis(diphenylphosphino)-ferrocene (16 mg, 0.03 mmol) in DMF/water (10 mL / 0.1 mL) is purged with dry nitrogen for 5 min and then
25 tris(dibenzylideneacetone)-dipalladium (0) (14 mg, 0.015 mmol) is added. After purging for

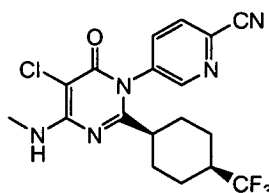
5 additional min, the reaction mixture is heated in a sealed tube at 115°C for 1 h. The mixture is partitioned between EtOAc and brine and the organic layer is washed 3 times with water, dried (Na₂SO₄) and concentrated under reduced pressure. The crude product is purified using preparative thin layer chromatography (EtOAc/hexanes eluent) to give the title compound.

- 5 4. *tert*-butyl 5-chloro-1-(6-cyanopyridin-3-yl)-6-oxo-2-(*cis*-4-(trifluoromethyl)cyclohexyl)-1,6-dihydropyrimidin-4-yl(methyl)carbamate



A solution of *tert*-butyl 1-(6-cyanopyridin-3-yl)-6-oxo-2-(*cis*-4-(trifluoromethyl)cyclohexyl)-1,6-dihydropyrimidin-4-yl(methyl)carbamate (200 mg, 0.411 mmol) in acetic acid (10 mL) is treated with N-chlorosuccinimide (71 mg, 0.543 mmol) and stirred for 16 h at RT. The reaction mixture is diluted with cold water and the precipitate collected via suction filtration and dried. Preparative thin layer chromatography (ethyl acetate/ hexanes eluent) provides the title compound.

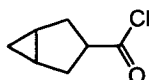
- 15 5. 5-(5-chloro-4-(methylamino)-6-oxo-2-(*cis*-4-(trifluoromethyl)cyclohexyl)pyrimidin-1(6H)-yl)picolinonitrile



To a flask containing *tert*-butyl 5-chloro-1-(6-cyanopyridin-3-yl)-6-oxo-2-(*cis*-4-(trifluoromethyl)cyclohexyl)-1,6-dihydropyrimidin-4-yl(methyl)carbamate (138 mg) is added about 6 mL of HCl-dioxane solution (4M) and the mixture is heated at 50°C for 30 min. The mixture is partitioned between DCM and saturated sodium bicarbonate solution, the organic layer is dried (Na₂SO₄) and concentrated under reduced pressure. The crude product is purified using preparative thin layer chromatography (ethyl acetate/ hexanes eluent) to give the title compound. ¹H NMR (300 MHz, CDCl₃): δ 1.41-1.70 (3H, br m), 1.85-2.22 (5H, br m), 2.41 (1H, br m), 3.12 (3H, d, J=4.8 Hz), 5.36 (1H, br m), 7.76 (1H, dd, J=2.4 Hz), 7.88 (1H, d, J=8.4 Hz), 8.57 (1H, d, J=2.4 Hz).

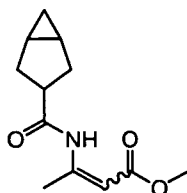
I. *cis*-2-bicyclo[3.1.0]hexan-3-yl)-3-(4-chlorophenyl)-6-methylpyrimidin-4(3H)-one
(Compound 25)

1. bicyclo[3.1.0]hexane-3-carbonyl chloride



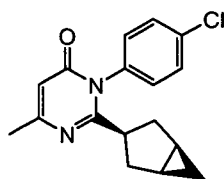
This compound is prepared by reaction of bicyclo[3.1.0]hexane-3-carboxylic acid (Gassman, P. G., *Journal of the American Chemical Society*, 1966, 88, 2252) with 1.2 equivalents of oxalyl chloride in DCM at RT followed by evaporation of the solvent.

2. methyl 3-(bicyclo[3.1.0]hexane-3-carboxamido)but-2-enoate



To a solution of methyl 3-aminocrotonate (1.38 g, 12.0 mmol) in pyridine (10 mL) and CHCl_3 (30 mL) add bicyclo[3.1.0]hexane-3-carbonyl chloride (10 mmol). Heat the mixture to reflux for 16 h, cool to RT, concentrate, and partition between EtOAc and water. Wash the organic layer with 6 M HCl, H_2O and brine. Dry over Na_2SO_4 , concentrate under vacuum. Purify using silica gel flash chromatography (ethyl acetate/hexanes eluent) to give the title compound.

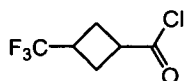
3. cis-2-bicyclo[3.1.0]hexan-3-yl)-3-(4-chlorophenyl)-6-methylpyrimidin-4(3H)-one



To a solution of 4-chloroaniline (1.83 g, 14.3 mmol) in dichloroethane (30 mL) under nitrogen add trimethylaluminum (2 M in hexane, 7.2 mL, 14.3 mmol). Stir the mixture at RT for 30 min and add a solution of methyl 3-(bicyclo[3.1.0]hexane-3-carboxamido)but-2-enoate (9.55 mmol) in dichloroethane (10 mL). Stir the mixture at 90°C for 16 h, cool to RT, quench with saturated Rochelle's salt, and extract with EtOAc. Dry over Na_2SO_4 , and concentrate under vacuum. Purify using flash chromatography (EtOAc/hexanes eluent) to give the title compound.

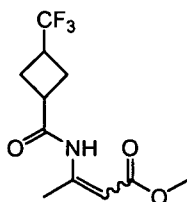
J. 3-(4-chlorophenyl)-6-methyl-2-cis-(3-(trifluoromethyl)cyclobutyl)pyrimidin-4(3H)-one
(Compound 26)

1. 3-(trifluoromethyl)cyclobutanecarbonyl chloride



This compound is prepared by reaction of 3-(trifluoromethyl)cyclobutanecarboxylic acid (Dolbier, W.R., *Journal of the American Chemical Society*, 1990, 112, 363) with 1.2 equivalents of oxalyl chloride in DCM at RT followed by careful evaporation of the solvent.

2. *methyl 3-(3-(trifluoromethyl)cyclobutanecarboxamido)but-2-enoate*

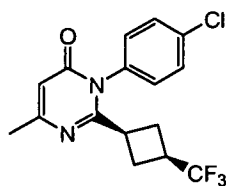


5

To a solution of methyl 3-aminocrotonate (1.38 g, 12.0 mmol) in pyridine (10 mL) and CHCl_3 (30 mL) add 3-(trifluoromethyl)cyclobutanecarbonyl chloride (10 mmol). Heat the mixture to reflux for 16 h, cool to RT, concentrate, and partition between EtOAc and water. Wash the organic layer with 6 M HCl, H_2O and brine. Dry over Na_2SO_4 , and concentrate under vacuum. Purify using silica gel flash chromatography (EtOAc/hexanes eluent) to give the title compound.

10

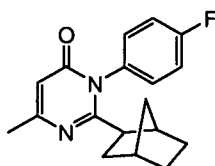
3. *3-(4-chlorophenyl)-6-methyl-2-cis-(3-(trifluoromethyl)cyclobutyl)pyrimidin-4(3H)-one*



To a solution of 4-chloroaniline (1.83 g, 14.3 mmol) in dichloroethane (30 mL) under nitrogen add trimethylaluminum (2 M in hexane, 7.2 mL, 14.3 mmol). Stir the mixture at RT for 30 min and add a solution of methyl 3-(3-(trifluoromethyl)cyclobutanecarboxamido)but-2-enoate (9.55 mmol) in dichloroethane (10 mL). Stir the mixture at 90°C for 16h, cool to RT, quench with saturated Rochelle's salt, and extract with EtOAc. Dry over Na_2SO_4 , and concentrate under vacuum. Purify using silica gel flash chromatography (EtOAc/hexanes eluent) to give the title compound.

20

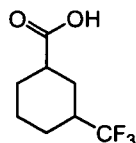
K. 2-(bicyclo[2.2.1]heptan-2-yl)-3-(4-fluorophenyl)-6-methylpyrimidin-4(3H)-one (Compound 27)



This compound is prepared using conditions analogous to those already described starting with bicyclo[2.2.1]heptane-2-carboxylic acid [common name norbornane-2-carboxylic acid].

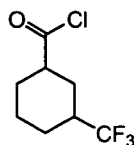
5 L. 3-(4-fluorophenyl)-6-methyl-2-(3-(trifluoromethyl)cyclohexyl)pyrimidin-4(3H)-one (trans isomer; Compound 28)

1. *3-(trifluoromethyl)cyclohexanecarboxylic acid*



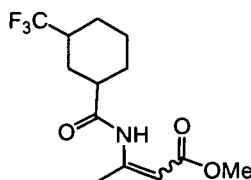
Dissolve 3-(trifluoromethyl)-benzoic acid (2 g) in acetic acid (100 mL) and add platinum oxide (400 mg). Hydrogenate the mixture under 50 psi of hydrogen at 60°C for 16
10 h. Filter the mixture through celite and concentrate under reduced pressure. Add toluene to the residue and concentrate again, repeating this procedure three additional times, to afford the title acid.

2. *3-(trifluoromethyl)cyclohexanecarbonyl chloride*



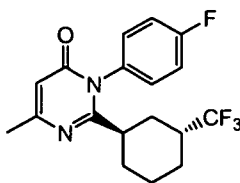
15 This compound is prepared by reaction of 3-(trifluoromethyl)cyclohexanecarboxylic acid with 1.2 equivalents of oxalyl chloride in DCM at RT followed by careful evaporation of the solvent.

3. *methyl 3-(3-(trifluoromethyl)cyclohexanecarboxamido)but-2-enoate*



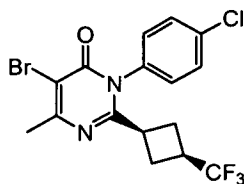
20 To a solution of methyl 3-aminocrotonate (1.38 g, 12.0 mmol) in pyridine (10 mL) and CHCl₃ (30 mL) add 3-(trifluoromethyl)cyclohexanecarbonyl chloride (10 mmol). Heat the mixture to reflux for 16 h, cool to RT, concentrate, and partition between EtOAc and water. Wash the organic layer with 6 M HCl, H₂O and brine. Dry over Na₂SO₄, concentrate under vacuum. Purify using silica gel flash chromatography (ethyl acetate/hexanes eluent) to give
25 the title compound.

4. 3-(4-fluorophenyl)-6-methyl-2-(3-(trifluoromethyl)cyclohexyl)pyrimidin-4(3H)-one
(*trans* isomer)



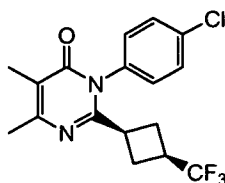
To a solution of 4-fluoroaniline (14 mmol) in dichloroethane (30 mL) under nitrogen
5 add trimethylaluminum (2 M in hexane, 7.2 mL, 14.3 mmol). Stir the mixture at RT for 30
min and add a solution of methyl 3-(3-(trifluoromethyl)cyclohexanecarboxamido)but-2-
enoate (9.55 mmol) in dichloroethane (10 mL). Stir the mixture at 90°C for 16 h, cool to RT,
quench with saturated Rochelle's salt, and extract with EtOAc. Dry over Na₂SO₄, and
concentrate under vacuum. Separate the *trans*-isomer from the *cis*-isomer using HPLC.

10 M. 5-bromo-3-(4-chlorophenyl)-6-methyl-2-(3-(trifluoromethyl)cyclobutyl)pyrimidin-4(3H)-one (cis isomer; Compound 29)



To a solution of 3-(4-chlorophenyl)-6-methyl-2-(3-(trifluoromethyl)cyclobutyl)pyrimidin-4(3H)-one (cis isomer) (6.71 mmol) in HOAc (30 mL)
15 add Br₂ (2.2 g, 13.48 mmol). Stir the mixture at RT for 16 h, dilute with H₂O, and collect the
solid. Purify using flash chromatography (10% ethyl acetate/hexanes eluent) to give the title
compound.

N. 3-(4-chlorophenyl)-5,6-dimethyl-2-(3-(trifluoromethyl)cyclobutyl)pyrimidin-4(3H)-one (cis isomer; Compound 30)



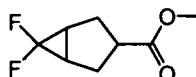
20 To a de-gassed mixture of 5-bromo-3-(4-chlorophenyl)-6-methyl-2-(3-(trifluoromethyl)cyclobutyl)pyrimidin-4(3H)-one (cis isomer) (0.22 mmol) and
trimethylaluminum (2 M in hexane, 0.33 mL, 0.66 mmol) in THF (6 mL) under nitrogen add
Pd(PPh₃)₄ (27 mg, 0.022 mmol). Stir the mixture at 80°C for 16 h, cool to RT, quench with
25 saturated Rochelle's salt, and extract with EtOAc. Dry over Na₂SO₄, concentrate under

vacuum. Purify using preparative TLC plates (1000 micron/ 15% ethyl acetate/hexanes eluent) to give the title compound.

O. 3-(4-chlorophenyl)-2-(6,6-difluorobicyclo[3.1.0]hexan-3-yl)-6-methylpyrimidin-4(3H)-one (Compound 31)

5

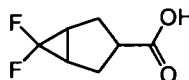
1. methyl 6,6-difluorobicyclo[3.1.0]hexane-3-carboxylate



This compound is prepared following a procedure similar to that used by Nelson, *J. Med. Chem.* **1990**, *33*, 833-838. A solution of methyl 3-cyclopentenecarboxylate in diglyme is heated to 160°C in an oil bath and stirred vigorously. Eight molar equivalents of sodium chloroacetate are added and the mixture heated for 1 h. An additional quantity (8 equivalents) of the reagent is added and heated for 30 min before cooling. The reaction mixture is partitioned between water and ethyl acetate and the organic layer is dried (Na₂SO₄) and concentrated under reduced pressure. Flash chromatography on silica gel yields the geminal-difluoro compound.

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2. 6,6-difluorobicyclo[3.1.0]hexane-3-carboxylic acid

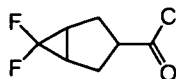


A solution of methyl 6,6-difluorobicyclo[3.1.0]hexane-3-carboxylate in THF/water (1:1) is treated with 5 equivalents of LiOH mono-hydrate at RT. A small amount of MeOH is added to improve the reaction homogeneity. After stirring for 16 h, the mixture is concentrated under reduced pressure and then dissolved in a small amount of water. Concentrated hydrochloric acid (5 equivalents) is added and the pH adjusted to ~6 using dilute hydrochloric acid. The aqueous is extracted with ethyl acetate and the combined organics are dried (Na₂SO₄) and concentrated under reduced pressure to give the title acid.

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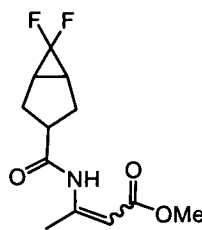
25

3. 6,6-difluorobicyclo[3.1.0]hexane-3-carbonyl chloride



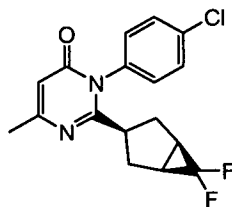
This compound is prepared by reaction of 6,6-difluorobicyclo[3.1.0]hexane-3-carboxylic acid with 1.2 equivalents of oxalyl chloride in DCM at RT followed by careful evaporation of the solvent.

4. methyl 3-(6,6-difluorobicyclo[3.1.0]hexane-3-carboxamido)but-2-enoate



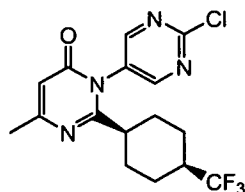
To a solution of methyl 3-aminocrotonate (1.38 g, 12.0 mmol) in pyridine (10 mL) and CHCl_3 (30 mL) add 6,6-difluorobicyclo[3.1.0]hexane-3-carbonyl chloride (10 mmol). Heat the mixture to reflux for 16 h, cool to RT, concentrate, and partition between EtOAc and water. Wash the organic layer with 6 M HCl, H_2O and brine. Dry over Na_2SO_4 , concentrate under vacuum. Purify using silica gel flash chromatography (ethyl acetate/hexanes eluent) to give the title compound.

5. 3-(4-chlorophenyl)-2-(6,6-difluorobicyclo[3.1.0]hexan-3-yl)-6-methylpyrimidin-4(3H)-one (cis isomer)



To a solution of 4-chloroaniline (1.83 g, 14.3 mmol) in dichloroethane (30 mL) under nitrogen add trimethylaluminum (2 M in hexane, 7.2 mL, 14.3 mmol). Stir the mixture at RT for 30 min and add a solution of methyl 3-(6,6-difluorobicyclo[3.1.0]hexane-3-carboxamido)but-2-enoate (9.55 mmol) in dichloroethane (10 mL). Stir the mixture at 90°C for 16 h, cool to RT, quench with saturated Rochelle's salt, and extract with EtOAc. Dry over Na_2SO_4 , and concentrate under vacuum. Purify using flash chromatography (EtOAc/hexanes eluent) to give the title compound.

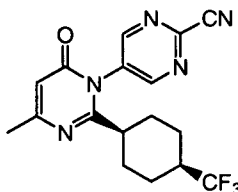
P. 3-(2-chloropyrimidin-5-yl)-6-methyl-2-(4-(trifluoromethyl)cyclohexyl)pyrimidin-4(3H)-one (cis isomer; Compound 32)



To a solution of 2-amino-5-chloropyrimidine (14.3 mmol) in DCE (30 mL) under nitrogen add trimethylaluminum (2 M in hexane, 7.2 mL, 14.3 mmol). Stir the mixture at RT

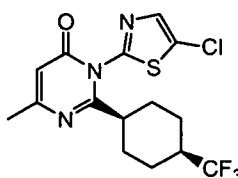
for 30 min and add a solution of methyl 3-(4-(trifluoromethyl)-cyclohexanecarboxamido)but-2-enoate (2.8 g, 9.55 mmol) in DCE (10 mL). Stir the mixture at 90°C for overnight, cool to RT, quench with saturated Rochelle's salt, and extract with EtOAc. Dry over Na₂SO₄, and concentrate under vacuum. Purify using flash chromatography (ethyl acetate/hexanes eluent) to give the title compound.

Q. 5-(4-methyl-6-oxo-2-(4-(trifluoromethyl)cyclohexyl)pyrimidin-1(6H)-yl)pyrimidine-2-carbonitrile (cis isomer; Compound 33)



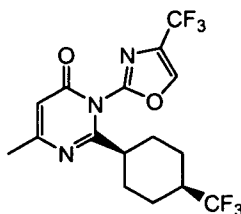
A solution of 3-(2-chloropyrimidin-5-yl)-6-methyl-2-(4-(trifluoromethyl)cyclohexyl)pyrimidin-4(3H)-one (0.513 mmol), Zn(CN)₂ (36 mg, 0.308 mmol), and bis(diphenylphosphino)-ferrocene (16 mg, 0.03 mmol) in DMF/water (10 mL / 0.1 mL) is purged with dry nitrogen for 5 min and then tris(dibenzylideneacetone)-dipalladium (0) (14 mg, 0.015 mmol) is added. After purging for 5 additional min, the reaction mixture is heated in a sealed tube at 115°C for 1 h. The mixture is partitioned between EtOAc and brine and the organic layer is washed 3 times with water, dried (Na₂SO₄) and concentrated under reduced pressure. The crude product is purified using preparative thin layer chromatography (EtOAc/hexanes eluent) to give the title compound.

R. 3-(5-chlorothiazol-2-yl)-6-methyl-2-(4-(trifluoromethyl)cyclohexyl)pyrimidin-4(3H)-one (cis isomer; Compound 34)



To a solution of 2-amino-5-chlorothiazole (14.3 mmol) in DCE (30 mL) under nitrogen add trimethylaluminum (2 M in hexane, 7.2 mL, 14.3 mmol). Stir the mixture at RT for 30 min and add a solution of methyl 3-(4-(trifluoromethyl)-cyclohexanecarboxamido)but-2-enoate (2.8 g, 9.55 mmol) in DCE (10 mL). Stir the mixture at 90°C for overnight, cool to RT, quench with saturated Rochelle's salt, and extract with EtOAc. Dry over Na₂SO₄, and concentrate under vacuum. Purify using flash chromatography (ethyl acetate/hexanes eluent) to give the title compound.

S. 6-methyl-2-(4-(trifluoromethyl)cyclohexyl)-3-(4-(trifluoromethyl)oxazol-2-yl)pyrimidin-4(3H)-one (cis isomer; Compound 35)



5 To a solution of 2-amino-4-(trifluoromethyl)-oxazole (14.3 mmol) in DCE (30 mL) under nitrogen add trimethylaluminum (2 M in hexane, 7.2 mL, 14.3 mmol). Stir the mixture at RT for 30 min and add a solution of methyl 3-(4-(trifluoromethyl)-cyclohexanecarboxamido)but-2-enoate (2.8 g, 9.55 mmol) in DCE (10 mL). Stir the mixture at 90°C for overnight, cool to RT, quench with saturated Rochelle's salt, and extract with
 10 EtOAc. Dry over Na₂SO₄, and concentrate under vacuum. Purify using flash chromatography (ethyl acetate/hexanes eluent) to give the title compound.

EXAMPLE 3

Additional Representative Substituted Pyrimidinones

Using routine modifications, the starting materials may be varied and additional steps
 15 employed to produce other compounds provided herein. Compounds listed in Table I and Table II are prepared using such methods. In Table I, a "*" in the column headed "IC₅₀" indicates that the IC₅₀ determined as described in Example 6 is 1 micromolar or less (*i.e.*, the concentration of such compounds that is required to provide a 50% decrease in the fluorescence response of cells exposed to one IC₅₀ of capsaicin is 1 micromolar or less). The
 20 determined molecular weight (presented as M+1) is shown in the column headed "MS" in Table I, with retention time (R_T) given in minutes.

Table I

Representative Substituted Pyrimidinone Derivatives

<u>Compound</u>	<u>Name</u>	<u>MS</u>	<u>R_T</u>	<u>IC₅₀</u>
36	3-(4-fluorophenyl)-6-methyl-2-[cis-4-(trifluoromethyl)cyclohexyl]pyrimidin-4(3H)-one	355.23	1.28	*

	<u>Compound</u>	<u>Name</u>	<u>MS</u>	<u>R_T</u>	<u>IC₅₀</u>
37		5-bromo-3-(4-fluorophenyl)-6-methyl-2-[cis-4-(trifluoromethyl)cyclohexyl]pyrimidin-4(3H)-one	433.15	1.32	*
38		6-methyl-3-phenyl-2-[cis-4-(trifluoromethyl)cyclohexyl]pyrimidin-4(3H)-one	337.23	1.29	
39		3-(3-chlorophenyl)-6-methyl-2-[cis-4-(trifluoromethyl)cyclohexyl]pyrimidin-4(3H)-one	371.21	1.31	
40		4-{4-methyl-6-oxo-2-[cis-4-(trifluoromethyl)cyclohexyl]pyrimidin-1(6H)-yl}benzonitrile	362.25	1.26	*
41		3-(3,4-difluorophenyl)-6-methyl-2-[cis-4-(trifluoromethyl)cyclohexyl]pyrimidin-4(3H)-one	373.23	1.3	*
42		3-(6-chloropyridin-3-yl)-6-methyl-2-[cis-4-(trifluoromethyl)cyclohexyl]pyrimidin-4(3H)-one	372.21	1.26	*

	<u>Compound</u>	<u>Name</u>	<u>MS</u>	<u>R_T</u>	<u>IC_{50}</u>
43		3-(4-bromophenyl)-6-methyl-2-[cis-4-(trifluoromethyl)cyclohexyl]pyrimidin-4(3H)-one	415.15	1.33	*
44		6-methyl-3-(4-methylphenyl)-2-[cis-4-(trifluoromethyl)cyclohexyl]pyrimidin-4(3H)-one	351.26	1.32	*
45		4-{5-bromo-4-methyl-6-oxo-2-[cis-4-(trifluoromethyl)cyclohexyl]pyrimidin-1(6H)-yl}benzonitrile	440.15	1.31	*
46		4-{4,5-dimethyl-6-oxo-2-[cis-4-(trifluoromethyl)cyclohexyl]pyrimidin-1(6H)-yl}benzonitrile	376.24	1.29	*
47		4-{5-chloro-4-methyl-6-oxo-2-[cis-4-(trifluoromethyl)cyclohexyl]pyrimidin-1(6H)-yl}benzonitrile	396.20	1.29	*
48		3-(4-chlorophenyl)-6-methyl-2-(4-methylcyclohexyl)pyrimidin-4(3H)-one	317.24	1.35	*
49		3-(4-chlorophenyl)-6-ethyl-2-[cis-4-(trifluoromethyl)cyclohexyl]pyrimidin-4(3H)-one	385.23	1.35	*

	<u>Compound</u>	<u>Name</u>	<u>PCT/US2008/007278</u> <u>MS</u>	<u>R_T</u>	<u>IC₅₀</u>
50		3-(4-chlorophenyl)-6-(trifluoromethyl)-2-[cis-4-(trifluoromethyl)cyclohexyl]pyrimidin-4(3H)-one	425.19	1.36	
51		3-(4-chlorophenyl)-6-isopropyl-2-[cis-4-(trifluoromethyl)cyclohexyl]pyrimidin-4(3H)-one	399.24	1.37	*
52		3-(4-chlorophenyl)-6-isopropyl-2-[trans-4-(trifluoromethyl)cyclohexyl]pyrimidin-4(3H)-one	399.24	1.39	
53		3-(4-chlorophenyl)-6-isopropyl-2-[cis-4-(trifluoromethyl)cyclohexyl]pyrimidin-4(3H)-one	399.24	1.37	*
54		3-(4-chlorophenyl)-6-isopropyl-2-[trans-4-(trifluoromethyl)cyclohexyl]pyrimidin-4(3H)-one	399.24	1.39	
55		3-(4-chlorophenyl)-6-(methoxymethyl)-2-[cis-4-(trifluoromethyl)cyclohexyl]pyrimidin-4(3H)-one	401.18	1.33	

	<u>Compound</u>	<u>Name</u>	<u>PCT/US2008/007278</u> <u>MS</u>	<u>R_T</u>	<u>IC₅₀</u>
56		3-(4-chlorophenyl)-6-(hydroxymethyl)-2-[cis-4-(trifluoromethyl)cyclohexyl]pyrimidin-4(3H)-one	387.18	1.28	*
57		3-(4-chlorophenyl)-6-(ethylamino)-2-[cis-4-(trifluoromethyl)cyclohexyl]pyrimidin-4(3H)-one	400.12	1.33	*
58		4-[4-(hydroxymethyl)-6-oxo-2-[cis-4-(trifluoromethyl)cyclohexyl]pyrimidin-1(6H)-yl]benzotrile	378.15	1.22	*
59		5-chloro-3-(4-chlorophenyl)-6-(methylamino)-2-[trans-4-(trifluoromethyl)cyclohexyl]pyrimidin-4(3H)-one	420.11	1.35	*
60		4-[4-(methylamino)-6-oxo-2-[cis-4-(trifluoromethyl)cyclohexyl]pyrimidin-1(6H)-yl]benzotrile	377.18	1.25	*
61		3-(4-chlorophenyl)-6-methyl-2-[4-(trifluoromethyl)cyclohex-3-en-1-yl]pyrimidin-4(3H)-one	369.13	1.33	*

	Compound	Name	MS	R _T	IC ₅₀
62		4-[5-chloro-4-(methylamino)-6-oxo-2-[cis-4-(trifluoromethyl)cyclohexyl]pyrimidin-1(6H)-yl]benzointrile	411.11	1.07	*
63		4-[5-methyl-4-(methylamino)-6-oxo-2-[cis-4-(trifluoromethyl)cyclohexyl]pyrimidin-1(6H)-yl]benzointrile	391.25	1.21	*
64		3-(4-chlorophenyl)-5-hydroxy-6-methyl-2-[cis-4-(trifluoromethyl)cyclohexyl]pyrimidin-4(3H)-one	387.10	1.09	*
65		3-(5-chloropyridin-2-yl)-6-ethyl-2-[cis-4-(trifluoromethyl)cyclohexyl]pyrimidin-4(3H)-one	386.12	1.26	*
66		5-bromo-3-(4-chlorophenyl)-2-cyclopentyl-6-ethylpyrimidin-4(3H)-one	383.08	1.42	*
67		5-chloro-3-(5-chloropyridin-2-yl)-6-ethyl-2-[cis-4-(trifluoromethyl)cyclohexyl]pyrimidin-4(3H)-one	420.14	1.39	*

	<u>Compound</u>	<u>Name</u>			
68		3-(6-chloropyridin-3-yl)-6-(hydroxymethyl)-2-[cis-4-(trifluoromethyl)cyclohexyl]pyrimidin-4(3H)-one	388.16	1.23	*
69		3-(1,3-benzothiazol-6-yl)-6-ethyl-2-[4-(trifluoromethyl)cyclohexyl]pyrimidin-4(3H)-one	408.13	1.53	*
70		5-chloro-3-(6-chloropyridin-3-yl)-6-(methylamino)-2-[cis-4-(trifluoromethyl)cyclohexyl]pyrimidin-4(3H)-one	421.07	0.96	*
71		5-[5-chloro-4-(methylamino)-6-oxo-2-[cis-4-(trifluoromethyl)cyclohexyl]pyrimidin-1(6H)-yl]pyridine-2-carboxamide	430.12	1.38	*

Table II

Additional Representative Substituted Pyrimidinone Derivatives

	<u>Compound</u>	<u>Name</u>
72		3-(4-chlorophenyl)-2-(6,6-difluorobicyclo[3.1.0]hexan-3-yl)-5,6-dimethylpyrimidin-4(3H)-one (cis isomer)

Compound	Name
73	5-chloro-3-(4-chlorophenyl)-6-methyl-2-(3-(trifluoromethyl)cyclobutyl)pyrimidin-4(3H)-one (cis isomer)
74	5-chloro-3-(5-chloropyridin-2-yl)-2-(6,6-difluorobicyclo[3.1.0]hexan-3-yl)-6-methylpyrimidin-4(3H)-one (cis isomer)
75	5-chloro-3-(5-chloropyridin-2-yl)-2-(6,6-difluorobicyclo[3.1.0]hexan-3-yl)-6-(methylamino)pyrimidin-4(3H)-one (cis isomer)
76	4-(5-chloro-2-(6,6-difluorobicyclo[3.1.0]hexan-3-yl)-4-(methylamino)-6-oxopyrimidin-1(6H)-yl)benzonitrile (cis isomer)
77	4-(2-(6,6-difluorobicyclo[3.1.0]hexan-3-yl)-4,5-dimethyl-6-oxopyrimidin-1(6H)-yl)benzonitrile (cis isomer)
78	3-(6-chloropyridin-3-yl)-2-(6,6-difluorobicyclo[3.1.0]hexan-3-yl)-6-methylpyrimidin-4(3H)-one (cis isomer)
79	4-(2-(6,6-difluorobicyclo[3.1.0]hexan-3-yl)-4-(methylamino)-6-oxopyrimidin-1(6H)-yl)benzonitrile (cis isomer)

Compound	Name	
80		2-(6,6-difluorobicyclo[3.1.0]hexan-3-yl)-3-(4-fluorophenyl)-6-(methylamino)pyrimidin-4(3H)-one (cis isomer)
81		5-(2-(6,6-difluorobicyclo[3.1.0]hexan-3-yl)-4-methyl-6-oxopyrimidin-1(6H)-yl)picolinonitrile (cis isomer)
82		5-bromo-3-(5-chloropyridin-2-yl)-2-(6,6-difluorobicyclo[3.1.0]hexan-3-yl)-6-(methylamino)pyrimidin-4(3H)-one (cis isomer)
83		2-(bicyclo[3.1.0]hexan-3-yl)-5-chloro-3-(4-fluorophenyl)-6-(methylamino)pyrimidin-4(3H)-one (cis isomer)
84		5-(4,5-dimethyl-6-oxo-2-(3-(trifluoromethyl)cyclobutyl)pyrimidin-1(6H)-yl)picolinonitrile (cis isomer)
85		6-(2-(bicyclo[3.1.0]hexan-3-yl)-5-chloro-4-methyl-6-oxopyrimidin-1(6H)-yl)nicotinonitrile (cis isomer)
86		2-(bicyclo[3.1.0]hexan-3-yl)-3-(4-fluorophenyl)-5-methyl-6-(methylamino)pyrimidin-4(3H)-one (cis isomer)
87		2-(bicyclo[3.1.0]hexan-3-yl)-3-(4-chlorophenyl)-6-(methylamino)pyrimidin-4(3H)-one (cis isomer)

	<u>Compound</u>	<u>Name</u>
88		2-(bicyclo[3.1.0]hexan-3-yl)-3-(5-chloropyridin-2-yl)-6-methylpyrimidin-4(3H)-one (cis isomer)
89		4-(2-(bicyclo[3.1.0]hexan-3-yl)-4-methyl-6-oxopyrimidin-1(6H)-yl)benzotrile (cis isomer)
90		2-(bicyclo[3.1.0]hexan-3-yl)-3-(4-fluorophenyl)-6-methylpyrimidin-4(3H)-one (cis isomer)
91		2-(bicyclo[3.1.0]hexan-3-yl)-3-(6-chloropyridin-3-yl)-6-(methylamino)pyrimidin-4(3H)-one (cis isomer)
92		6-(2-(bicyclo[3.1.0]hexan-3-yl)-5-bromo-4-(methylamino)-6-oxopyrimidin-1(6H)-yl)nicotinonitrile (cis isomer)
93		5-chloro-6-(methylamino)-3-(thiophen-2-yl)-2-(4-(trifluoromethyl)cyclohexyl)pyrimidin-4(3H)-one (cis isomer)
94		6-(methylamino)-3-(thiophen-3-yl)-2-(4-(trifluoromethyl)cyclohexyl)pyrimidin-4(3H)-one (cis isomer)
95		6-methyl-3-(5-(trifluoromethyl)-1,3,4-oxadiazol-2-yl)-2-(4-(trifluoromethyl)cyclohexyl)pyrimidin-4(3H)-one (cis isomer)
96		3-(5-chloropyrazin-2-yl)-6-methyl-2-(4-(trifluoromethyl)cyclohexyl)pyrimidin-4(3H)-one (cis isomer)

	<u>Compound</u>	<u>Name</u>
97		6-methyl-3-(thiazol-2-yl)-2-(4-(trifluoromethyl)cyclohexyl)pyrimidin-4(3H)-one (cis isomer)
98		3-(benzo[d]thiazol-5-yl)-5-chloro-6-methyl-2-(4-(trifluoromethyl)cyclohexyl)pyrimidin-4(3H)-one (cis isomer)
99		3-(benzo[d]oxazol-5-yl)-5-chloro-6-methyl-2-(4-(trifluoromethyl)cyclohexyl)pyrimidin-4(3H)-one (cis isomer)
100		5-(2-(bicyclo[2.2.1]heptan-2-yl)-4-methyl-6-oxopyrimidin-1(6H)-yl)picolinonitrile
101		5-(4-methyl-6-oxo-2-(3-(trifluoromethyl)cyclohexyl)picolinonitrile)pyrimidin-1(6H)-yl (trans isomer)
102		6-methyl-3-(5-methylthiazol-2-yl)-2-((1S,4S)-4-(trifluoromethyl)cyclohexyl)pyrimidin-4(3H)-one
103		5-chloro-6-(methylamino)-3-(5-methylthiophen-2-yl)-2-((1S,4S)-4-(trifluoromethyl)cyclohexyl)pyrimidin-4(3H)-one
104		5-chloro-2-((1S,3r,5R)-6,6-difluorobicyclo[3.1.0]hexan-3-yl)-6-methyl-3-(2-methylthiazol-5-yl)pyrimidin-4(3H)-one

EXAMPLE 4

VR1-Transfected Cells and Membrane Preparations

This Example illustrates the preparation of VR1-transfected cells and VR1-containing membrane preparations for use in capsaicin binding assays (Example 5).

5 A cDNA encoding full length human capsaicin receptor (SEQ ID NO:1, 2 or 3 of U.S. Patent No. 6,482,611) is subcloned in the plasmid pBK-CMV (Stratagene, La Jolla, CA) for recombinant expression in mammalian cells.

10 Human embryonic kidney (HEK293) cells are transfected with the pBK-CMV expression construct encoding the full length human capsaicin receptor using standard methods. The transfected cells are selected for two weeks in media containing G418 (400 µg/ml) to obtain a pool of stably transfected cells. Independent clones are isolated from this pool by limiting dilution to obtain clonal stable cell lines for use in subsequent experiments.

15 For radioligand binding experiments, cells are seeded in T175 cell culture flasks in media without antibiotics and grown to approximately 90% confluency. The flasks are then washed with PBS and harvested in PBS containing 5 mM EDTA. The cells are pelleted by gentle centrifugation and stored at -80°C until assayed.

20 Previously frozen cells are disrupted with the aid of a tissue homogenizer in ice-cold HEPES homogenization buffer (5mM KCl, 5.8mM NaCl, 0.75mM CaCl₂, 2mM MgCl₂, 320 mM sucrose, and 10 mM HEPES pH 7.4). Tissue homogenates are first centrifuged for 10 min at 1000 × g (4 °C) to remove the nuclear fraction and debris, and then the supernatant from the first centrifugation is further centrifuged for 30 min at 35,000 × g (4 °C) to obtain a partially purified membrane fraction. Membranes are resuspended in the HEPES homogenization buffer prior to the assay. An aliquot of this membrane homogenate is used to determine protein concentration via the Bradford method (BIO-RAD Protein Assay Kit, #500-25 0001, BIO-RAD, Hercules, CA).

EXAMPLE 5

Capsaicin Receptor Binding Assay

This Example illustrates a representative assay of capsaicin receptor binding that may be used to determine the binding affinity of compounds for the capsaicin (VR1) receptor.

30 Binding studies with [³H] Resiniferatoxin (RTX) are carried out essentially as described by Szallasi and Blumberg (1992) *J. Pharmacol. Exp. Ther.* 262:883-888. In this protocol, non-specific RTX binding is reduced by adding bovine alpha₁ acid glycoprotein (100 µg per tube) after the binding reaction has been terminated.

[³H] RTX (37 Ci/mmol) is synthesized by and obtained from the Chemical Synthesis and Analysis Laboratory, National Cancer Institute-Frederick Cancer Research and Development Center, Frederick, MD. [³H] RTX may also be obtained from commercial vendors (*e.g.*, Amersham Pharmacia Biotech, Inc.; Piscataway, NJ).

5 The membrane homogenate of Example 4 is centrifuged as before and resuspended to a protein concentration of 333 μg/ml in homogenization buffer. Binding assay mixtures are set up on ice and contain [³H]RTX (specific activity 2200 mCi/ml), 2 μl non-radioactive test compound, 0.25 mg/ml bovine serum albumin (Cohn fraction V), and 5×10^4 - 1×10^5 VR1-transfected cells. The final volume is adjusted to 500 μl (for competition binding assays) or
10 1,000 μl (for saturation binding assays) with the ice-cold HEPES homogenization buffer solution (pH 7.4) described above. Non-specific binding is defined as that occurring in the presence of 1 μM non-radioactive RTX (Alexis Corp.; San Diego, CA). For saturation binding, [³H]RTX is added in the concentration range of 7-1,000 pM, using 1 to 2 dilutions. Typically 11 concentration points are collected per saturation binding curve.

15 Competition binding assays are performed in the presence of 60 pM [³H]RTX and various concentrations of test compound. The binding reactions are initiated by transferring the assay mixtures into a 37°C water bath and are terminated following a 60 minute incubation period by cooling the tubes on ice. Membrane-bound RTX is separated from free, as well as any alpha₁-acid glycoprotein-bound RTX, by filtration onto WALLAC glass fiber
20 filters (PERKIN-ELMER, Gaithersburg, MD) which are pre-soaked with 1.0% PEI (polyethyleneimine) for 2 hours prior to use. Filters are allowed to dry overnight then counted in a WALLAC 1205 BETA PLATE counter after addition of WALLAC BETA SCINT scintillation fluid.

Equilibrium binding parameters are determined by fitting the allosteric Hill equation
25 to the measured values with the aid of the computer program FIT P (Biosoft, Ferguson, MO) as described by Szallasi, *et al.* (1993) *J. Pharmacol. Exp. Ther.* 266:678-683. Compounds provided herein generally exhibit K_i values for capsaicin receptor of less than 1 μM, 100 nM, 50 nM, 25 nM, 10 nM, or 1 nM in this assay.

EXAMPLE 6

30 Calcium Mobilization Assay

This Example illustrates representative calcium mobilization assays for use in evaluating test compounds for agonist and antagonist activity.

Cells transfected with expression plasmids (as described in Example 4) and thereby expressing human capsaicin receptor are seeded and grown to 70-90% confluency in

FALCON black-walled, clear-bottomed 96-well plates (#3904, BECTON-DICKINSON, Franklin Lakes, NJ). The culture medium is emptied from the 96 well plates and FLUO-3 AM calcium sensitive dye (Molecular Probes, Eugene, OR) is added to each well (dye solution: 1 mg FLUO-3 AM, 440 μ L DMSO and 440 μ l 20% pluronic acid in DMSO, diluted
5 1:250 in Krebs-Ringer HEPES (KRH) buffer (25 mM HEPES, 5 mM KCl, 0.96 mM NaH₂PO₄, 1 mM MgSO₄, 2 mM CaCl₂, 5 mM glucose, 1 mM probenecid, pH 7.4), 50 μ l diluted solution per well). Plates are covered with aluminum foil and incubated at 37 °C for 1-2 hours in an environment containing 5% CO₂. After the incubation, the dye is emptied from the plates, and the cells are washed once with KRH buffer, and resuspended in KRH
10 buffer.

DETERMINATION OF CAPSAICIN EC₅₀

To measure the ability of a test compound to agonize or antagonize a calcium mobilization response in cells expressing capsaicin receptors to capsaicin or other vanilloid agonist, the EC₅₀ of the agonist capsaicin is first determined. An additional 20 μ l of KRH
15 buffer and 1 μ l DMSO is added to each well of cells, prepared as described above. 100 μ l capsaicin in KRH buffer is automatically transferred by the FLIPR instrument to each well. Capsaicin-induced calcium mobilization is monitored using either FLUOROSKAN ASCENT (Labsystems; Franklin, MA) or FLIPR (fluorometric imaging plate reader system; Molecular Devices, Sunnyvale, CA) instruments. Data obtained between 30 and 60 seconds after
20 agonist application are used to generate an 8-point concentration response curve, with final capsaicin concentrations of 1 nM to 3 μ M. KALEIDAGRAPH software (Synergy Software, Reading, PA) is used to fit the data to the equation:

$$y=a*(1/(1+(b/x)^c))$$

to determine the 50% excitatory concentration (EC₅₀) for the response. In this equation, y is
25 the maximum fluorescence signal, x is the concentration of the agonist or antagonist (in this case, capsaicin), a is the E_{max}, b corresponds to the EC₅₀ value and c is the Hill coefficient.

DETERMINATION OF AGONIST ACTIVITY

Test compounds are dissolved in DMSO, diluted in KRH buffer, and immediately added to cells prepared as described above. 100 nM capsaicin (an approximate EC₉₀
30 concentration) is also added to cells in the same 96-well plate as a positive control. The final concentration of test compounds in the assay wells is between 0.1 nM and 5 μ M.

The ability of a test compound to act as an agonist of the capsaicin receptor is determined by measuring the fluorescence response of cells expressing capsaicin receptors elicited by the compound as function of compound concentration. This data is fit as described

above to obtain the EC₅₀, which is generally less than 1 micromolar, preferably less than 100 nM, and more preferably less than 10 nM. The extent of efficacy of each test compound is also determined by calculating the response elicited by a concentration of test compound (typically 1 μM) relative to the response elicited by 100 nM capsaicin. This value, called
5 Percent of Signal (POS), is calculated by the following equation:

$$\text{POS} = 100 * \text{test compound response} / 100 \text{ nM capsaicin response}$$

This analysis provides quantitative assessment of both the potency and efficacy of test compounds as human capsaicin receptor agonists. Agonists of the human capsaicin receptor generally elicit detectable responses at concentrations less than 100 μM, or preferably at
10 concentrations less than 1 μM, or most preferably at concentrations less than 10 nM. Extent of efficacy at human capsaicin receptor is preferably greater than 30 POS, more preferably greater than 80 POS at a concentration of 1 μM. Certain agonists are essentially free of antagonist activity as demonstrated by the absence of detectable antagonist activity in the assay described below at compound concentrations below 4 nM, more preferably at
15 concentrations below 10 μM and most preferably at concentrations less than or equal to 100 μM.

DETERMINATION OF ANTAGONIST ACTIVITY

Test compounds are dissolved in DMSO, diluted in 20 μl KRH buffer so that the final concentration of test compounds in the assay well is between 1 μM and 5 μM, and added to
20 cells prepared as described above. The 96 well plates containing prepared cells and test compounds are incubated in the dark, at RT for 0.5 to 6 hours. It is important that the incubation not continue beyond 6 hours. Just prior to determining the fluorescence response, 100 μl capsaicin in KRH buffer at twice the EC₅₀ concentration is automatically added by the FLIPR instrument to each well of the 96 well plate for a final sample volume of 200 μl and a
25 final capsaicin concentration equal to the EC₅₀. The final concentration of test compounds in the assay wells is between 1 μM and 5 μM. Antagonists of the capsaicin receptor decrease this response by at least about 20%, preferably by at least about 50%, and most preferably by at least 80%, as compared to matched control (*i.e.*, cells treated with capsaicin at twice the EC₅₀ concentration in the absence of test compound), at a concentration of 10 micromolar or
30 less, preferably 1 micromolar or less. The concentration of antagonist required to provide a 50% decrease, relative to the response observed in the presence of capsaicin and without antagonist, is the IC₅₀ for the antagonist, and is preferably below 1 micromolar, 100 nanomolar, 10 nanomolar or 1 nanomolar.

The data is analyzed as follows. First, the average maximum relative fluorescent unit (RFU) response from the negative control wells (no agonist) is subtracted from the maximum response detected for each of the other experimental wells. Second, average maximum RFU response is calculated for the positive control wells (agonist wells). Then, percent inhibition for each compound tested is calculated using the equation:

$$\text{Percent Inhibition} = 100 - 100 \times (\text{Peak Signal in Test Cells} / \text{Peak Signal in Control Cells})$$

The % inhibition data is plotted as a function of test compound concentration and test compound IC₅₀ is determined using, for example, KALEIDAGRAPH software (Synergy Software, Reading, PA) best fit of the data to the equation:

$$y = m_1 * (1 / (1 + (m_2 / m_0)^{m_3}))$$

where y is the percent inhibition, m₀ is the concentration of the agonist, m₁ is the maximum RFU, m₂ corresponds to the test compound IC₅₀ (the concentration required to provide a 50% decrease, relative to the response observed in the presence of agonist and without antagonist) and m₃ is the Hill coefficient. Alternatively, test compound IC₅₀ is determined using a linear regression in which x is ln(concentration of test compound) and y is ln(percent inhibition/(100 - percent inhibition)). Data with a percent inhibition that is greater than 90% or less than 15% are rejected and are not used in the regression. The IC₅₀ calculated in this fashion is e^(intercept/slope)

Certain preferred VR1 modulators are antagonists that are essentially free of agonist activity as demonstrated by the absence of detectable agonist activity in the assay described above at compound concentrations below 4 nM, more preferably at concentrations below 10 μM and most preferably at concentrations less than or equal to 100 μM.

EXAMPLE 7

Dorsal Root Ganglion Cell Assay

This Example illustrates a representative dorsal root ganglion cell assay for evaluating VR1 antagonist or agonist activity of a compound.

DRG are dissected from neonatal rats, dissociated and cultured using standard methods (Aguayo and White (1992) *Brain Research* 570:61-67). After 48 hour incubation, cells are washed once and incubated for 30-60 minutes with the calcium sensitive dye Fluo 4 AM (2.5-10 ug/ml; TefLabs, Austin, TX). Cells are then washed once. Addition of capsaicin to the cells results in a VR1-dependent increase in intracellular calcium levels which is monitored by a change in Fluo-4 fluorescence with a fluorometer. Data are collected for 60-180 seconds to determine the maximum fluorescent signal.

For antagonist assays, various concentrations of compound are added to the cells. Fluorescent signal is then plotted as a function of compound concentration to identify the concentration required to achieve a 50% inhibition of the capsaicin-activated response, or IC_{50} . Antagonists of the capsaicin receptor preferably have an IC_{50} below 1 micromolar, 100
5 nanomolar, 10 nanomolar or 1 nanomolar.

For agonist assays, various concentrations of compound are added to the cells without the addition of capsaicin. Compounds that are capsaicin receptor agonists result in a VR1-dependent increase in intracellular calcium levels which is monitored by a change in Fluo-4 fluorescence with a fluorometer. The EC_{50} , or concentration required to achieve 50% of the
10 maximum signal for a capsaicin-activated response, is preferably below 1 micromolar, below 100 nanomolar or below 10 nanomolar.

EXAMPLE 8

Animal Models for Determining Pain Relief

This Example illustrates representative methods for assessing the degree of pain relief
15 provided by a compound.

A. Pain Relief Testing

The following methods may be used to assess pain relief.

MECHANICAL ALLODYNIA

Mechanical allodynia (an abnormal response to an innocuous stimulus) is assessed
20 essentially as described by Chaplan *et al.* (1994) *J. Neurosci. Methods* 53:55-63 and Tal and Eliav (1998) *Pain* 64(3):511-518. A series of von Frey filaments of varying rigidity (typically 8-14 filaments in a series) are applied to the plantar surface of the hind paw with just enough force to bend the filament. The filaments are held in this position for no more than three seconds or until a positive allodynic response is displayed by the rat. A positive allodynic
25 response consists of lifting the affected paw followed immediately by licking or shaking of the paw. The order and frequency with which the individual filaments are applied are determined by using Dixon up-down method. Testing is initiated with the middle hair of the series with subsequent filaments being applied in consecutive fashion, ascending or descending, depending on whether a negative or positive response, respectively, is obtained
30 with the initial filament.

Compounds are effective in reversing or preventing mechanical allodynia-like symptoms if rats treated with such compounds require stimulation with a Von Frey filament of higher rigidity strength to provoke a positive allodynic response as compared to control untreated or vehicle treated rats. Alternatively, or in addition, testing of an animal in chronic

pain may be done before and after compound administration. In such an assay, an effective compound results in an increase in the rigidity of the filament needed to induce a response after treatment, as compared to the filament that induces a response before treatment or in an animal that is also in chronic pain but is left untreated or is treated with vehicle. Test compounds are administered before or after onset of pain. When a test compound is administered after pain onset, testing is performed 10 minutes to three hours after administration.

MECHANICAL HYPERALGESIA

Mechanical hyperalgesia (an exaggerated response to painful stimulus) is tested essentially as described by Koch et al. (1996) *Analgesia* 2(3):157-164. Rats are placed in individual compartments of a cage with a warmed, perforated metal floor. Hind paw withdrawal duration (*i.e.*, the amount of time for which the animal holds its paw up before placing it back on the floor) is measured after a mild pinprick to the plantar surface of either hind paw.

Compounds produce a reduction in mechanical hyperalgesia if there is a statistically significant decrease in the duration of hindpaw withdrawal. Test compound may be administered before or after onset of pain. For compounds administered after pain onset, testing is performed 10 minutes to three hours after administration.

THERMAL HYPERALGESIA

Thermal hyperalgesia (an exaggerated response to noxious thermal stimulus) is measured essentially as described by Hargreaves *et al.* (1988) *Pain*. 32(1):77-88. Briefly, a constant radiant heat source is applied the animals' plantar surface of either hind paw. The time to withdrawal (*i.e.*, the amount of time that heat is applied before the animal moves its paw), otherwise described as thermal threshold or latency, determines the animal's hind paw sensitivity to heat.

Compounds produce a reduction in thermal hyperalgesia if there is a statistically significant increase in the time to hindpaw withdrawal (*i.e.*, the thermal threshold to response or latency is increased). Test compound may be administered before or after onset of pain. For compounds administered after pain onset, testing is performed 10 minutes to three hours after administration.

B. Pain Models

Pain may be induced using any of the following methods, to allow testing of analgesic efficacy of a compound. In general, compounds provided herein result in a statistically

significant reduction in pain as determined by at least one of the previously described testing methods, using male SD rats and at least one of the following models.

ACUTE INFLAMMATORY PAIN MODEL

Acute inflammatory pain is induced using the carrageenan model essentially as described by Field *et al.* (1997) *Br. J. Pharmacol.* 121(8):1513-1522. 100-200 µl of 1-2% carrageenan solution is injected into the rats' hind paw. Three to four hours following injection, the animals' sensitivity to thermal and mechanical stimuli is tested using the methods described above. A test compound (0.01 to 50 mg/kg) is administered to the animal, prior to testing, or prior to injection of carrageenan. The compound can be administered orally or through any parenteral route, or topically on the paw. Compounds that relieve pain in this model result in a statistically significant reduction in mechanical allodynia and/or thermal hyperalgesia.

CHRONIC INFLAMMATORY PAIN MODEL

Chronic inflammatory pain is induced using one of the following protocols:

1. Essentially as described by Bertorelli *et al.* (1999) *Br. J. Pharmacol.* 128(6):1252-1258, and Stein *et al.* (1998) *Pharmacol. Biochem. Behav.* 31(2):455-51, 200 µl Complete Freund's Adjuvant (0.1 mg heat killed and dried *M. Tuberculosis*) is injected to the rats' hind paw: 100 µl into the dorsal surface and 100 µl into the plantar surface.
2. Essentially as described by Abbadie *et al.* (1994) *J Neurosci.* 14(10):5865-5871 rats are injected with 150 µl of CFA (1.5 mg) in the tibio-tarsal joint.

Prior to injection with CFA in either protocol, an individual baseline sensitivity to mechanical and thermal stimulation of the animals' hind paws is obtained for each experimental animal.

Following injection of CFA, rats are tested for thermal hyperalgesia, mechanical allodynia and mechanical hyperalgesia as described above. To verify the development of symptoms, rats are tested on days 5, 6, and 7 following CFA injection. On day 7, animals are treated with a test compound, morphine or vehicle. An oral dose of morphine of 1-5 mg/kg is suitable as positive control. Typically, a dose of 0.01-50 mg/kg of test compound is used. Compounds can be administered as a single bolus prior to testing or once or twice or three times daily, for several days prior to testing. Drugs are administered orally or through any parenteral route, or applied topically to the animal.

Results are expressed as Percent Maximum Potential Efficacy (MPE). 0% MPE is defined as analgesic effect of vehicle, 100% MPE is defined as an animal's return to pre-CFA

baseline sensitivity. Compounds that relieve pain in this model result in a MPE of at least 30%.

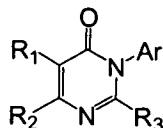
CHRONIC NEUROPATHIC PAIN MODEL

Chronic neuropathic pain is induced using the chronic constriction injury (CCI) to the rat's sciatic nerve essentially as described by Bennett and Xie (1988) *Pain* 33:87-107. Rats are anesthetized (*e.g.* with an intraperitoneal dose of 50-65 mg/kg pentobarbital with additional doses administered as needed). The lateral aspect of each hind limb is shaved and disinfected. Using aseptic technique, an incision is made on the lateral aspect of the hind limb at the mid thigh level. The biceps femoris is bluntly dissected and the sciatic nerve is exposed. On one hind limb of each animal, four loosely tied ligatures are made around the sciatic nerve approximately 1-2 mm apart. On the other side the sciatic nerve is not ligated and is not manipulated. The muscle is closed with continuous pattern and the skin is closed with wound clips or sutures. Rats are assessed for mechanical allodynia, mechanical hyperalgesia and thermal hyperalgesia as described above.

Compounds that relieve pain in this model result in a statistically significant reduction in mechanical allodynia, mechanical hyperalgesia and/or thermal hyperalgesia when administered (0.01-50 mg/kg, orally, parenterally or topically) immediately prior to testing as a single bolus, or for several days: once or twice or three times daily prior to testing.

What is claimed is:

- 5 1. A compound of the formula:



or a pharmaceutically acceptable salt thereof, wherein:

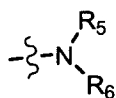
Ar is a 6- to 10-membered aryl or a 5- to 10-membered heteroaryl, each of which is substituted with from 1 to 3 substituents independently chosen from halogen, cyano, amino, nitro, C₁-C₆alkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, C₁-C₆haloalkyl, C₁-C₆hydroxyalkyl, C₁-C₆alkoxy, C₁-C₆haloalkoxy, (C₃-C₇cycloalkyl)C₀-C₄alkyl, and mono- or di-(C₁-C₆alkyl)amino;

R₁ is:

- (i) hydrogen, halogen, hydroxy, amino or cyano; or
(ii) C₁-C₆alkyl, C₁-C₆alkoxy, mono- or di-(C₁-C₆alkyl)amino, (C₃-C₇cycloalkyl)C₀-C₄alkyl, phenyl or 5- or 6-membered heteroaryl, each of which is optionally substituted and each of which is substituted with from 0 to 4 substituents independently chosen from R₇;

R₂ is:

- (i) hydrogen, hydroxy, halogen or cyano;
(ii) C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆alkoxy, C₂-C₆alkyl ether, (C₃-C₇cycloalkyl)C₀-C₄alkyl, or phenyl, each of which is substituted with from 0 to 4 substituents independently chosen from R₇; or
(iii) a group of the formula:



wherein R₅ and R₆ are independently chosen from hydrogen, C₁-C₆alkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, (C₃-C₇cycloalkyl)C₀-C₄alkyl, C₁-C₆alkanoyl, C₁-C₆alkylsulfonyl and (4- to 7-membered heterocycle)C₀-C₄alkyl, each of which is substituted with from 0 to 2 substituents independently chosen from R₇; or R₅ and R₆ are taken together to form a 4- to 7-membered heterocycle that is substituted with from 0 to 2 substituents independently chosen from R₇; and

R₃ is:

- (i) (C₃-C₇cycloalkyl)C₀-C₄alkyl that is substituted with from 0 to 4 substituents independently chosen from C₁-C₆alkyl, C₁-C₆haloalkyl and substituents that are taken together to form a fused C₃-C₇cycloalkyl or a C₁-C₃alkylene bridge;

(ii) C₁-C₆haloalkyl, C₁-C₆alkoxy, C₁-C₆haloalkoxy, C₁-C₆alkylthio, C₁-C₆haloalkylthio or mono- or di-(C₁-C₆alkyl)amino, each of which is substituted with from 0 to 4 substituents independently chosen from R₇, phenyl and 5- or 6-membered heteroaryl, which phenyl and heteroaryl are substituted with from 0 to 4 substituents independently chosen from R₇, such that R₃ is not unsubstituted benzylthio; or

(iii) phenoxy that is substituted with from 0 to 4 substituents independently chosen from R₇; and each R₇ is independently chosen from halogen, hydroxy, cyano, amino, nitro, oxo, C₁-C₆alkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, C₁-C₆haloalkyl, C₁-C₆hydroxyalkyl, C₁-C₆alkoxy, C₁-C₆haloalkoxy, (C₃-C₇cycloalkyl)C₀-C₄alkyl, and mono- or di-(C₁-C₆alkyl)amino.

2. A compound or salt thereof according to claim 1, wherein Ar is phenyl that is substituted with from 1 to 3 substituents independently chosen from halogen, cyano, nitro or C₁-C₆alkyl.

3. A compound or salt thereof according to claim 1, wherein Ar is pyridyl that is substituted with from 1 to 3 substituents independently chosen from halogen, cyano, nitro or C₁-C₆alkyl.

4. A compound or salt thereof according to any one of claims 1-3, wherein R₁ is hydrogen, halogen, cyano, C₁-C₄alkyl, (C₃-C₅cycloalkyl)C₀-C₂alkyl, or phenyl that is unsubstituted or substituted with from 1 to 3 substituents independently chosen from halogen, cyano, oxo, C₁-C₄alkyl, C₁-C₄haloalkyl, C₁-C₄alkoxy and C₁-C₄haloalkoxy.

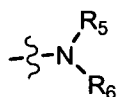
5. A compound or salt thereof according to claim 4, wherein R₁ is hydrogen, cyano, halogen, C₁-C₄alkyl or C₁-C₄alkanoyl.

6. A compound or salt thereof according to claim 5, wherein R₁ is bromo, chloro, fluoro, iodo, methyl or ethyl.

7. A compound or salt thereof according to any one of claims 1-6, wherein R₂ is C₁-C₆alkyl.

8. A compound or salt thereof according to any one of claims 1-6, wherein R₂ is C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₂-C₆alkyl ether or C₁-C₆haloalkyl.

9. A compound or salt thereof according to any one of claims 1-6, wherein R₂ is a group of the formula:



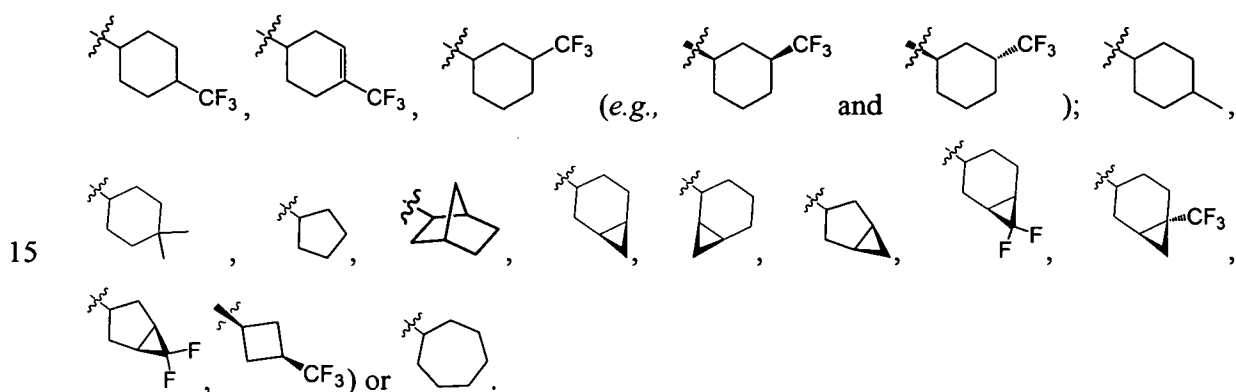
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wherein R_5 and R_6 are independently chosen from hydrogen, C_1 - C_6 alkyl, (C_3 - C_7 cycloalkyl) C_0 - C_4 alkyl, C_1 - C_6 alkanoyl, and C_1 - C_6 alkylsulfonyl, each of which is substituted with from 0 to 2 substituents independently chosen from R_7 , such that at least one of R_5 and R_6 is not hydrogen; or R_5 and R_6 are taken together to form a 4- to 7-membered heterocycloalkyl that is substituted with from 0 to 2 substituents independently chosen from R_7 .

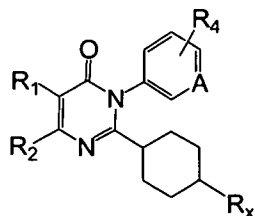
10. A compound or salt thereof according to any one of claims 1-9, wherein R_3 is (C_3 - C_7 cycloalkyl) C_0 - C_4 alkyl that is substituted with from 1 to 4 substituents independently chosen from C_1 - C_6 alkyl, halogen, C_1 - C_6 haloalkyl and substituents that are taken together to form a fused C_3 - C_7 cycloalkyl or a C_1 - C_3 alkylene bridge.

10 11. A compound or salt thereof according to claim 10, wherein R_3 is C_5 - C_7 cycloalkyl that is substituted with from 1 to 2 substituents independently chosen from C_1 - C_4 alkyl, halogen and C_1 - C_4 haloalkyl.

12. A compound or salt thereof according to claim 11, wherein R_3 is:



13. A compound or salt thereof according to claim 12, wherein the compound has the formula:



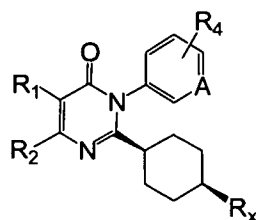
20 wherein:

A is CH or N;

R_4 represents from 0 to 3 substituents independently chosen from halogen, cyano, amino, nitro, C_1 - C_6 alkyl, C_1 - C_6 haloalkyl, C_1 - C_6 hydroxyalkyl, C_1 - C_6 alkoxy and C_1 - C_6 haloalkoxy; and

25 R_x is C_1 - C_4 alkyl or C_1 - C_4 haloalkyl.

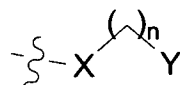
14. A compound or salt thereof according to claim 13, wherein the compound has the formula:



wherein:

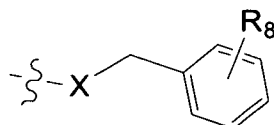
- 5 A is CH or N;
 R₄ represents from 0 to 3 substituents independently chosen from halogen, cyano, amino, nitro, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆hydroxyalkyl, C₁-C₆alkoxy and C₁-C₆haloalkoxy; and
 R_x is C₁-C₄alkyl or C₁-C₄haloalkyl.
- 10 15. A compound or salt thereof according to claim 13 or claim 14, wherein R_x is methyl, ethyl, isopropyl, t-butyl, difluoromethyl or trifluoromethyl.

16. A compound or salt thereof according to any one of claims 1-9, wherein R₃ is a group of the formula:



- 15 wherein:
 X is O, S or NH;
 n is 1, 2 or 3; and
 Y is C₁-C₂haloalkyl, phenyl or a 5- or 6-membered heteroaryl, each of which phenyl or heteroaryl is substituted with from 0 to 4 substituents independently chosen from halogen, C₁-C₆alkyl, or C₁-C₆haloalkyl, such that R₃ is not benzylthio.
- 20

17. A compound or salt thereof according to claim 16, wherein R₃ is C₂-C₆haloalkylthio, or a group of the formula:



- wherein R₈ represents from 0 to 4 substituents independently chosen from halogen, C₁-C₆alkyl, or C₁-C₆haloalkyl.
- 25

18. A compound or salt thereof according to any one of claims 1-9, wherein R₃ is phenoxy that is substituted with from 0 to 4 substituents independently chosen from halogen, C₁-C₆alkyl, or C₁-C₆haloalkyl.

19. A compound or salt thereof according to claim 1, wherein the compound is:
3-(4-chlorophenyl)-6-methyl-2-[cis-4-(trifluoromethyl)cyclohexyl]pyrimidin-4(3H)-one;
5-bromo-3-(4-chlorophenyl)-6-methyl-2-[cis-4-(trifluoromethyl)cyclohexyl]pyrimidin-4(3H)-one;
3-(4-fluorophenyl)-6-methyl-2-[cis-4-(trifluoromethyl)cyclohexyl]pyrimidin-4(3H)-one;
5-bromo-3-(4-fluorophenyl)-6-methyl-2-[cis-4-(trifluoromethyl)cyclohexyl]pyrimidin-4(3H)-one;
6-methyl-3-phenyl-2-[cis-4-(trifluoromethyl)cyclohexyl]pyrimidin-4(3H)-one;
3-(3-chlorophenyl)-6-methyl-2-[cis-4-(trifluoromethyl)cyclohexyl]pyrimidin-4(3H)-one;
4-{4-methyl-6-oxo-2-[cis-4-(trifluoromethyl)cyclohexyl]pyrimidin-1(6H)-yl} benzonitrile;
3-(3,4-difluorophenyl)-6-methyl-2-[cis-4-(trifluoromethyl)cyclohexyl]pyrimidin-4(3H)-one;
3-(6-chloropyridin-3-yl)-6-methyl-2-[cis-4-(trifluoromethyl)cyclohexyl]pyrimidin-4(3H)-one;
3-(4-bromophenyl)-6-methyl-2-[cis-4-(trifluoromethyl)cyclohexyl]pyrimidin-4(3H)-one;
6-methyl-3-(4-methylphenyl)-2-[cis-4-(trifluoromethyl)cyclohexyl]pyrimidin-4(3H)-one;
3-(4-chlorophenyl)-6-(2-methoxyethyl)-2-[cis-4-(trifluoromethyl)cyclohexyl]pyrimidin-4(3H)-one;
3-(4-chlorophenyl)-6-(2-hydroxyethyl)-2-[cis-4-(trifluoromethyl)cyclohexyl]pyrimidin-4(3H)-one;
3-(4-chloro-2-nitrophenyl)-6-methyl-2-[cis-4-(trifluoromethyl)cyclohexyl]pyrimidin-4(3H)-one;
3-(4-chlorophenyl)-5,6-dimethyl-2-[cis-4-(trifluoromethyl)cyclohexyl]pyrimidin-4(3H)-one;
3-(4-chlorophenyl)-5-cyclopropyl-6-methyl-2-[cis-4-(trifluoromethyl)cyclohexyl]pyrimidin-4(3H)-one;
1-(4-chlorophenyl)-4-methyl-6-oxo-2-[cis-4-(trifluoromethyl)cyclohexyl]-1,6-dihydropyrimidine-5-carbonitrile;
3-(4-chlorophenyl)-5-fluoro-6-methyl-2-[cis-4-(trifluoromethyl)cyclohexyl]pyrimidin-4(3H)-one;
4-{5-bromo-4-methyl-6-oxo-2-[cis-4-(trifluoromethyl)cyclohexyl]pyrimidin-1(6H)-yl} benzonitrile;
4-{4,5-dimethyl-6-oxo-2-[cis-4-(trifluoromethyl)cyclohexyl]pyrimidin-1(6H)-yl} benzonitrile;

5-chloro-3-(4-chlorophenyl)-6-methyl-2-[cis-4-(trifluoromethyl)cyclohexyl]pyrimidin-4(3H)-one;

3-(4-chlorophenyl)-5-ethyl-6-methyl-2-[cis-4-(trifluoromethyl)cyclohexyl]pyrimidin-4(3H)-one;

5-acetyl-3-(4-chlorophenyl)-6-methyl-2-[cis-4-(trifluoromethyl)cyclohexyl]pyrimidin-4(3H)-one;

4-{5-chloro-4-methyl-6-oxo-2-[cis-4-(trifluoromethyl)cyclohexyl]pyrimidin-1(6H)-yl}benzotrile;

3-(4-chlorophenyl)-6-methyl-2-(4-methylcyclohexyl)pyrimidin-4(3H)-one;

3-(4-chlorophenyl)-6-ethyl-2-[cis-4-(trifluoromethyl)cyclohexyl]pyrimidin-4(3H)-one;

3-(4-chlorophenyl)-6-(trifluoromethyl)-2-[cis-4-(trifluoromethyl)cyclohexyl]pyrimidin-4(3H)-one;

3-(4-chlorophenyl)-5-iodo-6-methyl-2-[cis-4-(trifluoromethyl)cyclohexyl]pyrimidin-4(3H)-one;

3-(4-chlorophenyl)-6-isopropyl-2-[cis-4-(trifluoromethyl)cyclohexyl]pyrimidin-4(3H)-one;

3-(4-chlorophenyl)-6-isopropyl-2-[trans-4-(trifluoromethyl)cyclohexyl]pyrimidin-4(3H)-one;

3-(4-chlorophenyl)-6-methyl-5-phenyl-2-[cis-4-(trifluoromethyl)cyclohexyl]pyrimidin-4(3H)-one;

3-(4-chlorophenyl)-6-isopropyl-2-[cis-4-(trifluoromethyl)cyclohexyl]pyrimidin-4(3H)-one;

3-(4-chlorophenyl)-6-isopropyl-2-[trans-4-(trifluoromethyl)cyclohexyl]pyrimidin-4(3H)-one;

3-(4-chlorophenyl)-6-(methoxymethyl)-2-[cis-4-(trifluoromethyl)cyclohexyl]pyrimidin-4(3H)-one;

3-(4-chlorophenyl)-6-(hydroxymethyl)-2-[cis-4-(trifluoromethyl)cyclohexyl]pyrimidin-4(3H)-one;

3-(4-chlorophenyl)-6-methyl-5-(1,3-thiazol-2-yl)-2-[cis-4-(trifluoromethyl)cyclohexyl]pyrimidin-4(3H)-one;

6-(aminomethyl)-3-(4-chlorophenyl)-2-[cis-4-(trifluoromethyl)cyclohexyl]pyrimidin-4(3H)-one;

6-amino-3-(4-chlorophenyl)-2-[cis-4-(trifluoromethyl)cyclohexyl]pyrimidin-4(3H)-one;

3-(4-chlorophenyl)-6-(dimethylamino)-2-[cis-4-(trifluoromethyl)cyclohexyl]pyrimidin-4(3H)-one;

3-(4-chlorophenyl)-6-(methylamino)-2-[cis-4-(trifluoromethyl)cyclohexyl]pyrimidin-4(3H)-one;

3-(4-chlorophenyl)-6-(ethylamino)-2-[cis-4-(trifluoromethyl)cyclohexyl]pyrimidin-4(3H)-one;

- 4-[4-(hydroxymethyl)-6-oxo-2-[cis-4-(trifluoromethyl)cyclohexyl]pyrimidin-1(6H)-yl]benzotrile
- 5-chloro-3-(4-chlorophenyl)-6-(methylamino)-2-[cis-4-(trifluoromethyl)cyclohexyl]pyrimidin-4(3H)-one;
- 5-chloro-3-(4-chlorophenyl)-6-(methylamino)-2-[trans-4-(trifluoromethyl)cyclohexyl]pyrimidin-4(3H)-one;
- 4-[4-(methylamino)-6-oxo-2-[cis-4-(trifluoromethyl)cyclohexyl]pyrimidin-1(6H)-yl]benzotrile;
- 3-(4-chlorophenyl)-5-methyl-6-(methylamino)-2-[cis-4-(trifluoromethyl)cyclohexyl]pyrimidin-4(3H)-one;
- 2-(3-(trifluoromethyl)benzylamino)-3-(4-chlorophenyl)-5,6-dimethylpyrimidin-4(3H)-one;
- 3-(4-chlorophenyl)-5,6-dimethyl-2-(3,3,3-trifluoropropylthio)pyrimidin-4(3H)-one;
- 3-(benzo[d]thiazol-6-yl)-5-chloro-6-ethyl-2-(4-(trifluoromethyl)cyclohexyl)pyrimidin-4(3H)-one;
- 5-(5-chloro-4-(methylamino)-6-oxo-2-(cis-4-(trifluoromethyl)cyclohexyl)pyrimidin-1(6H)-yl)picolinonitrile;
- cis-2-bicyclo[3.1.0]hexan-3-yl)-3-(4-chlorophenyl)-6-methylpyrimidin-4(3H)-one);
- 3-(4-chlorophenyl)-6-methyl-2-cis-(3-(trifluoromethyl)cyclobutyl)pyrimidin-4(3H)-one;
- 2-(bicyclo[2.2.1]heptan-2-yl)-3-(4-fluorophenyl)-6-methylpyrimidin-4(3H)-one;
- 3-(4-chlorophenyl)-6-methyl-2-[4-(trifluoromethyl)cyclohex-3-en-1-yl]pyrimidin-4(3H)-one;
- 4-[5-chloro-4-(methylamino)-6-oxo-2-[cis-4-(trifluoromethyl)cyclohexyl]pyrimidin-1(6H)-yl]benzotrile;
- 4-[5-methyl-4-(methylamino)-6-oxo-2-[cis-4-(trifluoromethyl)cyclohexyl]pyrimidin-1(6H)-yl]benzotrile;
- 3-(4-chlorophenyl)-5-hydroxy-6-methyl-2-[cis-4-(trifluoromethyl)cyclohexyl]pyrimidin-4(3H)-one;
- 3-(5-chloropyridin-2-yl)-6-ethyl-2-[cis-4-(trifluoromethyl)cyclohexyl]pyrimidin-4(3H)-one;
- 5-bromo-3-(4-chlorophenyl)-2-cyclopentyl-6-ethylpyrimidin-4(3H)-one;
- 5-chloro-3-(5-chloropyridin-2-yl)-6-ethyl-2-[cis-4-(trifluoromethyl)cyclohexyl]pyrimidin-4(3H)-one;
- 3-(6-chloropyridin-3-yl)-6-(hydroxymethyl)-2-[cis-4-(trifluoromethyl)cyclohexyl]pyrimidin-4(3H)-one;
- 3-(1,3-benzothiazol-6-yl)-6-ethyl-2-[4-(trifluoromethyl)cyclohexyl]pyrimidin-4(3H)-one;
- 5-chloro-3-(6-chloropyridin-3-yl)-6-(methylamino)-2-[cis-4-(trifluoromethyl)cyclohexyl]pyrimidin-4(3H)-one;
- 5-[5-chloro-4-(methylamino)-6-oxo-2-[cis-4-(trifluoromethyl)cyclohexyl]pyrimidin-1(6H)-yl]pyridine-2-carboxamide;
- 3-(4-fluorophenyl)-6-methyl-2-(3-(trifluoromethyl)cyclohexyl)pyrimidin-4(3H)-one;
- 5-bromo-3-(4-chlorophenyl)-6-methyl-2-(3-(trifluoromethyl)cyclobutyl)pyrimidin-4(3H)-one;

3-(4-chlorophenyl)-5,6-dimethyl-2-(3-(trifluoromethyl)cyclobutyl)pyrimidin-4(3H)-one;
3-(4-chlorophenyl)-2-(6,6-difluorobicyclo[3.1.0]hexan-3-yl)-6-methylpyrimidin-4(3H)-one;
3-(2-chloropyrimidin-5-yl)-6-methyl-2-(4-(trifluoromethyl)cyclohexyl)pyrimidin-4(3H)-one;
5-(4-methyl-6-oxo-2-(4-(trifluoromethyl)cyclohexyl)pyrimidin-1(6H)-yl)pyrimidine-2-
carbonitrile;
3-(5-chlorothiazol-2-yl)-6-methyl-2-(4-(trifluoromethyl)cyclohexyl)pyrimidin-4(3H)-one;

6-methyl-2-(4-(trifluoromethyl)cyclohexyl)-3-(4-(trifluoromethyl)oxazol-2-yl)pyrimidin-4(3H)-one;

3-(4-chlorophenyl)-2-(6,6-difluorobicyclo[3.1.0]hexan-3-yl)-5,6-dimethylpyrimidin-4(3H)-one;

5-chloro-3-(4-chlorophenyl)-6-methyl-2-(3-(trifluoromethyl)cyclobutyl)pyrimidin-4(3H)-one;

5-chloro-3-(5-chloropyridin-2-yl)-2-(6,6-difluorobicyclo[3.1.0]hexan-3-yl)-6-methylpyrimidin-4(3H)-one;

5-chloro-3-(5-chloropyridin-2-yl)-2-(6,6-difluorobicyclo[3.1.0]hexan-3-yl)-6-(methylamino)pyrimidin-4(3H)-one;

4-(5-chloro-2-(6,6-difluorobicyclo[3.1.0]hexan-3-yl)-4-(methylamino)-6-oxopyrimidin-1(6H)-yl)benzotrile;

4-(2-(6,6-difluorobicyclo[3.1.0]hexan-3-yl)-4,5-dimethyl-6-oxopyrimidin-1(6H)-yl)benzotrile;

3-(6-chloropyridin-3-yl)-2-(6,6-difluorobicyclo[3.1.0]hexan-3-yl)-6-methylpyrimidin-4(3H)-one;

4-(2-(6,6-difluorobicyclo[3.1.0]hexan-3-yl)-4-(methylamino)-6-oxopyrimidin-1(6H)-yl)benzotrile;

2-(6,6-difluorobicyclo[3.1.0]hexan-3-yl)-3-(4-fluorophenyl)-6-(methylamino)pyrimidin-4(3H)-one;

5-(2-(6,6-difluorobicyclo[3.1.0]hexan-3-yl)-4-methyl-6-oxopyrimidin-1(6H)-yl)picolinonitrile;

5-bromo-3-(5-chloropyridin-2-yl)-2-(6,6-difluorobicyclo[3.1.0]hexan-3-yl)-6-(methylamino)pyrimidin-4(3H)-one;

2-(bicyclo[3.1.0]hexan-3-yl)-5-chloro-3-(4-fluorophenyl)-6-(methylamino)pyrimidin-4(3H)-one;

5-(4,5-dimethyl-6-oxo-2-(3-(trifluoromethyl)cyclobutyl)pyrimidin-1(6H)-yl)picolinonitrile;

6-(2-(bicyclo[3.1.0]hexan-3-yl)-5-chloro-4-methyl-6-oxopyrimidin-1(6H)-yl)nicotinonitrile;

2-(bicyclo[3.1.0]hexan-3-yl)-3-(4-fluorophenyl)-5-methyl-6-(methylamino)pyrimidin-4(3H)-one;

2-(bicyclo[3.1.0]hexan-3-yl)-3-(4-chlorophenyl)-6-(methylamino)pyrimidin-4(3H)-one;

2-(bicyclo[3.1.0]hexan-3-yl)-3-(5-chloropyridin-2-yl)-6-methylpyrimidin-4(3H)-one;

4-(2-(bicyclo[3.1.0]hexan-3-yl)-4-methyl-6-oxopyrimidin-1(6H)-yl)benzotrile;

2-(bicyclo[3.1.0]hexan-3-yl)-3-(4-fluorophenyl)-6-methylpyrimidin-4(3H)-one;

2-(bicyclo[3.1.0]hexan-3-yl)-3-(6-chloropyridin-3-yl)-6-(methylamino)pyrimidin-4(3H)-one;

6-(2-(bicyclo[3.1.0]hexan-3-yl)-5-bromo-4-(methylamino)-6-oxopyrimidin-1(6H)-yl)nicotinonitrile;

5-chloro-6-(methylamino)-3-(thiophen-2-yl)-2-(4-(trifluoromethyl)cyclohexyl)pyrimidin-4(3H)-one;

6-(methylamino)-3-(thiophen-3-yl)-2-(4-(trifluoromethyl)cyclohexyl)pyrimidin-4(3H)-one;

6-methyl-3-(5-(trifluoromethyl)-1,3,4-oxadiazol-2-yl)-2-(4-(trifluoromethyl)cyclohexyl)pyrimidin-4(3H)-one;

3-(5-chloropyrazin-2-yl)-6-methyl-2-(4-(trifluoromethyl)cyclohexyl)pyrimidin-4(3H)-one;

6-methyl-3-(thiazol-2-yl)-2-(4-(trifluoromethyl)cyclohexyl)pyrimidin-4(3H)-one;
3-(benzo[d]thiazol-5-yl)-5-chloro-6-methyl-2-(4-(trifluoromethyl)cyclohexyl)pyrimidin-4(3H)-one;
3-(benzo[d]oxazol-5-yl)-5-chloro-6-methyl-2-(4-(trifluoromethyl)cyclohexyl)pyrimidin-4(3H)-one;
5-(2-(bicyclo[2.2.1]heptan-2-yl)-4-methyl-6-oxopyrimidin-1(6H)-yl)picolinonitrile;
5-(4-methyl-6-oxo-2-(3-(trifluoromethyl)cyclohexyl)pyrimidin-1(6H)-yl)picolinonitrile;
6-methyl-3-(5-methylthiazol-2-yl)-2-((1s,4s)-4-(trifluoromethyl)cyclohexyl)pyrimidin-4(3H)-one;
5-chloro-6-(methylamino)-3-(5-methylthiophen-2-yl)-2-((1s,4s)-4-(trifluoromethyl)cyclohexyl)pyrimidin-4(3H)-one; or
5-chloro-2-((1S,3r,5R)-6,6-difluorobicyclo[3.1.0]hexan-3-yl)-6-methyl-3-(2-methylthiazol-5-yl)pyrimidin-4(3H)-one.

20. A compound or salt thereof according to any one of claims 1-19, wherein the compound exhibits no detectable agonist activity an *in vitro* assay of capsaicin receptor agonism.

21. A compound or salt thereof according to any one of claims 1-20, wherein the compound is capable of exhibiting an IC₅₀ value of 1 micromolar or less in a capsaicin receptor calcium mobilization assay.

22. A pharmaceutical composition, comprising at least one compound or salt thereof according to any one of claims 1-21 in combination with a physiologically acceptable carrier or excipient.

23. A pharmaceutical composition according to claim 22, wherein the composition is formulated as an injectible fluid, an aerosol, a cream, an oral liquid, a tablet, a gel, a pill, a capsule, a syrup, or a transdermal patch.

24. A method for reducing calcium conductance of a cellular capsaicin receptor, comprising contacting a cell expressing a capsaicin receptor with at least one compound or salt thereof according to any one of claims 1-21, and thereby reducing calcium conductance of the capsaicin receptor.

25. A method according to claim 24, wherein the cell is contacted *in vivo* in an animal.

26. A method according to claim 25, wherein the cell is a neuronal cell.

27. A method according to claim 25, wherein the cell is a urothelial cell.

28. A method according to claim 25, wherein during contact the compound or salt thereof is present within a body fluid of the animal.

29. A method according to claim 25, wherein the animal is a human.

30. A method according to claim 25, wherein the compound is administered orally.

5 31. A method for inhibiting binding of vanilloid ligand to a capsaicin receptor *in vitro*, the method comprising contacting capsaicin receptor with at least one compound or salt thereof according to any one of claims 1-21, under conditions and in an amount sufficient to detectably inhibit vanilloid ligand binding to capsaicin receptor.

10 32. A method for inhibiting binding of vanilloid ligand to capsaicin receptor in a patient, comprising contacting cells expressing capsaicin receptor with at least one compound or salt thereof according to any one of claims 1-21, in an amount sufficient to detectably inhibit vanilloid ligand binding to cells expressing a cloned capsaicin receptor *in vitro*, and thereby inhibiting binding of vanilloid ligand to the capsaicin receptor in the patient.

33. A method according to claim 32, wherein the patient is a human.

15 34. A method for treating a condition responsive to capsaicin receptor modulation in a patient, comprising administering to the patient a therapeutically effective amount of at least one compound or salt thereof according to any one of claims 1-21, and thereby alleviating the condition in the patient.

20 35. A method according to claim 34, wherein the patient is suffering from (i) exposure to capsaicin, (ii) burn or irritation due to exposure to heat, (iii) burns or irritation due to exposure to light, (iv) burn, bronchoconstriction or irritation due to exposure to tear gas, infectious agents, air pollutants or pepper spray, or (v) burn or irritation due to exposure to acid.

36. A method according to claim 34, wherein the condition is asthma or chronic obstructive pulmonary disease.

25 37. A method for treating pain in a patient, comprising administering to a patient suffering from pain a therapeutically effective amount of at least one compound or salt thereof according to any one of claims 1-21, and thereby alleviating pain in the patient.

38. A method according to claim 37, wherein the patient is suffering from neuropathic pain.

39. A method according to claim 37, wherein the pain is associated with a condition selected from: postmastectomy pain syndrome, stump pain, phantom limb pain, oral neuropathic pain, toothache, postherpetic neuralgia, diabetic neuropathy, reflex sympathetic dystrophy, trigeminal neuralgia, osteoarthritis, rheumatoid arthritis, fibromyalgia, Guillain-Barre syndrome, meralgia paresthetica, burning-mouth syndrome, bilateral peripheral neuropathy, causalgia, neuritis, neuronitis, neuralgia, AIDS-related neuropathy, MS-related neuropathy, spinal cord injury-related pain, surgery-related pain, musculoskeletal pain, back pain, headache, migraine, angina, labor, hemorrhoids, dyspepsia, Charcot's pains, intestinal gas, menstruation, cancer, venom exposure, irritable bowel syndrome, inflammatory bowel disease and trauma.

10 40. A method according to claim 37, wherein the patient is a human.

41. A method for treating itch in a patient, comprising administering to a patient a therapeutically effective amount of a compound or salt thereof according to any one of claims 1-21, and thereby alleviating itch in the patient.

15 42. A method for treating cough or hiccup in a patient, comprising administering to a patient a therapeutically effective amount of a compound or salt thereof according to any one of claims 1-21, and thereby alleviating cough or hiccup in the patient.

20 43. A method for treating symptoms of menopause in a patient, comprising administering to a patient a therapeutically effective amount of a compound or salt thereof according to any one of claims 1-21, and thereby alleviating symptoms of menopause in the patient.

44. A method for treating urinary incontinence or overactive bladder in a patient, comprising administering to a patient a therapeutically effective amount of a compound or salt thereof according to any one of claims 1-21, and thereby alleviating urinary incontinence or overactive bladder in the patient.

25 45. A compound or salt thereof according to claim 1, wherein the compound is radiolabeled.

46. A method for determining the presence or absence of capsaicin receptor in a sample, comprising the steps of:

30 (a) contacting a sample with a compound or salt thereof according to any one of claims 1-21, under conditions that permit binding of the compound to capsaicin receptor; and

(b) detecting a signal indicative of a level of the compound or salt thereof bound to capsaicin receptor, and therefrom determining the presence or absence of capsaicin receptor in the sample.

47. A method according to claim 46, wherein the compound or salt thereof is
5 radiolabeled, and wherein the step of detection comprises the steps of:

- (i) separating unbound compound from bound compound; and
- (ii) detecting the presence or absence of bound radiolabel in the sample.

48. A packaged pharmaceutical preparation, comprising:

- (a) a pharmaceutical composition according to claim 22 in a container; and
- 10 (b) instructions for using the composition to treat pain.

49. A packaged pharmaceutical preparation, comprising:

- (a) a pharmaceutical composition according to claim 22 in a container; and
- (b) instructions for using the composition to treat cough or hiccup.

50. A packaged pharmaceutical preparation, comprising:

- 15 (a) a pharmaceutical composition according to claim 22 in a container; and
- (b) instructions for using the composition to treat urinary incontinence or overactive bladder.

51. The use of a compound or salt thereof according to any one of claims 1-21 for the
20 manufacture of a medicament for the treatment of a condition responsive to capsaicin receptor modulation.

52. A use according to claim 51, wherein the condition is pain; asthma; chronic
obstructive pulmonary disease; cough; hiccup; urinary incontinence; overactive bladder;
menopause; exposure to capsaicin; burn or irritation due to exposure to heat; burn or irritation
due to exposure to light; burn, bronchoconstriction or irritation due to exposure to tear gas,
25 infectious agents, air pollutants or pepper spray; or burn or irritation due to exposure to acid.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 08/07278

A. CLASSIFICATION OF SUBJECT MATTER
 IPC(8) - A01N 43/54; A61K 31/505 (2008.04)
 USPC - 514/269
 According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
 USPC: 514/269

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
 USPC: 514/49, 256, 258.1, 259.5 (see search terms below)

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
 PubWEST(USPT,PGPB,EPAB,JPAB); GoogleScholar
 Search pyrimidinone, vanilloid receptor, VR1 receptor, pain

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO2006/122200 A1 (BROWN et al.) 16 November 2006 (16.11.2006) pg 2, ln 10-15; pg 3, ln 7-30	1-6, 19 and 45
Y	US 5,100,897 A (ALLEN et al.) 31 March 1992 (31.03.1992) col 5, ln 10-15, ln 20-25	1-6, 19 and 45
Y	US 2004/0259887 A1 (DOW) 23 December 2004 (23.12.2004) para [0292]	45

Further documents are listed in the continuation of Box C.

* Special categories of cited documents:

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

Date of the actual completion of the international search
 24 September 2008 (24.09.2008)

Date of mailing of the international search report

15 OCT 2008

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INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 08/07278

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

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

1. Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. Claims Nos.: 7-18, 20-44 and 46-52
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

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

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

1. As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.
3. As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

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