US 20090275649A1

(19) **United States**

(12) **Patent Application Publication**

Qin et al.

(10) **Pub. No.: US 2009/0275649 A1**

(43) **Pub. Date: Nov. 5, 2009**

(54) **COMPOSITIONS AND METHODS FOR IDENTIFYING MODULARS OF TRPV2**

(76) Inventors: **Ning Qin**, Blue Bell, PA (US); **Yi Liu**, Jenkintown, PA (US); **Christopher M. Flores**, Lansdale, PA (US); **Tasha Hutchinson**, Green Lane, PA (US); **Michael P. Neeper**, Collegeville, PA (US)

Correspondence Address:
PHILIP S. JOHNSON
JOHNSON & JOHNSON
ONE JOHNSON & JOHNSON PLAZA
NEW BRUNSWICK, NJ 08933-7003 (US)

(21) Appl. No.: **12/499,891**

(22) Filed: **Jul. 9, 2009**

Related U.S. Application Data

(62) Division of application No. 11/589,340, filed on Oct. 30, 2006, now Pat. No. 7,575,882.

(60) Provisional application No. 60/731,686, filed on Oct. 31, 2005, provisional application No. 60/782,656, filed on Mar. 15, 2006.

Publication Classification

(51) **Int. Cl.**

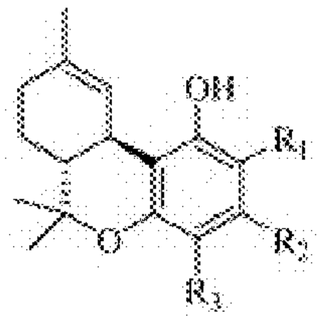
A61K 31/352	(2006.01)
G01N 33/53	(2006.01)
C12Q 1/02	(2006.01)
C12P 21/02	(2006.01)
C12N 5/10	(2006.01)
C12N 1/21	(2006.01)
C12N 1/15	(2006.01)
C12N 15/63	(2006.01)
A61K 31/192	(2006.01)
A61K 31/05	(2006.01)
C07K 14/00	(2006.01)
C07H 21/00	(2006.01)

(52) **U.S. Cl.** **514/454**; 435/7.21; 435/29; 435/69.1; 435/325; 435/252.3; 435/254.11; 435/320.1; 514/568; 514/729; 530/350; 536/23.1

(57) **ABSTRACT**

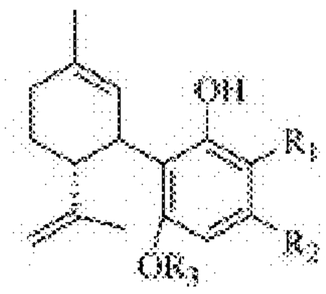
It has now been discovered that certain cannabinoids specifically activate TRPV2 channel activity. Based on the discovery, novel compositions and methods for screening, identifying and characterizing compounds that increase or decrease the biological activity of a TRPV2.

Figure 1



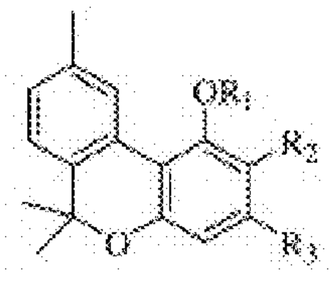
Δ^9-Tetrahydrocannabinols (THCs)

R_1 or R_2 = H or COOH
R_3 = C_1, C_3, C_4, C_5 side chain



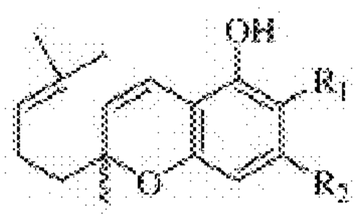
Cannabidiols (CBDs)

R_1 = H or COOH
R_2 = C_1, C_3, C_4, C_5 side chain
R_3 = H or CH_3



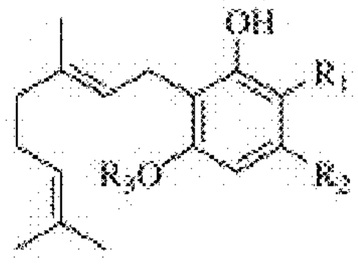
Cannabinols (CBNs)

R_1 = H or CH_3
R_2 = H or COOH
R_3 = C_1, C_3, C_8, C_5 side chain



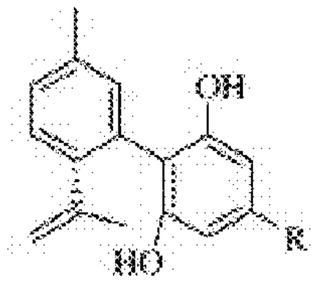
Cannabichromenes (CBCs)

R_1 = H or COOH
R_2 = C_3, C_5 side chain



Cannabigerols (CBGs)

R_1 = H or COOH
R_2 = C_3, C_5
R_3 = H, CH_3



Cannabinodiols (CBNDs)

R = C_3, C_5 side chain

Figure 2

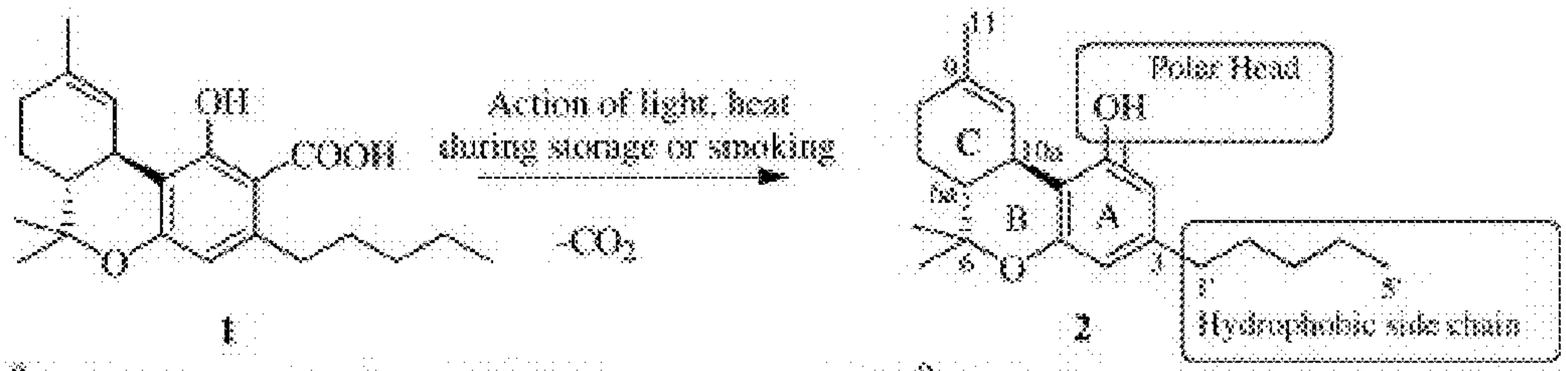
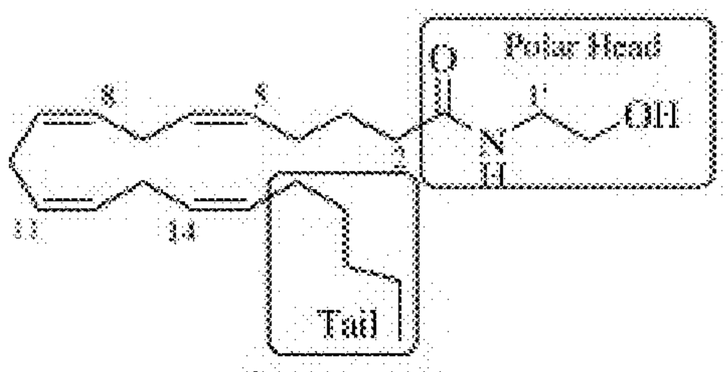
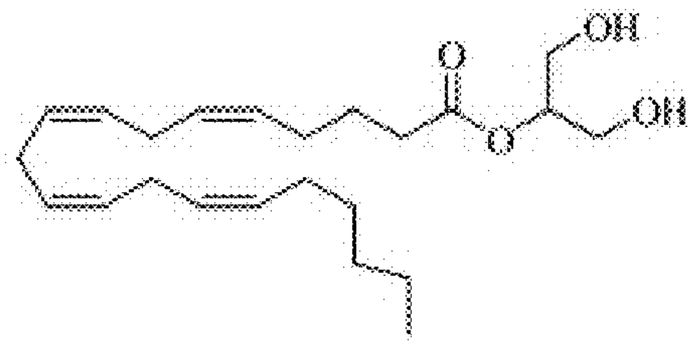

OH
COOH
O
Action of light, heat
during storage or smoking
-CO2
1
(-)-Δ9-Tetrahydrocannabinolic acid (THCA)
11
9
Polar Head
OH
C
10a
8a
B
A
6
O
3
1'
5'
Hydrophobic side chain
2
(-)-Δ9-Tetrahydrocannabinol (THC)

Figure 3



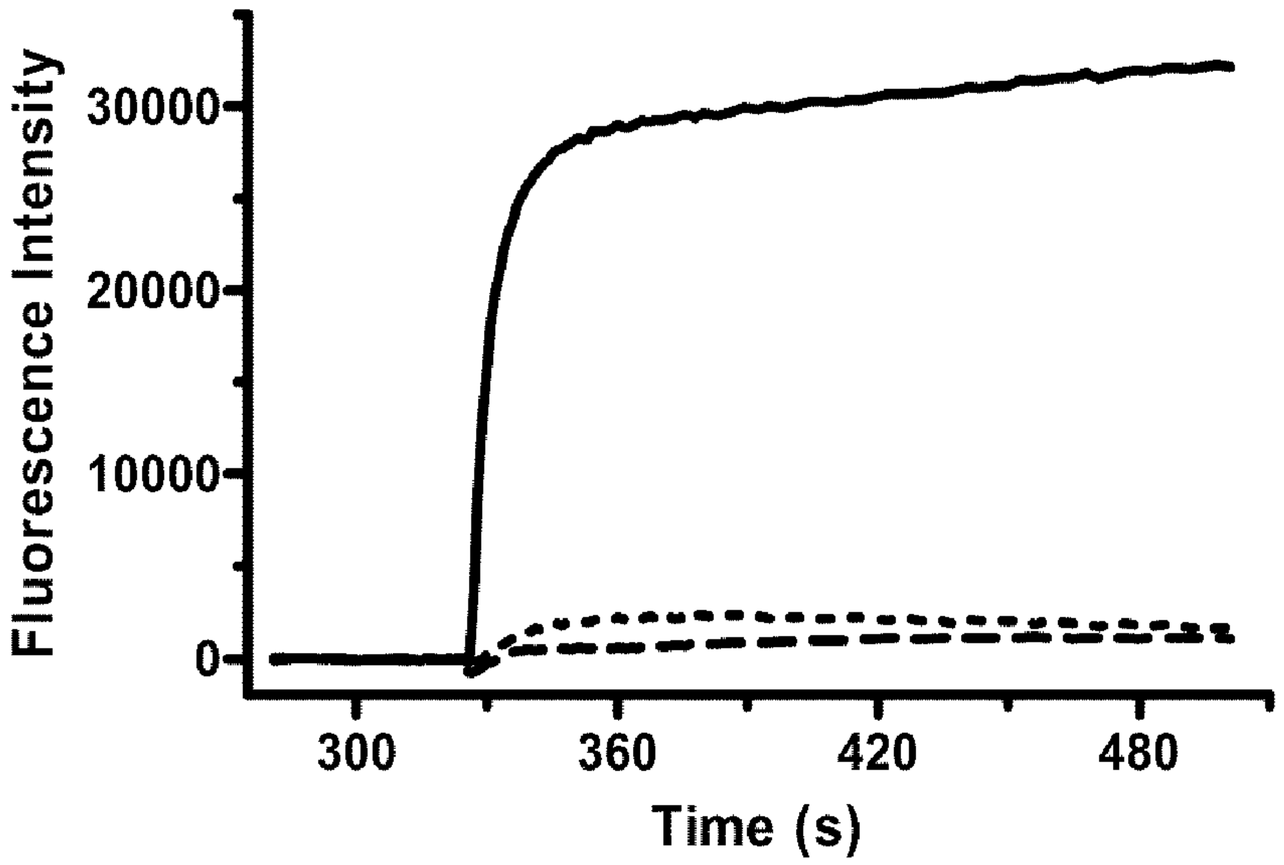
3
Anandamide (AEA)
K_i = 61 nM (CB1)
= 1930 nM (CB2)



4
2-Arachidonoylglycerol (2-AG)
K_i = 472 nM (CB1)
= 1400 nM (CB2)

Figure 4

A.


Fluorescence Intensity
30000
20000
10000
0
300
360
420
480
Time (s)

B.

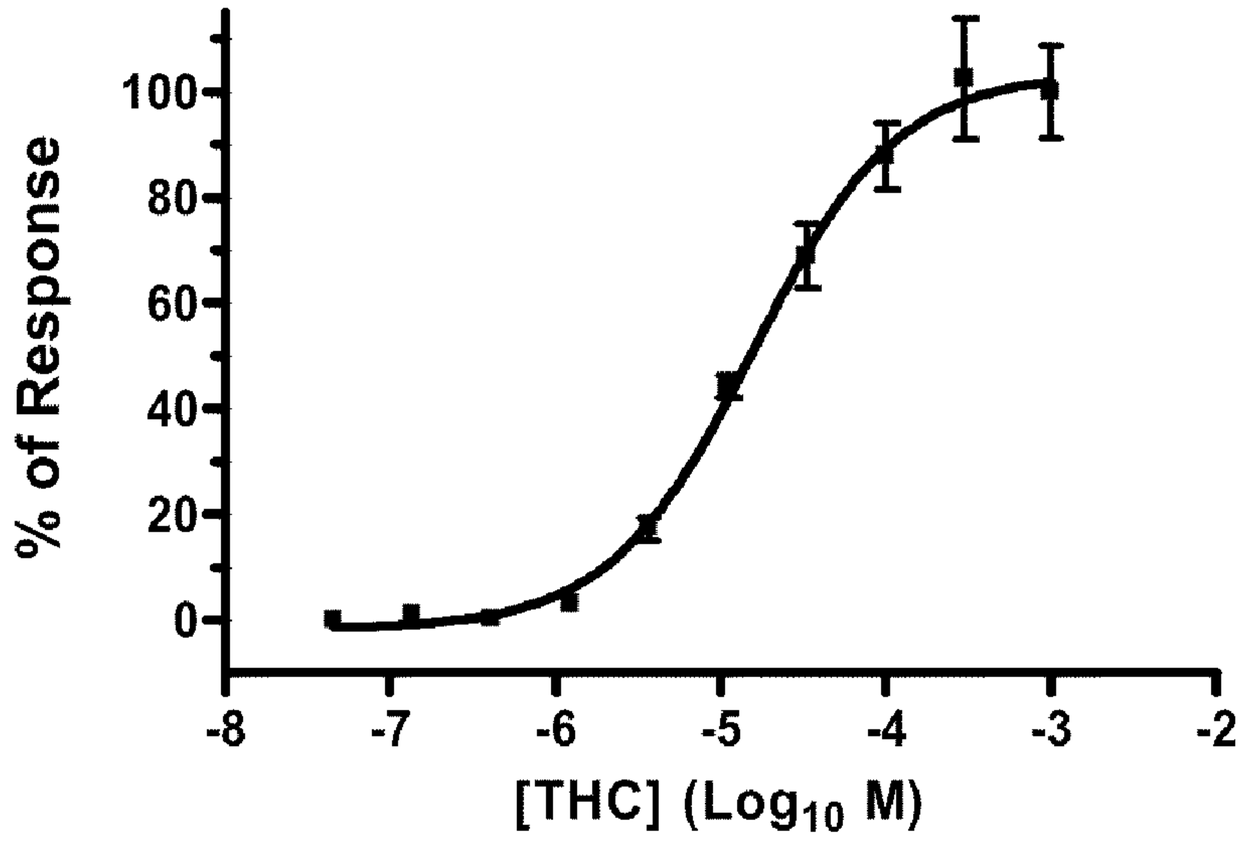
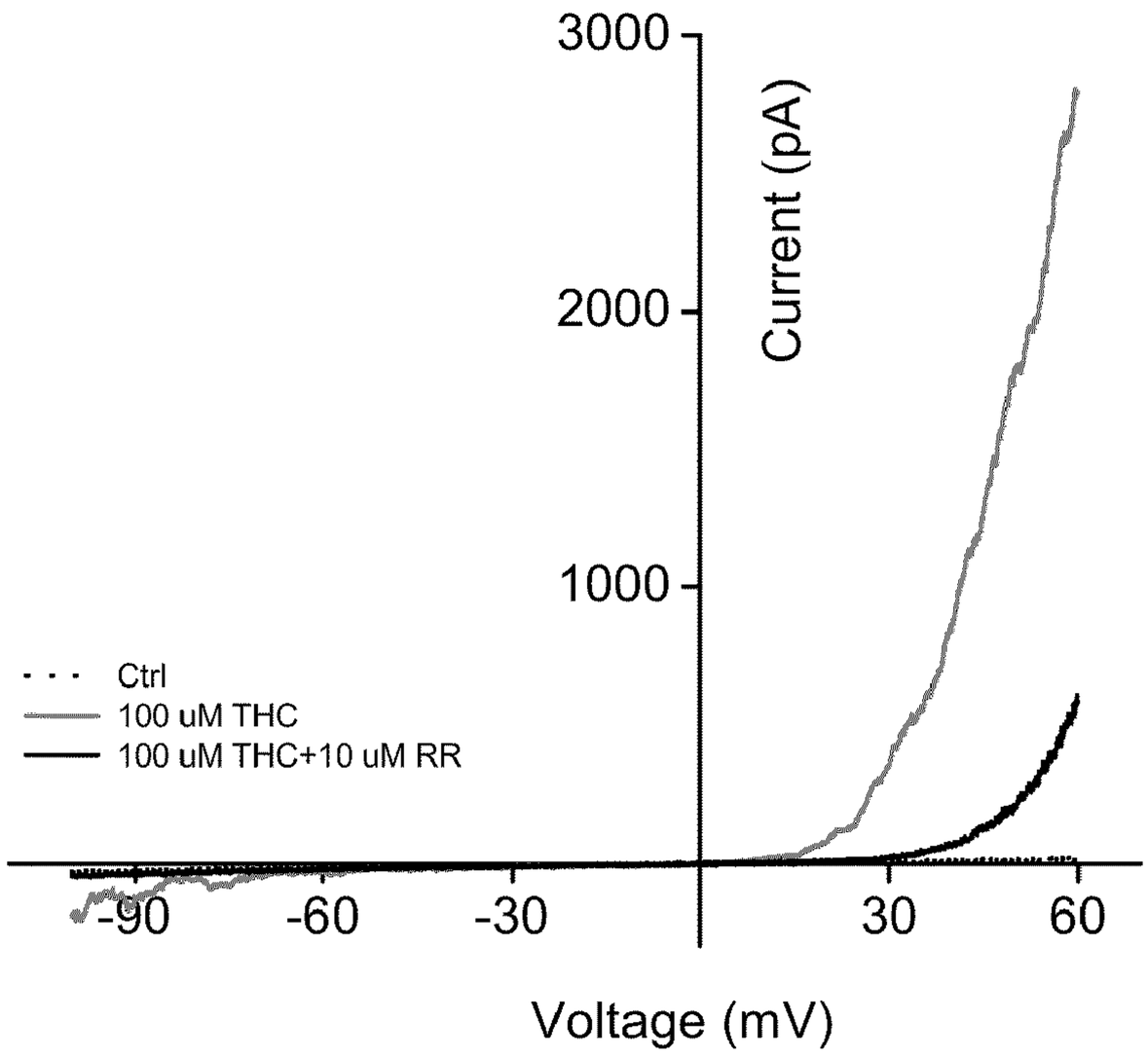

% of Response
100
80
60
40
20
0
-8
-7
-6
-5
-4
-3
-2
[THC] (Log10 M)

Figure 5

A.


3000
2000
1000
Current (pA)
Ctrl
100 uM THC
100 uM THC+10 uM RR
-90
-60
-30
30
60
Voltage (mV)

B.

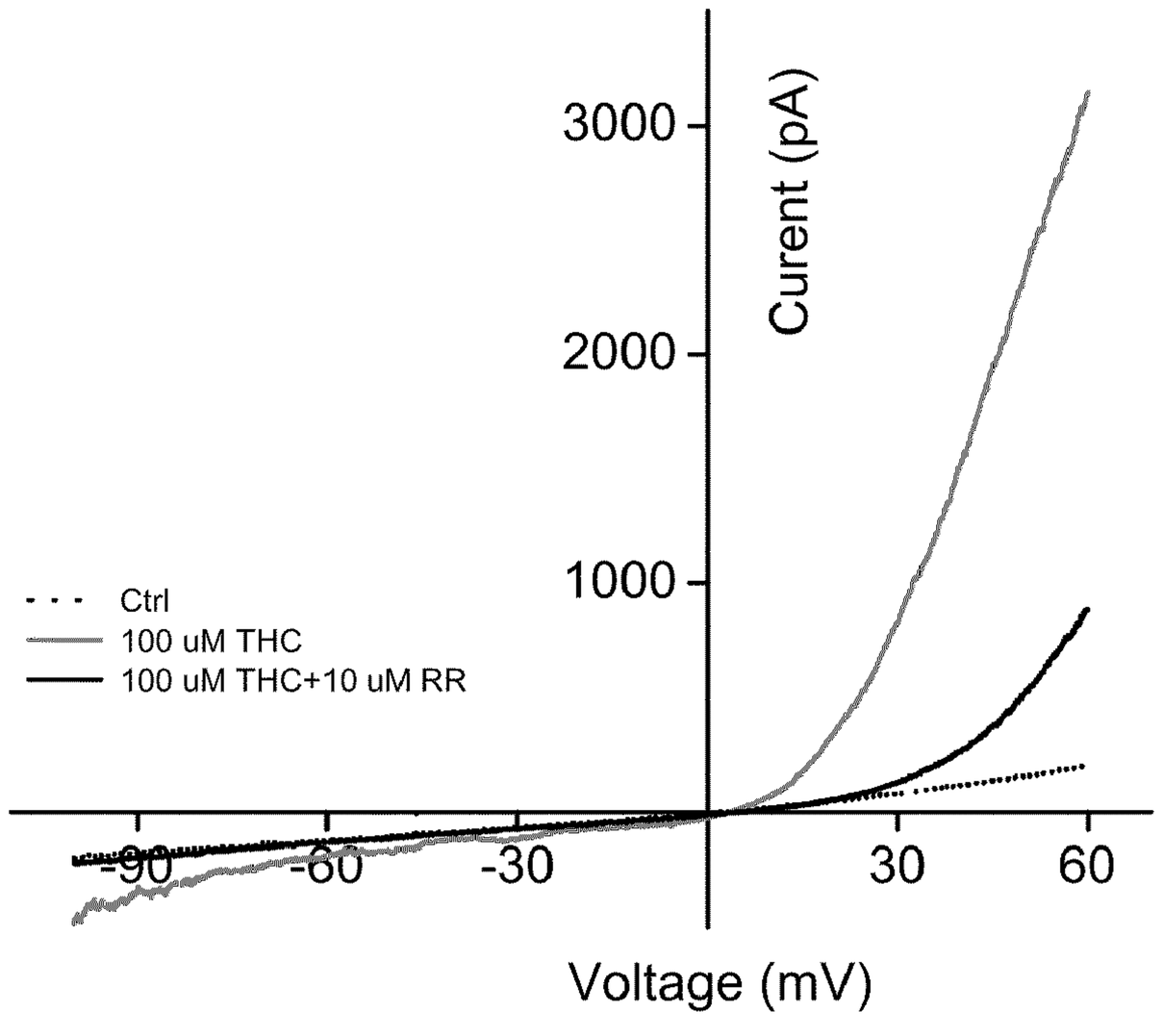
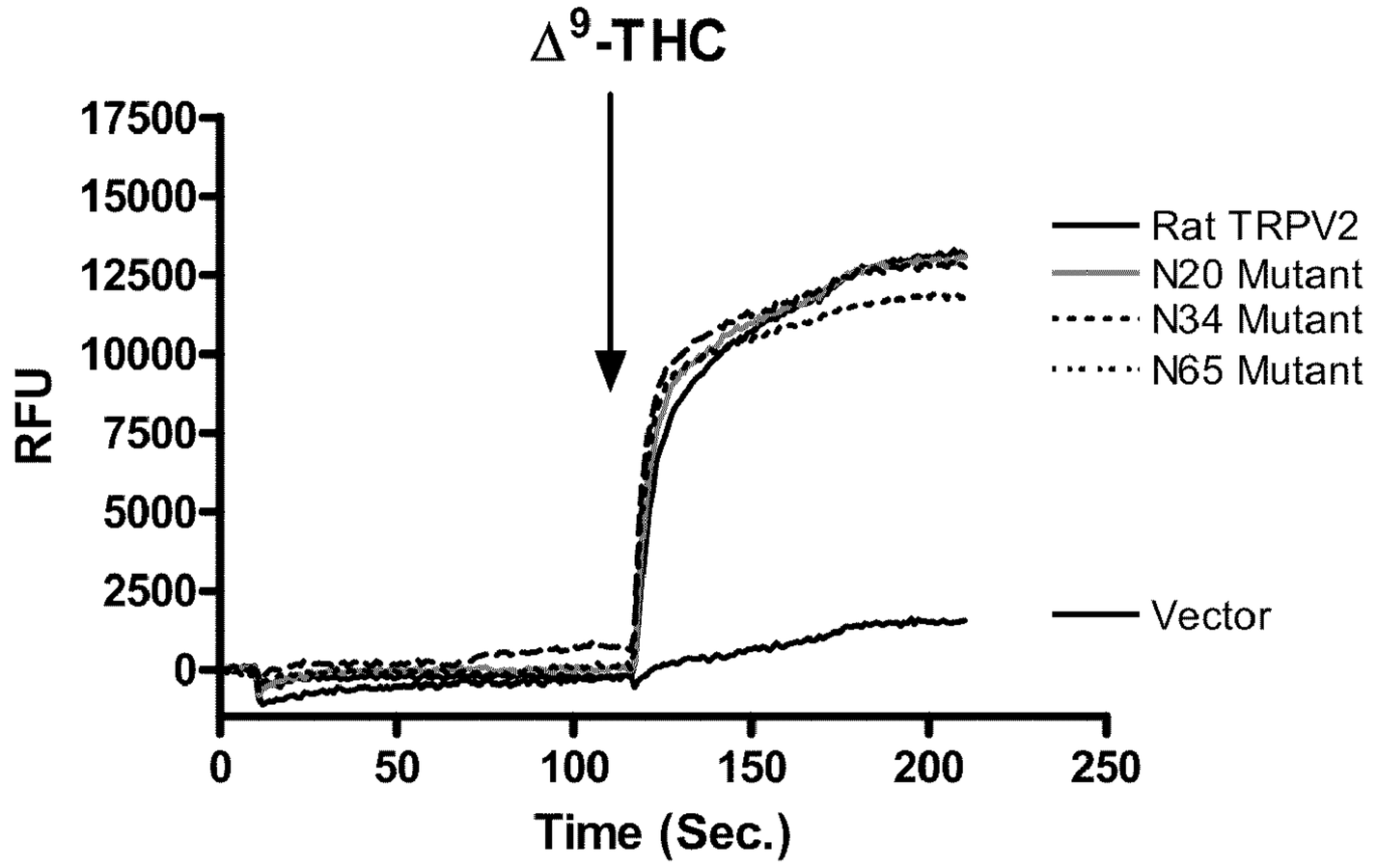

3000
2000
1000
Curent (pA)
Ctrl
100 uM THC
100 uM THC+10 uM RR
-90
-60
-30
30
60
Voltage (mV)

Figure 6

A.


Δ9-THC
17500
15000
12500
10000
7500
5000
2500
0
RFU
0
50
100
150
200
250
Time (Sec.)
Rat TRPV2
N20 Mutant
N34 Mutant
N65 Mutant
Vector

B.

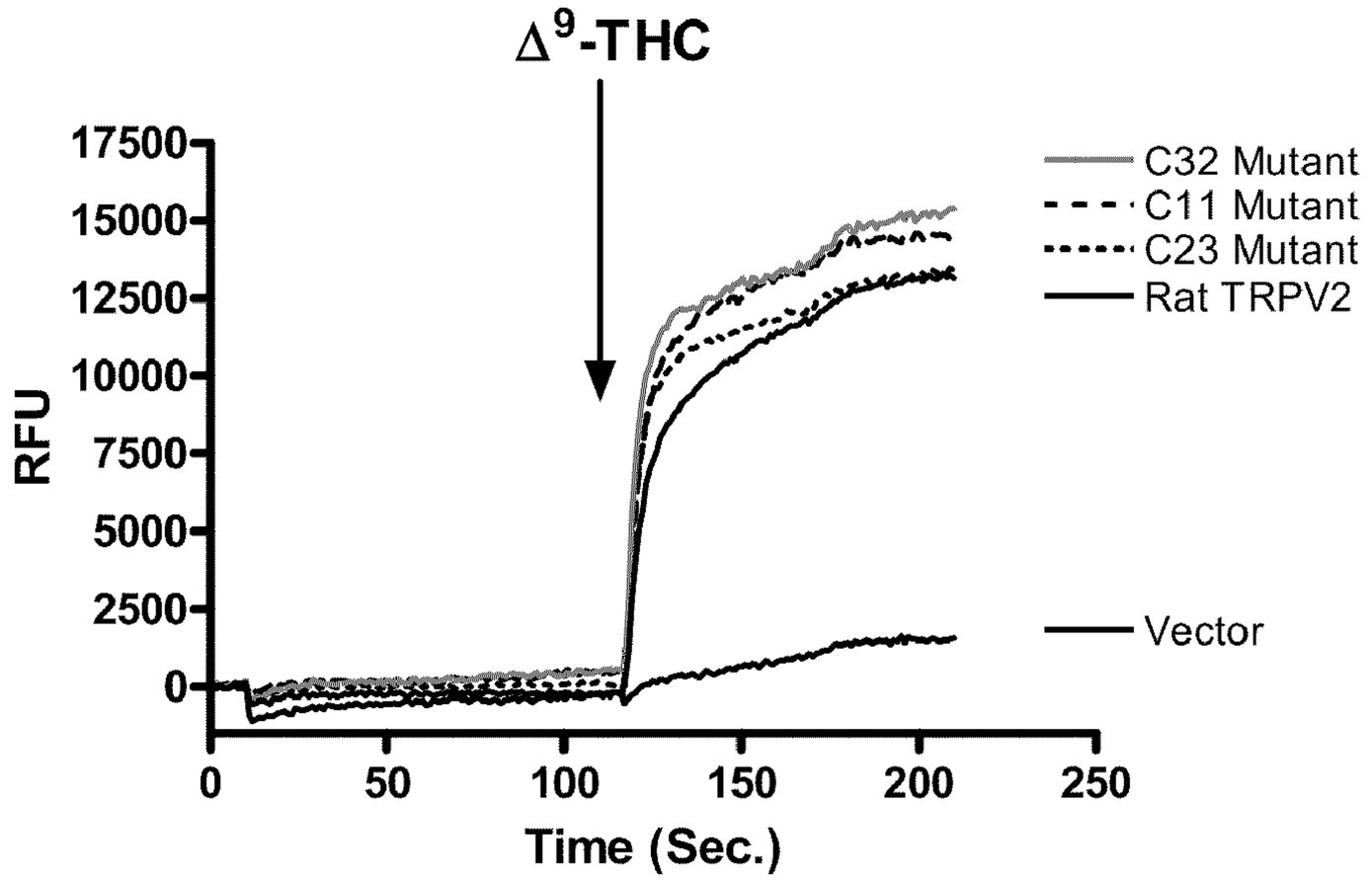
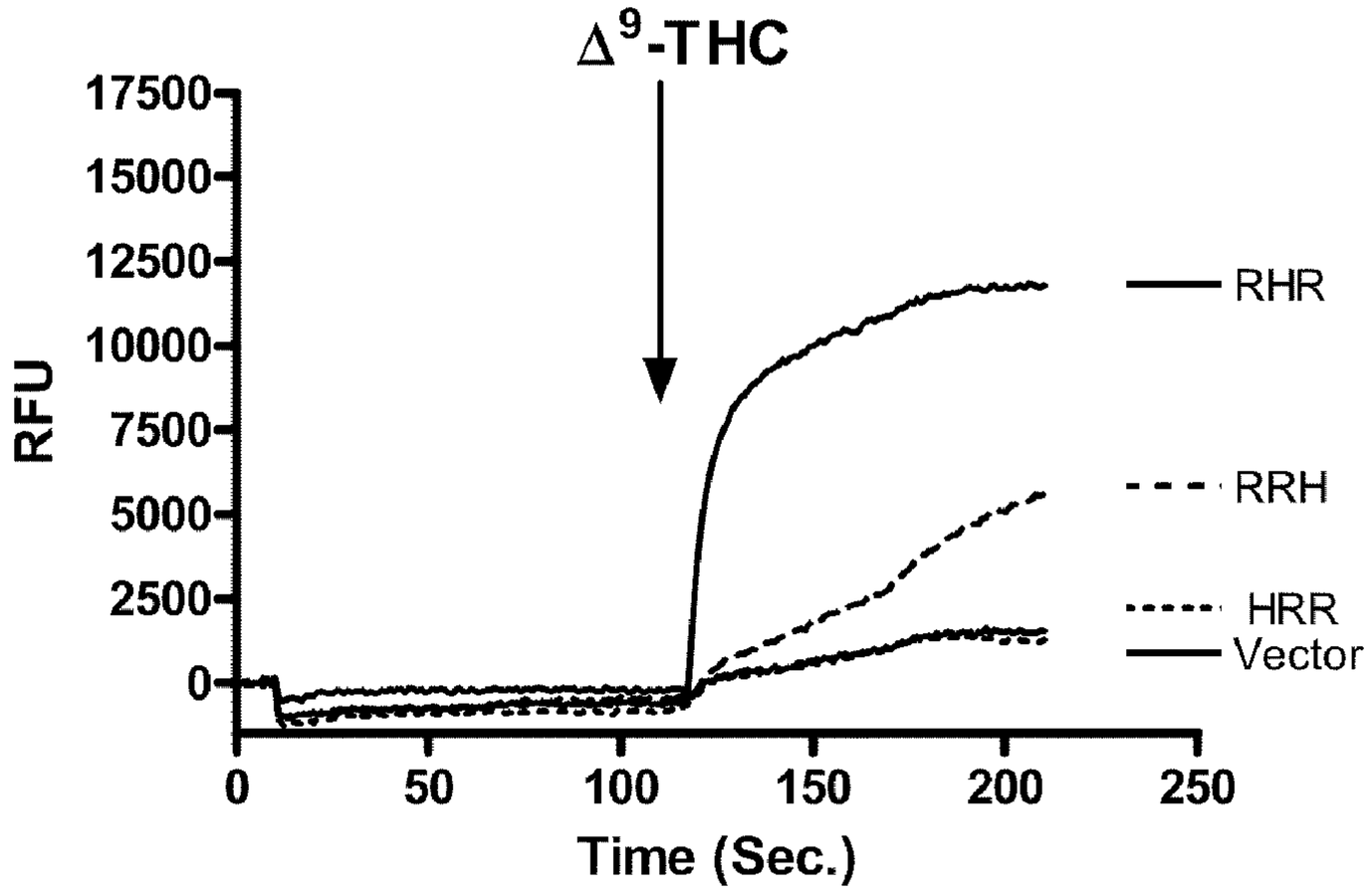
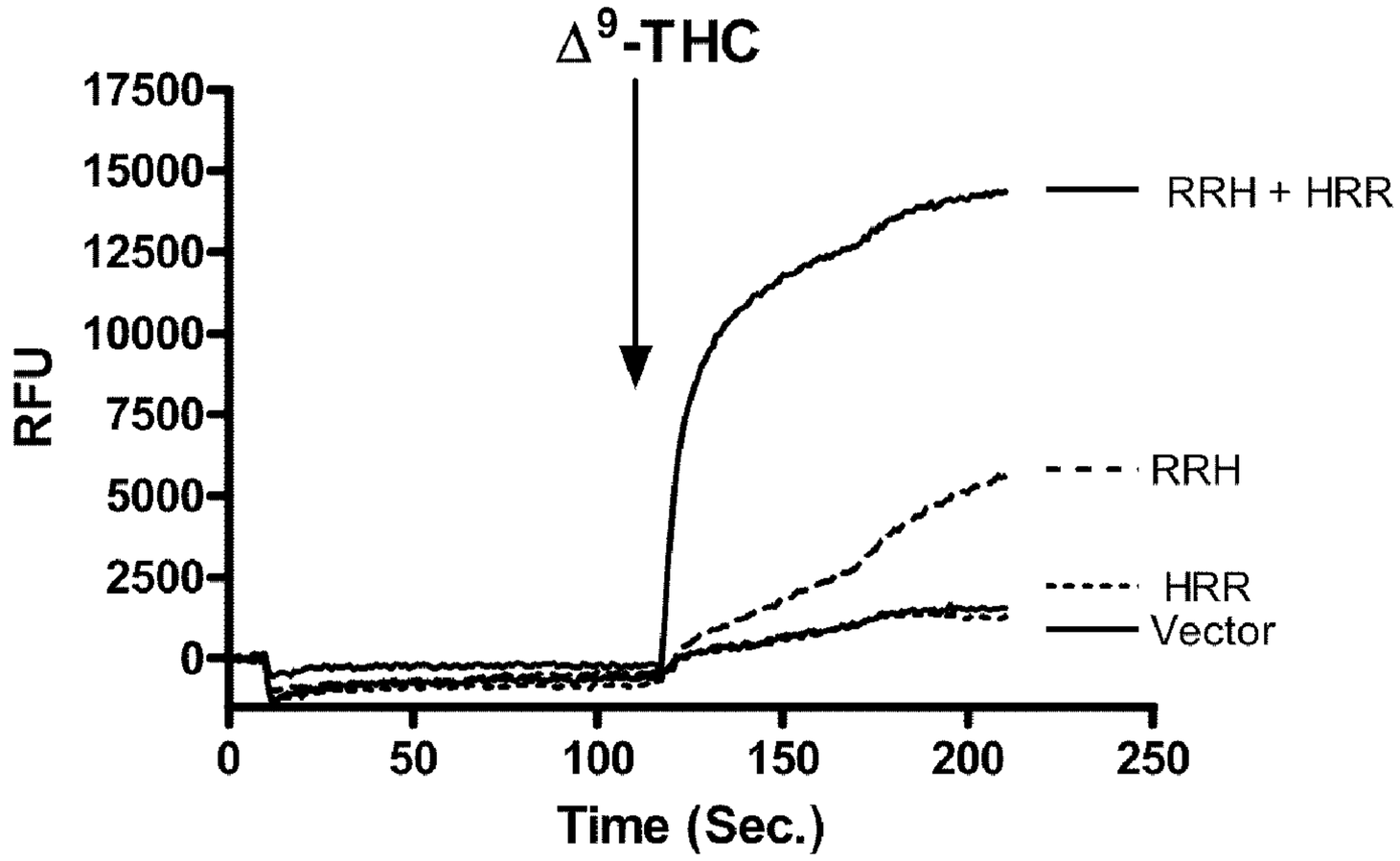

Δ9-THC
17500
15000
12500
10000
7500
5000
2500
0
RFU
0
50
100
150
200
250
Time (Sec.)
C32 Mutant
C11 Mutant
C23 Mutant
Rat TRPV2
Vector

Figure 7

A.


Δ9-THC
17500
15000
12500
10000
7500
5000
2500
0
RFU
0
50
100
150
200
250
Time (Sec.)
RHR
RRH
HRR
Vector

B.


Δ9-THC
17500
15000
12500
10000
7500
5000
2500
0
RFU
0
50
100
150
200
250
Time (Sec.)
RRH + HRR
RRH
HRR
Vector

COMPOSITIONS AND METHODS FOR IDENTIFYING MODULARS OF TRPV2

CROSS REFERENCE TO RELATED APPLICATIONS

[0001] This application claims priority to Application No. 60/731,686 filed on Oct. 31, 2005 and Application No. 60/782,656 filed on Mar. 15, 2006, the entire contents of which are incorporated by reference herein.

FIELD OF THE INVENTION

[0002] The present invention relates to the regulation of thermal receptor ion channel proteins. In particular, the present invention relates to compositions and methods for screening, identifying and characterizing compounds that increase or decrease the biological activity of a TRPV2.

BACKGROUND

[0003] In mammals, the sensation of pain triggered by thermal, mechanical or chemical stimuli is a useful warning and protective system. Considerable efforts have been put into elucidating the biochemical mechanisms involved in the detection, transduction and transmission of hot and cold sensations in neuronal tissues. Thermal stimuli activate specialized receptors located on sensory neurons, such as those deriving from the dorsal root ganglion (DRG) and the trigeminal ganglion (TG). When these stimuli are in the noxious range (i.e., very hot or cold), they activate a certain subset of thermal receptors on a sub-population of sensory neurons called nociceptors (pain-sensing neurons). Upon activation, the thermal receptors (e.g., ion channels) transduce the noxious stimulus into an electrical signal that is propagated along the sensory neuron to the spinal cord, where it is relayed to the brain, ultimately leading to the perception of pain. Accordingly, these thermal receptors represent highly promising targets for developing drugs for the treatment of various painful conditions.

[0004] Several temperature-activated receptors have been identified with wide ranging temperature sensitivities from noxious heat to noxious cold. These temperature-activated receptors belong to the transient receptor potential (TRP) family of non-selective cation channels, which in *C. elegans* and *D. melanogaster* are involved in mechano- and osmoregulation. Several of these temperature-activated receptors, including TRPV1 and TRPV2, are implicated in noxious heat sensation (Caterina et al., 1997, *Nature,* 389: 816; and Caterina et al., 1999, *Nature* 398: 436). TRPV1, the most extensively characterized member of the thermo-TRP family, is activated by moderate heat (~43° C.), capsaicin, protons and certain endocannabinoids, such as anandamide and 2-AG. It is well accepted that TRPV1 contributes to acute thermal nociception and hyperalgesia after injury (Clapham, Nature. 2003, 426(6966): 517-24).

[0005] TRPV2, also termed VRL-1, has been proposed as a sensor of noxious temperatures (>52° C.), which presumably mediates "first" pain, i.e. the rapid, acute, and sharp pain evoked by noxious stimuli (Caterina et al., 1999, supra; Story et al., *Cell,* 2003, 112:819-829, and references therein). TRPV2 is structurally most closely related to TRPV1 (~50% sequence identity at the protein level). TRPV2 is expressed in medium- to large-diameter neurons of sensory ganglia, as well as at lower levels in brain, spinal cord, spleen and lung. Furthermore, TRPV2 is upregulated in sympathetic postganglionic neurons following injury, suggesting a potential role for TRPV2 in sympathetically mediated pain (Gaudet et al., *Brain Res.* 2004, 1017(1-2):155-62). Thus, modulation of TRPV2 may potentially have many therapeutic applications.

[0006] Despite great interest in TRPV2 modulation, a system for screening, identifying and characterizing TRPV2 modulators has yet to be developed. This is in part due to the lack of known, and in particular, selective TRPV2 agonists, as well as the technical difficulty of assaying these channels in a high temperature environment. In general, TRPV2 does not respond to known TRPV1 agonists (Benham et al., 2003, *Cell Calcium* 33:479-487). However, a recent study reported that 2-aminoethoxydiphenyl borate (2-APB), a non-selective TRP modulator, was able to activate TRPV1, TRPV2, and TRPV3 (Hu et al (2004), *J. Biol. Chem.,* 279: 35741-8), although TRPV2 activation by 2-APB was not observed by others (Chung et al. (2004), *J Neurosci.* 24: 5177-82).

[0007] In an effort to overcome the above-mentioned challenges, the present invention provides novel compositions and methods for screening, identifying and characterizing TRPV2 agonists.

SUMMARY

[0008] It has now been discovered that certain cannabinoids specifically activate TRPV2 channel activity.

[0009] In one general aspect, the present invention provides a method for identifying a compound that decreases the biological activity of TRPV2, comprising the steps of: a) contacting a TRPV2 polypeptide with a cannabinoid that is capable of activating TRPV2 activity under a condition in which the TRPV2 is activated by the cannabinoid; b) contacting the TRPV2 polypeptide with a test compound; c) measuring the biological activity of the TRPV2 in the presence of both the cannabinoid and the test compound; d) repeating step a); e) measuring the biological activity of the TRPV2 in the presence of the cannabinoid but not the test compound; and f) comparing the TRPV2 activity measured from step c) with that from step e); thereby identifying the compound that decreases the biological activity of TRPV2 when the TRPV2 activity measured from step c) is less than that from step e).

[0010] In another general aspect, the present invention provides a method for identifying a compound that increases the biological activity of TRPV2, comprising the steps of: a) obtaining atomic coordinates defining a three-dimensional structure of a complex comprising a TRPV2 interacting with a cannabinoid that is capable of activating the TRPV2; b) elucidating a structural relationship between the TRPV2 and the interacting cannabinoid; c) designing a structural analog of the cannabinoid based on the structural relationship; d) synthesizing the structural analog; and e) determining the extent to which the structural analog alters the biological activity of the TRPV2, thereby identifying the compound that increases the biological activity of TRPV2.

[0011] Another general aspect of the present invention is a method for increasing the biological activity of a TRPV2, comprising the step of contacting the TRPV2 with a cannabinoid that is capable of activating the TRPV2 activity.

[0012] The present invention further provides a method for stimulating noxious thermo-sensation in a subject, comprising administering to the subject a pharmaceutical composition comprising an effective amount of a cannabinoid that is capable of activating the TRPV2 activity, thereby stimulating the noxious thermo-sensation in the subject.

[0013] Other aspects, features and advantages of the invention will be apparent from the following disclosure, including the detailed description of the invention and its preferred embodiments and the appended claims.

DESCRIPTION OF THE FIGURES

[0014] FIG. **1** shows the subclasses of cannabinoids present in *Cannabis* (Thakur et al., *Life Sci.* 2005 Oct. 17, Epub ahead of print).

[0015] FIG. **2** shows non-enzymatic formation of Δ^9-THC from its precursor (Thakur et al., supra).

[0016] FIG. **3** shows the structures of two representative endocannabinoid (Thakur et al., supra).

[0017] FIG. **4** shows concentration-dependent activation of rat TRPV2 by Δ^9-THC in a FLIPR assay.

[0018] FIG. **5** illustrates activation of both rat and human TRPV2 by Δ^9-THC and subsequent block of the Δ^9-THC-activated currents by ruthenium red from whole-cell patch clamp studies.

[0019] FIG. **6** shows Δ^9-THC activated deletion mutants of TRPV2 recombinantly expressed from HEK293 cells: (A) the N-terminal deletion mutants; and (B) the C-terminal deletion mutants.

[0020] FIG. **7** illustrates the activation of the human and rat TRPV2 chimera recombinantly expressed from HEK293 cells: (A) the chimera was expressed individually from the cells; and (B) the complementary effect of RRH and HRR when they were co-expressed from the cells.

DETAILED DESCRIPTION

[0021] All publications cited herein are hereby incorporated by reference. Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood to one of ordinary skill in the art to which this invention pertains.

[0022] As used herein, the terms "comprising", "containing", "having" and "including" are used in their open, non-limiting sense.

[0023] The following are abbreviations that are at times used in this specification:

[0024] 2-AG=2-arachidonylglycerol

[0025] AEA=anandamide=N-arachidonoylethanolamine

[0026] bp=base pair

[0027] cDNA=complementary DNA

[0028] Ca^{2+}=calcium

[0029] Δ^9-THC=Delta-9-tetrahydrocannabinol

[0030] DRG=dorsal root ganglion

[0031] FLIPR=fluorescence imaging plate reader

[0032] kb=kilobase; 1000 base pairs

[0033] PAGE=polyacrylamide gel electrophoresis

[0034] PCR=polymerase chain reaction

[0035] SDS=sodium dodecyl sulfate

[0036] TG=trigeminal ganglion

[0037] TRPV2=transient receptor potential cation channel, subfamily V, member 2

[0038] As used herein, the term "biological activity of a TRPV2" refers to an activity exerted by the TRPV2 protein as determined in vivo or in vitro, according to standard techniques. Such an activity can be a direct activity such as the ability of a TRPV2 to bind to a ligand, such as a cannabinoid or an analog thereof. The activity can be the conductivity of an ion channel formed by the TRPV2. The activity can also be functional changes of cell physiology, such as calcium mobilization or nociceptive response of the cell. The biological activity of a TRPV2 can be an indirect activity, such as a signal transduction activity mediated by TRPV2 via its interaction with one or more than one additional protein or other molecule(s).

[0039] "Binding affinity" refers to the ability of two or more molecular entities to bind or interact with each other. The binding can be from the formation of one or more chemical bonds that results in continual and stable proximity of the two interacting entities. The binding can also be based solely on physical affinities, which can be equally effective in co-localizing the two interacting entities. Examples of physical affinities and chemical bonds include but are not limited to, forces caused by electrical charge differences, hydrophobicity, hydrogen bonds, van der Waals force, ionic force, covalent linkages, and combinations thereof. The state of proximity between the interacting entities can be transient or permanent, reversible or irreversible. In any event, it is in contrast to and distinguishable from contact caused by natural random movement of two entities.

[0040] "Cannabinoid" includes any of various compounds that activate a cannabinoid receptor or a structural analog of the compounds.

[0041] In one embodiment, "cannabinoid" includes herbal cannabinoids, a class of compounds that were originally extracted from the plant *Cannabis* sativa L or a metabolite thereof. *Cannabis* sativa L. is one of the oldest known medicinal plants and has been extensively studied with respect to its phytochemistry. The plant biosynthesizes a total of 483 identified chemical entities belonging to different chemical classes (ElSohly, 2002, In: F. Grotenhermen and E. Russo, Editors, *Cannabis and Cannabinoids*, Haworth Press, Binghamton (2002), pp. 27-36.), of which the cannabinoids are the most distinctive class of compounds, known to exist only in this plant. There are 66 known plant-derived cannabinoids (Thakur et al., *Life Sci.* 2005 Oct. 17, Epub ahead of print). The most prevalent of which are the tetrahydrocannabinols (THCs), the cannabidiols (CBDs), and the cannabinols (CBNs). The next most abundant cannabinoids are the cannabigerols (CBGs), the cannabichromenes (CBCs), and cannabinodiols (CBNDs).

[0042] FIG. **1** shows the representative structures of subclasses of cannabinoids present in *Cannabis* sativa. Most cannabinoids contain 21 carbon atoms, but there are some variations in the length of the C-3 side chain attached to the aromatic ring. In the most common homologues, the n-pentyl side chain is replaced with an n-propyl (De Zeeuw et al., *Science.* 1972, 175:778-779); and Vree et al., *Journal of Pharmacy and Pharmacology.* 1972, 24:7-12). These analogues are named using the suffix "varin" and are designated as THCV, CBDV, or CBNV, as examples. Cannabinoids with one (Vree et al., 1972, supra) and four (Smith, 1997, *Journal of Forensic Sciences* 42 (1997), pp. 610-618) carbons also exist but are minor components. Classical cannabinoids (CCs) are ABC tricyclic terpenoid compounds bearing a benzopyran moiety and are insoluble in water but soluble in lipids, alcohols, and other non-polar organic solvents (Thakur et al., 2005, supra). These phenolic derivatives are more water-soluble as their phenolate salts formed under strong alkaline conditions.

[0043] One particular example of "cannabinoid" is Delta-9-tetrahydrocannabinol (Delta-9-THC, Δ^9-THC), the key psychoactive ingredient of *cannabis* (marijuana) (Gaoni and Mechoulam 1964, *Journal of the American Chemical Society*

86 (1964), pp. 1646-1647). As illustrated in FIG. **2**, Δ^9-THC is formed by the decarboxylation of its non-psychoactive precursor Δ^9-THCA by the action of light or heat during storage or smoking or under alkaline conditions. Δ^9-THCA is biosynthesized by a well-established pathway involving the action of several specific enzymes.

[0044] It was discovered that Δ^9-THC interacts with the two known cannabinoid (CB) receptors, CB1 (Devane et al., 1988, *Molecular Pharmacology* 34 (1988), pp. 605-613; Gerard et al., 1990, *Nucleic Acids Research* 18 (1990), p. 7142; Gerard et al., 1991, *Biochemical Journal* 279 (1991), pp. 129-134; and Matsuda et al., 1990, *Nature* 346 (1990), pp. 561-564.) and CB2 (Munro et al., 1993, *Nature* 365 (1993), pp. 61-65). Both cannabinoid receptors belong to the super family of G-protein coupled receptors, and produce a broad spectrum of physiological effects (Grotenhermen, 2002, In: R. Grotenhermen and E. Russo, Editors, *Cannabis and Cannabinoids*, Haworth Press, Binghamton (2002), pp. 123-142) including antiemetic, appetite enhancing, analgesic, and lowering of intraocular pressure. The discovery of specific cannabinoid receptors inside animal ultimately led to the search and identification of endocannabinoid.

[0045] Thus, the term "cannabinoid" also includes endocannabinoid. The term "endocannabinoid" refers to a ligand to a cannabinoid receptor, wherein said ligand is endogenously produced by in the bodies of an animal. Exemplary endocannabinoids include, but are not limited to, N-arachidonoylethanolamine (AEA, anandamide) and 2-arachidonylglycerol (2-AG), the structures of which are shown in FIG. **3**. Anandamide was shown to bind to the CB1 receptor with modest affinity (K_i=61 nM), have low affinity for the CB2 receptor (K_i=1930 nM) (Lin et al., 1998, *Journal of Medicinal Chemistry* 41 (1998), pp. 5353-5361), and behave as a partial agonist in the biochemical and pharmacological tests used to characterize cannabinoid activity. It was reported that anandamide can also bind to and activate TRPV1 (Di Marzo et al., *Prostaglandins Leukot Essent Fatty Acids* 2002; 66: 377-91). 2-AG binds weakly to both CB1 (K_i=472 nM) and CB2 (K_i=1400 nM) receptors (Mechoulam et al., 1995, *Biochemical Pharmacology* 50 (1995), pp. 83-90). 2-AG was isolated from intestinal and brain tissues and is present in the brain at concentrations approximately 170-fold higher than AEA (3) (Stella et al., 1997, *Nature* 388 (1997), pp. 773-778).

[0046] In yet another embodiment, the term "cannabinoid" covers the synthetic cannabinoids are produced by chemical synthesis and do not occur naturally. The synthetic cannabinoids can be synthesized based on the structure of herbal cannabinoids or endocannabinoid. Synthetic cannabinoids are particularly useful in experiments to determine the relationship between the structure and activity of cannabinoid compounds, by making systematic, incremental modifications of cannabinoid molecule. Exemplary synthetic cannabinoids includes dronabinol (synthetic THC), nabilone, and any other synthetic compounds that activate a cannabinoid receptor or a structural analog of the compounds.

[0047] A "cannabinoid that is capable of activating the TRPV2 activity" refers to any cannabinoid that is capable of binding to a TRPV2 channel and, in the absence of other stimulation, exhibits at least a 10% increase in the conductivity of the TRPV2 channel compared to the baseline. A person skilled in the art can experimentally determine whether a cannabinoid is capable of activating the TRPV2 activity. In some embodiments, "cannabinoid that is capable of activating the TRPV2 activity" is a cannabinoid which, upon binding to a TRPV2 channel, results in at least a 15%, 20%, 25%, 30%, 35%, 40%, 45%, or 50% increase in the conductivity of the channel compared to the baseline. "Cannabinoid that is capable of activating the TRPV2 activity" includes, but is not limited to, Δ^9-tetrahydrocannabinol, cannabinol, cannabidiol nabilone, CP55940, HU210, and 2-AG. Interestingly, the other endocannabinoid tested, anandamide, showed no or minimal activation effect on TRPV2 (Table 2, Example 4 infra).

[0048] A "cannabinoid receptor" or a "CB receptor" each refers to a protein that functions as a specific receptor for a cannabinoid. The "CB receptor" can be a CB1 receptor or a CB2 receptor.

[0049] The CB1 receptor has been detected primarily in brain, specifically in the basal ganglia and in the limbic system, including the hippocampus. They are also found in other tissues such as the cerebellum and in both male and female reproductive systems. CB1 receptors appear to be responsible for the euphoric and anticonvulsive effects of *cannabis*. A CB1 can (1) have greater than about 70% amino acid sequence identity to a human CB1 receptor depicted in GenBank protein ID: NP_057167 (the longer isoform of human CB1 receptor) or NP_149421 (the shorter isoform of human CB1 receptor); or (2) bind to antibodies, e.g., polyclonal or monoclonal antibodies, raised against the human CB1 receptor depicted in GenBank protein ID NP_057167 or NP_149421. In some embodiments, the CB1 receptor has greater than about 75, 80, 85, 90, or 95 percent amino acid sequence identity to the human CB1 receptor depicted in GenBank protein ID NP_057167 or NP_149421. The CB1 receptor includes orthologs of the CB1 receptors in animals including human, rat, mouse, pig, dog and monkey, etc. The CB1 receptor also includes structural and functional polymorphisms of the CB1 receptor. "Polymorphism" refers to a set of genetic variants at a particular genetic locus among individuals in a population. The CB1 receptor includes the structural and functional polymorphisms of the CB1 receptor from human (GenBank protein ID NP_057167 or NP_149421), rat (GenBank protein ID: NP_036916), or mouse (GenBank protein ID: NP_031752), or etc.

[0050] The CB2 receptor has been detected almost exclusively in the immune system, with the greatest density in the peripheral blood cells. CB2 receptors appear to be responsible for the anti-inflammatory and possible other therapeutic. A CB2 can (1) have greater than about 70% amino acid sequence identity to a human CB2 receptor depicted in GenBank protein ID: NP_001832; or (2) bind to antibodies, e.g., polyclonal or monoclonal antibodies, raised against the human CB2 receptor depicted in GenBank protein ID NP_001832. In some embodiments, the CB2 receptor has greater than about 75, 80, 85, 90, or 95 percent amino acid sequence identity to the human CB2 receptor depicted in GenBank protein ID NP_001832. The CB2 receptor includes orthologs of the CB2 receptors in animals including human, rat, mouse, pig, dog and monkey, etc. The CB2 receptor also includes structural and functional polymorphisms of the CB2 receptor. The CB2 receptor includes the structural and functional polymorphisms of the CB2 receptor from human (GenBank protein ID NP_001832), rat (GenBank protein ID: NP_065418), mouse (GenBank protein ID: NP_034054), or etc.

[0051] A "cell" refers to at least one cell or a plurality of cells appropriate for the sensitivity of the detection method.

The cell can be present in a cultivated cell culture. The cell can also be present in its natural environment, such as a biological tissue or fluid. Cells suitable for the present invention may be bacterial, but are preferably eukaryotic, and are most preferably mammalian.

[0052] A "compound that increases the conductivity of a TRPV2 channel" includes any compound that results in increased passage of ions through the TRPV2 channel. In one embodiment, such a compound is an agonist for the TRPV2 channel that binds to the TRPV2 channel to increase its conductivity. Such a compound triggers, initiates, propagates, or otherwise enhances the channel conductivity. In another embodiment, such a compound is a positive allosteric modulator, which interacts with the TRPV2 channel at allosteric sites different from the agonist-binding site, and potentiates the response of the channel to an agonist.

[0053] A "compound that decreases the conductivity of a TRPV2 channel" includes any compound that results in decreased passage of ions through the TRPV2 channel. In one embodiment, such a compound is an antagonist for the TRPV2 channel that binds to the TRPV2 channel to counter, decrease or limit the action of an agonist in either a competitive or non-competitive fashion. In another embodiment, such a compound is a negative allosteric modulator, which interacts with the TRPV2 channel at allosteric sites different from the agonist or antagonist-binding site, and decreases the response of the channel to an agonist. In yet another embodiment, such a compound is an inverse agonist that binds to the TRPV2 channel and decreases the conductivity of the channel in the absence of any other compound, such as an agonist.

[0054] "Nucleotide sequence" refers to the arrangement of either deoxyribonucleotide or ribonucleotide residues in a polymer in either single- or double-stranded form. Nucleic acid sequences can be composed of natural nucleotides of the following bases: thymidine, adenine, cytosine, guanine, and uracil; abbreviated T, A, C, G, and U, respectively, and/or synthetic analogs of the natural nucleotides.

[0055] An "isolated" nucleic acid molecule is one that is substantially separated from at least one of the other nucleic acid molecules present in the natural source of the nucleic acid, or is substantially free of at least one of the chemical precursors or other chemicals when the nucleic acid molecule is chemically synthesized. An "isolated" nucleic acid molecule can also be, for example, a nucleic acid molecule that is substantially free of at least one of the nucleotide sequences that naturally flank the nucleic acid molecule at its 5' and 3' ends in the genomic DNA of the organism from which the nucleic acid is derived. A nucleic acid molecule is "substantially separated from" or "substantially free of" other nucleic acid molecule(s) or other chemical(s) in preparations of the nucleic acid molecule when there is less than about 30%, 20%, 10%, or 5% (by dry weight) of the other nucleic acid molecule(s) or the other chemical(s) (also referred to herein as a "contaminating nucleic acid molecule" or a "contaminating chemical").

[0056] Isolated nucleic acid molecules include, without limitation, separate nucleic acid molecules (e.g., cDNA or genomic DNA fragments produced by PCR or restriction endonuclease treatment) independent of other sequences, as well as nucleic acid molecules that are incorporated into a vector, an autonomously replicating plasmid, a virus (e.g., a retrovirus, adenovirus, or herpes virus), or into the genomic DNA of a prokaryote or eukaryote. In addition, an isolated nucleic acid molecule can include a nucleic acid molecule that is part of a hybrid or fusion nucleic acid molecule. An isolated nucleic acid molecule can be a nucleic acid sequence that is: (i) amplified in vitro by, for example, polymerase chain reaction (PCR); (ii) synthesized by, for example, chemical synthesis; (iii) recombinantly produced by cloning; or (iv) purified, as by cleavage and electrophoretic or chromatographic separation.

[0057] The term "oligonucleotide" or "oligo" refers to a single-stranded DNA or RNA sequence of a relatively short length, for example, less than 100 residues long. For many methods, oligonucleotides of about 16-25 nucleotides in length are useful, although longer oligonucleotides of greater than about 25 nucleotides may sometimes be utilized. Some oligonucleotides can be used as "primers" for the synthesis of complimentary nucleic acid strands. For example, DNA primers can hybridize to a complimentary nucleic acid sequence to prime the synthesis of a complimentary DNA strand in reactions using DNA polymerases. Oligonucleotides are also useful for hybridization in several methods of nucleic acid detection, for example, in Northern blotting or in situ hybridization.

[0058] The terms "polypeptide," "protein," and "peptide" are used herein interchangeably to refer to amino acid chains in which the amino acid residues are linked by peptide bonds or modified peptide bonds. The amino acid chains can be of any length of greater than two amino acids. Unless otherwise specified, the terms "polypeptide," "protein," and "peptide" also encompass various modified forms thereof. Such modified forms may be naturally occurring modified forms or chemically modified forms. Examples of modified forms include, but are not limited to, glycosylated forms, phosphorylated forms, myristoylated forms, palmitoylated forms, ribosylated forms, acetylated forms, ubiquitinated forms, etc. Modifications also include intra-molecular crosslinking and covalent attachment to various moieties such as lipids, flavin, biotin, polyethylene glycol or derivatives thereof, etc. In addition, modifications may also include cyclization, branching and cross-linking. Further, amino acids other than the conventional twenty amino acids encoded by the codons of genes may also be included in a polypeptide.

[0059] An "isolated protein" is one that is substantially separated from at least one of the other proteins present in the natural source of the protein, or is substantially free of at least one of the chemical precursors or other chemicals when the protein is chemically synthesized. A protein is "substantially separated from" or "substantially free of" other protein(s) or other chemical(s) in preparations of the protein when there is less than about 30%, 20%, 10%, or 5% (by dry weight) of the other protein(s) or the other chemical(s) (also referred to herein as a "contaminating protein" or a "contaminating chemical").

[0060] Isolated proteins can have several different physical forms. The isolated protein can exist as a full-length nascent or unprocessed polypeptide, or as a partially processed polypeptide or as a combination of processed polypeptides. The full-length nascent polypeptide can be postranslationally modified by specific proteolytic cleavage events that result in the formation of fragments of the full-length nascent polypeptide. A fragment, or physical association of fragments can have the biological activity associated with the full-length polypeptide; however, the degree of biological activity associated with individual fragments can vary.

[0061] An isolated polypeptide can be a non-naturally occurring polypeptide. For example, an "isolated polypep-

tide" can be a "hybrid polypeptide." An "isolated polypeptide" can also be a polypeptide derived from a naturally occurring polypeptide by additions or deletions or substitutions of amino acids. An isolated polypeptide can also be a "purified polypeptide" which is used herein to mean a specified polypeptide in a substantially homogeneous preparation substantially free of other cellular components, other polypeptides, viral materials, or culture medium, or when the polypeptide is chemically synthesized, chemical precursors or by-products associated with the chemical synthesis. A "purified polypeptide" can be obtained from natural or recombinant host cells by standard purification techniques, or by chemical synthesis, as will be apparent to skilled artisans.

[0062] "Recombinant" refers to a nucleic acid, a protein encoded by a nucleic acid, a cell, or a viral particle, that has been modified using molecular biology techniques to something other than its natural state. For example, recombinant cells can contain nucleotide sequence that is not found within the native (non-recombinant) form of the cell or can express native genes that are otherwise abnormally, under-expressed, or not expressed at all. Recombinant cells can also contain genes found in the native form of the cell wherein the genes are modified and re-introduced into the cell by artificial means. The term also encompasses cells that contain an endogenous nucleic acid that has been modified without removing the nucleic acid from the cell; such modifications include those obtained, for example, by gene replacement, and site-specific mutation.

[0063] A "recombinant host cell" is a cell that has had introduced into it a recombinant DNA sequence. Recombinant DNA sequence can be introduced into host cells using any suitable method including, for example, electroporation, calcium phosphate precipitation, microinjection, transformation, biolistics and viral infection. Recombinant DNA may or may not be integrated (covalently linked) into chromosomal DNA making up the genome of the cell. For example, the recombinant DNA can be maintained on an episomal element, such as a plasmid. Alternatively, with respect to a stably transformed or transfected cell, the recombinant DNA has become integrated into the chromosome so that it is inherited by daughter cells through chromosome replication. This stability is demonstrated by the ability of the stably transformed or transfected cell to establish cell lines or clones comprised of a population of daughter cells containing the exogenous DNA. Recombinant host cells may be prokaryotic or eukaryotic, including bacteria such as *E. coli*, fungal cells such as yeast, mammalian cells such as cell lines of human, bovine, porcine, monkey and rodent origin, and insect cells such as *Drosophila*- and silkworm-derived cell lines. It is further understood that the term "recombinant host cell" refers not only to the particular subject cell, but also to the progeny or potential progeny of such a cell. Because certain modifications can occur in succeeding generations due to either mutation or environmental influences, such progeny may not, in fact, be identical to the parent cell, but are still included within the scope of the term as used herein.

[0064] "Sequence identity or similarity", as known in the art, is the relationship between two or more polypeptide sequences or two or more polynucleotide sequences, as determined by comparing the sequences. As used herein, "identity", in the context of the relationship between two or more nucleic acid sequences or two or more polypeptide sequences, refers to the percentage of nucleotide or amino acid residues, respectively, that are the same when the sequences are optimally aligned and analyzed. For purposes of comparing a queried sequence against, for example, the amino acid sequence SEQ ID NO:2, the queried sequence is optimally aligned with SEQ ID NO: 2 and the best local alignment over the entire length of SEQ ID NO:2 is obtained.

[0065] Analysis can be carried out manually or using sequence comparison algorithms. For sequence comparison, typically one sequence acts as a reference sequence, to which a queried sequence is compared. When using a sequence comparison algorithm, test and reference sequences are input into a computer, sub-sequence coordinates are designated, if necessary, and sequence algorithm program parameters are designated.

[0066] Optimal alignment of sequences for comparison can be conducted, for example, by using the homology alignment algorithm of Needleman & Wunsch, J. Mol. Biol., 48:443 (1970). Software for performing Needleman & Wunsch analyses is publicly available through the Institut Pasteur (France) Biological Software website: http://bioweb.pasteur.fr/seqanal/interfaces/needle.html. The NEEDLE program uses the Needleman-Wunsch global alignment algorithm to find the optimum alignment (including gaps) of two sequences when considering their entire length. The identity is calculated along with the percentage of identical matches between the two sequences over the reported aligned region, including any gaps in the length. Similarity scores are also provided wherein the similarity is calculated as the percentage of matches between the two sequences over the reported aligned region, including any gaps in the length. Standard comparisons utilize the EBLOSUM62 matrix for protein sequences and the EDNAFULL matrix for nucleotide sequences. The gap open penalty is the score taken away when a gap is created; the default setting using the gap open penalty is 10.0. For gap extension, a penalty is added to the standard gap penalty for each base or residue in the gap; the default setting is 0.5.

[0067] Hybridization can also be used as a test to indicate that two polynucleotides are substantially identical to each other. Polynucleotides that share a high degree of identity will hybridize to each other under stringent hybridization conditions. "Stringent hybridization conditions" has the meaning known in the art, as described in Sambrook et al., *Molecular Cloning: A Laboratory Manual*, Second Edition, Cold Spring Harbor Laboratory, Cold Spring Harbor, N.Y., (1989). An exemplary stringent hybridization condition comprises hybridization in 6× sodium chloride/sodium citrate (SSC) at about 45° C., followed by one or more washes in 0.2×SSC and 0.1% SDS at 50-65° C., depending upon the length over which the hybridizing polynucleotides share complementarity.

[0068] A "TRPV2", "transient receptor potential cation channel, subfamily V, member 2", "VRL", "VRL1", "VRL-1", or "vanilloid receptor-like protein 1" each refers to a protein that forms an ion channel, the TRPV2 channel, that can be activated by high temperature and/or low osmolarity, and transduces heat responses in sensory ganglia. The TRPV2 channel can also be activated by certain compounds. An activated TRPV2 channel gates the influx of Ca^{2+} and other cations (e.g., Na^{+}) through the channel, resulting in membrane depolarization. A TRPV2 protein can (1) have greater than about 70% amino acid sequence identity to a human TRPV2 (hTRPV2) protein depicted in SEQ ID NO: 2 (GenBank protein ID: NP_057197); or (2) bind to antibodies, e.g., polyclonal or monoclonal antibodies, raised against

a hTRPV2 protein depicted in SEQ ID NO: 2. In some embodiments, the TRPV2 has greater than about 75, 80, 85, 90, or 95 percent amino acid sequence identity to SEQ ID NO: 2. TRPV2 includes orthologs of the TRPV2 in animals including human, rat, mouse, pig, dog and monkey, etc. TRPV2 also includes structural and functional polymorphisms of the TRPV2. TRPV2 includes the structural and functional polymorphisms of the TRPV2 from human, rat (GenBank protein ID: NP_058903, SEQ ID NO:4), mouse (GenBank protein ID: NP_035836, SEQ ID NO:6), or etc. For example, it was found that addition of a hemagglutinin A (HA) epitope tag to the end of the rat TRPV2 C-terminus did not alter the channel properties; and that deletion mutants of rat TRPV2-HA lacking the N-terminal 20, 32, and 65 and C-terminal 11, 23, or 32 amino acid residues of rat TRPV2 were still active in their responses to an elevated temperature of about 53° C., lowered osmolarity, Δ9-THC or 2-APB. Therefore, TRPV2 also includes deletion or modifications of the wild-type TRPV2 that maintains the biological activity of the TRPV2, such as the deletion mutants of rat TRPV2 consisting of the amino acid sequence of SEQ ID NOs: 7-14. Furthermore, TRPV2 also includes chimeras between TRPV2 of different animals. For example, it was found that chimeras (SEQ ID NO: 16) between rat and human TRPV2, named RHR (i.e. Rat 1-392/Human 391-646/Rat 647-761), was also active in its response to an elevation of temperature of about 53° C., Δ^9-THC and to 2-APB. In addition, TRPV2 further includes an active ion channel formed by the combination of two or more TRPV2 subunits, which by themselves are inactive or less active. For example, TRPV2 can be an active ion channel formed by the co-expression of the chimera RRH (Rat 1-392/Rat 393-646/Human 647-764) and HRR (Human 1-390/Rat 393-646/Rat 647-761).

[0069] "TRPV2 activation temperature" is the temperature at which a TRPV2 channel, in the absence of other stimulation, exhibits at least a 10% increase in its conductivity compared to the baseline. A person skilled in the art can experimentally determine the activation temperature for a TRPV2 channel. In some embodiments, "TRPV2 activation temperature" is the temperature at which a TRPV2 channel exhibits at least a 15%, 20%, 25%, 30%, 35%, 40%, 45%, or 50% increase in its conductivity compared to the baseline. "TRPV2 activation temperature" is typically greater than of about 52° C. In some embodiments, the TRPV2 activation temperature is about 52° C.-55° C. or 55° C.-60° C.

[0070] "TRPV2 non-activation temperature" is the temperature that falls outside of the range for a "TRPV2 activation temperature". An exemplary TRPV2 non-activation temperature is room temperature (about 22° C.) or any temperature that is below about 52° C.

[0071] "Vector" refers to a nucleic acid molecule into which a heterologous nucleic acid can be or is inserted. Some vectors can be introduced into a host cell allowing for replication of the vector or for expression of a protein that is encoded by the vector or construct. Vectors typically have selectable markers, for example, genes that encode proteins allowing for drug resistance, origins of replication sequences, and multiple cloning sites that allow for insertion of a heterologous sequence. Vectors are typically plasmid-based and are designated by a lower case "p" followed by a combination of letters and/or numbers. Starting plasmids disclosed herein are either commercially available, publicly available on an unrestricted basis, or can be constructed from available plasmids by application of procedures known in the art. Many plasmids and other cloning and expression vectors that can be used in accordance with the present invention are well-known and readily available to those of skill in the art. Moreover, those of skill readily may construct any number of other plasmids suitable for use in the invention. The properties, construction and use of such plasmids, as well as other vectors, in the present invention will be readily apparent to those of skill from the present disclosure.

[0072] "Sequence" means the linear order in which monomers occur in a polymer, for example, the order of amino acids in a polypeptide or the order of nucleotides in a polynucleotide.

[0073] In practicing the present invention, many conventional techniques in molecular biology, microbiology and recombinant DNA are used. These techniques are well-known and are explained in, for example, Current Protocols in Molecular Biology, Vols. I, II, and III, F. M. Ausubel, ed. (1997); and Sambrook et al., *Molecular Cloning: A Laboratory Manual*, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, N.Y. (2001).

[0074] It was discovered in the present invention that a group of cannabinoids are capable of activating the TRPV2 but not TRPV1 activity. Thus, the present invention provides new methods for regulating the biological activity of TRPV2 and new methods for identifying compounds that regulate biological activity of TRPV2.

[0075] In one embodiment, the TRPV2 used in the present invention is present in a cell. The cell can express TRPV2 endogeneously or recombinantly. One exemplary endogeneous cell for TRPV2 is a dorsal root ganglia (DRG) neuron or trigeminal neurons. Other examples of endogeneous cell for TRPV2 include, but are not limited to, intestine intrinsic neurons, vascular smooth muscle cells, and human hepatoblastoma (HepG2).

[0076] It will be apparent to skilled artisans that any recombinant expression methods may be used in the present invention for purposes of expressing the TRPV2. Generally, a nucleic acid encoding TRPV2 can be introduced into a suitable host cell. Exemplary nucleic acid molecules that can be used in the present invention include cDNA that encodes for the full length TRPV2 from human (SEQ ID: 1, GenBank accession No: NM_016113), mouse (SEQ ID NO:5, GenBank accession No: NM_011706), or rat (SEQ ID NO:3 GenBank accession No: NM_017207).

[0077] Typically, the nucleic acids, preferably in the form of DNA, are incorporated into a vector to form expression vectors capable of directing the production of the interacting protein member(s) once introduced into a host cell. Many types of vectors can be used for the present invention. Methods for the construction of an expression vector for purposes of this invention should be apparent to skilled artisans apprised of the present disclosure. (See generally, *Current Protocols in Molecular Biology*, Vol. 2, Ed. Ausubel, et al., Greene Publish. Assoc. & Wiley Interscience, Ch. 13, 1988; Glover, DNA Cloning, Vol. II, IRL Press, Wash., D.C., Ch. 3, 1986; Bitter, et al., in *Methods in Enzymology* 153:516-544 (1987); *The Molecular Biology of the Yeast Saccharomyces*, Eds. Strathern et al., Cold Spring Harbor Press, Vols. I and II, 1982; and Sambrook et al., *Molecular Cloning: A Laboratory Manual*, Cold Spring Harbor Press, 1989.)

[0078] Generally, the expression vectors include an expression cassette having a promoter operably linked to a DNA encoding an interacting protein member. The promoter can be a native promoter, i.e., the promoter found in naturally occur-

ring cells to be responsible for the expression of the interacting protein member in the cells. Alternatively, the expression cassette can be a chimeric one, i.e., having a heterologous promoter that is not the native promoter responsible for the expression of the interacting protein member in naturally occurring cells. The expression vector may further include an origin of DNA replication for the replication of the vectors in host cells. Preferably, the expression vectors also include a replication origin for the amplification of the vectors in, e.g., *E. coli*, and selection marker(s) for selecting and maintaining only those host cells harboring the expression vectors.

[0079] The thus constructed expression vectors can be introduced into the host cells by any techniques known in the art, e.g., by direct DNA transformation, microinjection, electroporation, viral infection, lipofection, gene gun, and the like. The expression of the protein of interest may be transient or stable. The expression vectors can be maintained in host cells in an extrachromosomal state, i.e., as self-replicating plasmids or viruses. Alternatively, the expression vectors can be integrated into chromosomes of the host cells by conventional techniques such as selection of stable cell lines or site-specific recombination. In stable cell lines, at least the expression cassette portion of the expression vector is integrated into a chromosome of the host cells.

[0080] The vector construct can be designed to be suitable for expression in various host cells, including but not limited to bacteria, yeast cells, plant cells, insect cells, and mammalian and human cells. Methods for preparing expression vectors for expression in different host cells should be apparent to a skilled artisan. As described in the Example 1, infra, rat and human TRPV2 has been successfully expressed in HEK293.

[0081] Homologues and fragments of TRPV2 can also be easily expressed using the recombinant methods described above. For example, to express a protein fragment, the DNA fragment incorporated into the expression vector can be selected such that it only encodes the protein fragment. Likewise, a specific hybrid protein can be expressed using a recombinant DNA encoding the hybrid protein. Similarly, a homologue protein may be expressed from a DNA sequence encoding the homologue protein. A homologue-encoding DNA sequence may be obtained by manipulating the native protein-encoding sequence using recombinant DNA techniques. For this purpose, random or site-directed mutagenesis can be conducted using techniques generally known in the art. To make protein derivatives, for example, the amino acid sequence of a native interacting protein member may be changed in predetermined manners by site-directed DNA mutagenesis to create or remove consensus sequences.

[0082] In other embodiments, the TRPV2 is provided in a cell membrane. The membrane preparation can be isolated from a native host cell, for example, a DRG or TG cell, which expresses TRPV2 on its cell surface. The membrane preparation can also be isolated from a recombinant host cell, for example, a CHO, HEK293, or COS cell, which expresses a TRPV2 recombinantly on its cell surface. The membrane preparation can be further prepared from the biological membranes, such as the tissue membrane, plasma membrane, cell membrane, or internal organelle membrane expressing the TRPV2 channels. Methods are known to those skilled in the art for isolation and preparation of biological membrane preparations. For example, such a method can include the steps of mechanical or enzymatic disruption of the tissue or cells, centrifugation to separate the membranes from other components, and resuspending the membrane fragments or vesicles in suitable buffer solution. Alternatively, the membrane-containing preparation can also be derived from artificial membranes. Purified TRPV2 protein can be reconstituted into lipid bilayers to form artificial membrane vesicles (see Chen et al., 1996, *J. Gen. Physiol.* 108:237-250). Such type of membrane vesicle can be very specific to the channel of interest, avoiding the problem of contamination from other channels. For example, such artificial membranes can include an electrode to which is tethered a lipid membrane containing ion channels and forming ion reservoirs. Methods are known to those skilled in the art to prepare artificial membrane vesicles.

[0083] In some preferred embodiments, membranes can be broken under controlled conditions, yielding portions of cell membranes and/or membrane vesicles. Cell membrane portions and/or vesicles can, in some embodiments, provide an easier format for the inventive assays and methods, since cell lysis and/or shear is not as much of a concern during the assay. Cell membranes can be derived from tissues and/or cultured cells. Such methods of breaking cell membranes and stabilizing them are known in the art. Methods of treating tissues to obtain cell membranes are known in the art.

[0084] Preferably, human TRPV2 is used in the assays of the invention. Optionally, TRPV2 orthologs from other species such as rat or mouse, preferably a mammalian species, are used in assays of the invention.

[0085] The compound identification methods can be performed using conventional laboratory formats or in assays adapted for high throughput. The term "high throughput" refers to an assay design that allows easy screening of multiple samples simultaneously and/or in rapid succession, and can include the capacity for robotic manipulation. Another desired feature of high throughput assays is an assay design that is optimized to reduce reagent usage, or minimize the number of manipulations in order to achieve the analysis desired. Examples of assay formats include 96-well or 384-well plates, levitating droplets, and "lab on a chip" microchannel chips used for liquid handling experiments. It is well known by those in the art that as miniaturization of plastic molds and liquid handling devices are advanced, or as improved assay devices are designed, greater numbers of samples can be processed using the design of the present invention.

[0086] Any test compounds may be screened in the screening assays of the present invention to select modulators of the protein complex of the invention. By the term "selecting" or "select" compounds it is intended to encompass both (a) choosing compounds from a group previously unknown to be modulators of a protein complex or interacting protein members thereof, and (b) testing compounds that are known to be capable of binding, or modulating the functions and activities of, a protein complex or interacting protein members thereof. Both types of compounds are generally referred to herein as "test compounds" or "candidate compound". The candidate compounds encompass numerous chemical classes, including but not limited to, small organic or inorganic compounds, natural or synthetic molecules, such as antibodies, proteins or fragments thereof, antisense nucleotides, interfering RNA (iRNA) and ribozymes, and derivatives, mimetics and analogs thereof. Preferably, they are small organic compounds, i.e., those having a molecular weight of no greater than 10,000 daltons, more preferably less than 5,000 daltons. Preferably, the test compounds are provided in library formats known in the art, e.g., in chemically synthesized libraries (See

generally, Gordan et al. *J. Med. Chem.,* 37:1385-1401 (1994)), recombinantly expressed libraries (e.g., phage display libraries), and in vitro translation-based libraries (e.g., ribosome display libraries).

[0087] Candidate compounds comprise functional chemical groups necessary for structural interactions with polypeptides, and typically include at least an amine, carbonyl, hydroxyl or carboxyl group, preferably at least two of the functional chemical groups and more preferably at least three of the functional chemical groups. The candidate compounds can comprise cyclic carbon or heterocyclic structure and/or aromatic or polyaromatic structures substituted with one or more of the above-identified functional groups. Candidate compounds also can be biomolecules such as peptides, saccharides, fatty acids, sterols, isoprenoids, purines, pyrimidines, derivatives or structural analogs of the above, or combinations thereof and the like. Where the compound is a nucleic acid, the compound typically is a DNA or RNA molecule, although modified nucleic acids having non-natural bonds or subunits are also contemplated.

[0088] Candidate compounds are obtained from a wide variety of sources including libraries of synthetic or natural compounds. For example, numerous means are available for random and directed synthesis of a wide variety of organic compounds and biomolecules, including expression of randomized oligonucleotides, synthetic organic combinatorial libraries, phage display libraries of random peptides, and the like. Candidate compounds can also be obtained using any of the numerous approaches in combinatorial library methods known in the art, including biological libraries; spatially addressable parallel solid phase or solution phase libraries: synthetic library methods requiring deconvolution; the "one-bead one-compound" library method; and synthetic library methods using affinity chromatography selection (Lam (1997) *Anticancer Drug Des.* 12: 145). Alternatively, libraries of natural compounds in the form of bacterial, fungal, plant and animal extracts are available or readily produced. Additionally, natural and synthetically produced libraries and compounds can be readily modified through conventional chemical, physical, and biochemical means.

[0089] Further, known pharmacological agents can be subjected to directed or random chemical modifications such as acylation, alkylation, esterification, amidation, etc. to produce structural analogs of the agents. Candidate compounds can be selected randomly or can be based on existing compounds that bind to and/or modulate the function of TRPV2 activity. Therefore, a source of candidate agents is one or more than one library of molecules based on one or more than one known compound that increases or decreases TRPV2 channel conductivity in which the structure of the compound is changed at one or more positions of the molecule to contain more or fewer chemical moieties or different chemical moieties. The structural changes made to the molecules in creating the libraries of analog activators/inhibitors can be directed, random, or a combination of both directed and random substitutions and/or additions. One of ordinary skill in the art in the preparation of combinatorial libraries can readily prepare such libraries based on the existing compounds.

[0090] A variety of other reagents also can be included in the mixture. These include reagents such as salts, buffers, neutral proteins (e.g., albumin), detergents, etc. that can be used to facilitate optimal protein-protein and/or protein-nucleic acid binding. Such a reagent can also reduce non-specific or background interactions of the reaction components. Other reagents that improve the efficiency of the assay such as nuclease inhibitors, antimicrobial agents, and the like can also be used.

[0091] Examples of methods for the synthesis of molecular libraries can be found in the art, for example in: Zuckermann et al. (1994). *J. Med. Chem.* 37:2678. Libraries of compounds can be presented in solution (e.g., Houghten (1992) *Biotechniques* 13:412-421), or on beads (Lam (1991) *Nature* 354:82-84), chips (Fodor (1993) *Nature* 364:555-556), bacteria (U.S. Pat. No. 5,223,409), spores (U.S. Pat. No. 5,571,698), plasmids (Cull et al. (1992) *Proc. Natl. Acad. Sci. USA* 89:1865-1869) or phage (see e.g., Scott and Smith (1990) *Science* 249:386-390).

[0092] The selected compounds can be tested for their ability to decrease the channel conductivity of the TRPV2, or for their ability to decrease the binding activity of the TRPV2 to a cannabinoid that is capable of activating the TRPV2. During the test, the test compound can be added to the TRPV2 prior to, after, or simultaneously with cannabinoid that is capable of activating the TRPV2. In addition, the compounds can be tested in an animal model for pain, or inflammation, etc.

[0093] Generally, a control assay is performed in which the above screening assay is conducted in the absence of the test compound. The result of this assay is then compared with that obtained in the presence of the test compound.

[0094] The test compounds may be screened in an in vitro assay to identify compounds capable of binding to a TRPV2. For this purpose, a test compound is contacted with TRPV2 under conditions and for a time sufficient to allow specific interaction between the test compound and the TRPV2 to occur, thereby resulting in the binding of the compound to the TRPV2, and the formation of a complex. Subsequently, the binding event is detected.

[0095] In one particular embodiment, the TRPV2 is immobilized on a solid support (such as a protein microchip) or on a cell surface or a membrane. For example, the protein complex can be immobilized directly onto a microchip substrate such as glass slides or onto multi-well plates using non-neutralizing antibodies, i.e., antibodies capable of binding to the complex but do not substantially affect its biological activities. A cannabinoid labeled with a detectable marker is contacted with the immobilized TRPV2. Test compounds can be contacted with the immobilized TRPV2 protein to allow binding to occur under standard binding assay conditions. To identify compound binding to a TRPV2, one can measure the detectable marker associated with TRPV2 or disassociated from the TRPV2. A test compound that binds competitively with the labeled cannabinoid to the TRPV2 will result in less binding of TRPV2 to the cannabinoid, thus less labeling associated with TRPV2.

[0096] In one embodiment, the test compound can be further evaluated for its ability to increase or decrease the ion conductivity of a TRPV2 channel. Known to those skilled in the art are methods for measuring a TRPV2 channel conductivity, for example, via the cellular depolarization/hyperpolarization or an increase in intracellular calcium ion levels. The level of intracellular calcium can be assessed using a calcium ion-sensitive fluorescent indicator, such as a calcium ion-sensitive fluorescent dye. Suitable calcium ion-sensitive fluorescent dyes include, for example, quin-2 (see, e.g., Tsien et al., J. Cell BioL, 94:325, 1982), fura-2 (see, e.g., Grynkiewicz et al., J. BioL Chem., 260:3440, 1985), fluo-3 (see, e.g., Kao et al., J. BioL-43 Chem., 264:8179, 1989) and

rhod-2 (see, e.g., Tsien et al., J. BioL Chem., Abstract 89a, 1987). Suitable calcium ion-sensitive fluorescent dyes are commercially available from, for example, Invitrogen (Molecular Probes Products, Eugene, Oreg.). Cellular fluorescence can also be monitored using a fluorometer or a flow cytometer having a fluorescence lamp and detector. FLIPR assay has been used routinely in measuring the ion conductivity.

[0097] The TRPV2 cation channels function to transport not only divalent cations, for example, Ca^{2+}, but also monovalent cations, for example, Na^{+} or K^{+}. Therefore, assays for determining changes in the transport of monovalent cation can also be performed to measure the conductivity of a TRPV2 channel. Na^{+}- and K^{+}-sensitive dyes are known in the art and commercially available from, for example, Invitrogen (Molecular Probes Products, Eugene, Oreg.).

[0098] The conductivity of a TRPV2 channel can also be measured by electrophysiologic techniques such as patch clamp. Patch clamp techniques are routinely used for studying electrical activities in cells, cell membranes, and isolated tissues. It involves forming an electrically tight, high-resistance seal between a micropipette and the plasma membrane. The current flowing through individual ion channels within the plasma membrane can then be measured. Different variants on the techniques allow different surfaces of the plasma membrane to be exposed to the bathing medium. The four most common variants include cell-attached, inside-out, outside-out and whole-cell patch clamp.

[0099] A patch-clamp method is commonly used with a voltage clamp that controls the voltage across the membrane and measures current flow. For example, in the case of whole-cell patch clamp, during the voltage clamp process, a microelectrode is inserted into a cell and current injected through the electrode so as to hold the cell membrane potential at some predefined level. A patch-clamp method can also be used in the current-clamp configuration, in which the current is controlled and the membrane potential is measured.

[0100] In another embodiment, the test compound can be further evaluated by administering it to a live animal. This can be useful to establish efficacy, toxicity and other pharmacological parameters important for establishing dosing regimens. For example, the compound can be administered to a dog to examine various pharmacological aspects of the compound in the dog. The dog testing can be particularly advantageous for identifying and establishing dosing regimens in humans, because dogs, particularly large breeds, are closer in weight to humans as compared to rats or mice and therefore provide a more suitable animal model for estimating human dosing.

[0101] The compound can also be administered to animals to assess the ability of the compound to alter nociceptive processes. Various animal models of pain exist. For example, the rat spinal nerve ligation (SNL) model of nerve injury is a model of neuropathic pain (Kim and Chung, Pain, 50:355-363, 1992).

[0102] Other suitable animal models of pain can be utilized in connection with the teachings herein. Commonly studied rodent models of neuropathic pain include the chronic constriction injury (CCI) or the Bennett model; neuroma or axotomy model; and the partial sciatic transection or Seltzer model (Shir et al., *Neurosci. Lett.,* 115:62-67, 1990). Exemplary neuropathic pain models include several traumatic nerve injury preparations (Bennett et al, *Pain* 33: 87-107, 1988; Decosterd et al., *Pain* 87: 149-58, 2000; Kim et al, *Pain* 50: 355-363, 1992; Shir et al., *Neurosci Lett* 115: 62-7, 1990), neuroinflammation models (Chacur et al., *Pain* 94: 231-44, 2001; Milligan et al., *Brain Res* 861: 105-16, 2000), diabetic neuropathy (Calcutt et al., *Br J Pharmacol* 122: 1478-82, 1997), virus-induced neuropathy (Fleetwood-Walker et al., *J Gen Virol* 80: 2433-6, 1999), vincristine neuropathy (Aley et al., *Neuroscience* 73: 259-65, 1996; Nozaki-Taguchi et al., *Pain* 93: 69-76, 2001), and paclitaxel neuropathy (Cavaletti et al., *Exp Neurol* 133: 64-72, 1995), as well as acute nociceptive models and inflammatory models (Brennan, T. J. et al. *Pain* 64:493, 1996; D'Amour, F. E. and Smith, D. L. *J Pharmacol* 72: 74-79, 1941; Eddy, N. B. et al. *J Pharmacol Exp Ther* 98:121, 1950; Haffner, F. *Dtsch Med Wochenschr* 55:731, 1929; Hargreaves, K. et al. *Pain* 32: 77-88, 1988; Hunskaar, S. et al. *J Neurosci Meth* 14:69, 1985; Randall, L. O. and Selitto, J. J. *Arch. Int. Pharmacodyn* 111: 409-419, 1957; Siegmund, E. et al. *Proc Soc Exp Bio Med* 95:729, 1957).

[0103] The discovery that certain cannabinoids activate TRPV2 also provides new methods for identifying additional compounds that increase the biological activity of TRPV2. Such methods can be based on rational drug design. Structural analogs or mimetics of the cannabinoid can be produced based on rational drug design with the aim of improving drug potency, efficacy and stability, and reducing side effects. Methods known in the art for rational drug design can be used in the present invention. See, e.g., Hodgson et al., *Bio/Technology,* 9:19-21 (1991); U.S. Pat. Nos. 5,800,998 and 5,891,628, all of which are incorporated herein by reference.

[0104] Molecular modeling programs can be used to determine whether a small molecule can fit into a functionally relevant portion, for example, an active site, of the TRPV2 polypeptide. Basic information on molecular modeling is provided in, for example, M. Schlecht, Molecular Modeling on the PC, 1998, John Wiley & Sons; Gans et al., Fundamental Principals of Molecular Modeling, 1996, Plenum Pub. Corp.; N. C. Cohen (editor), Guidebook on Molecular Modeling in Drug Design, 1996, Academic Press; and W. B. Smith, Introduction to Theoretical Organic Chemistry and Molecular Modeling, 1996. U.S. patents that provide detailed information on molecular modeling include U.S. Pat. Nos. 6,093,573; 6,080,576; 5,612,894; and 5,583,973.

[0105] Programs that can be useful for molecular modeling studies include, for example, GRID (Goodford, P. J., "A Computational Procedure for Determining Energetically Favorable Binding Sites on Biologically Important Macromolecules" J. Med. Chem., 28, pp. 849-857, 1985), available from Oxford University, Oxford, UK; MCSS (Miranker, A. and M. Karplus, "Functionality Maps of Binding Sites: A Multiple Copy Simultaneous Search Method." Proteins: Structure, Function and Genetics, 11, pp. 29-34, 1991), available from Molecular Simulations, Burlington, Mass.; AUTODOCK (Goodsell, D. S. and A. J. Olsen, "Automated Docking of Substrates to Proteins by Simulated Annealing" Proteins: Structure. Function, and Genetics, 8, pp. 195-202, 1990); available from Scripps Research Institute, La Jolla, Calif.; and DOCK (Kuntz, I. D. et al., "A Geometric Approach to Macromolecule-Ligand Interactions" J. Mol. Biol., 161, pp. 269-288, 1982), available from University of California, San Francisco, Calif.

[0106] In this respect, structural information on the TRPV2-cannabinoid complex is obtained. Preferably, atomic coordinates defining a three-dimensional structure of the complex can be obtained. For example, the interacting

TRPV2-cannabinoid complex can be studied using various biophysical techniques including, e.g., X-ray crystallography, NMR, computer modeling, mass spectrometry, and the like. Likewise, structural information can also be obtained from protein complexes formed by interacting proteins and a compound that initiates or stabilizes the interaction of the proteins. Methods for obtaining such atomic coordinates by X-ray crystallography, NMR, and the like are known in the art and the application thereof to the target protein or protein complex of the present invention should be apparent to skilled persons in the art of structural biology. See Smyth and Martin, *Mol. Pathol.,* 53:8-14 (2000); Oakley and Wilce, *Clin. Exp. Pharmacol. Physiol.,* 27(3):145-151 (2000); Ferentz and Wagner, Q. *Rev. Biophys.,* 33:29-65 (2000); Hicks, *Curr. Med. Chem.,* 8(6):627-650 (2001); and Roberts, *Curr. Opin. Biotechnol.,* 10:42-47 (1999).

[0107] The domains, residues or moieties of a cannabinoid critical to TRPV2-cannabinoid interaction constitute the active region of the cannabinoid known as its "pharmacophore." Once the pharmacophore has been elucidated, a structural model can be established by a modeling process that may incorporate data from NMR analysis, X-ray diffraction data, alanine scanning, spectroscopic techniques and the like. Various techniques including computational analysis (e.g., molecular modeling and simulated annealing), similarity mapping and the like can all be used in this modeling process. See e.g., Perry et al., in *OSAR: Quantitative Structure-Activity Relationships in Drug Design*, pp. 189-193, Alan R. Liss, Inc., 1989; Rotivinen et al., *Acta Pharmaceutical Fennica,* 97:159-166 (1988); Lewis et al., *Proc. R. Soc. Lond.,* 236: 125-140 (1989); McKinaly et al., *Annu. Rev. Pharmacol. Toxiciol.,* 29:111-122 (1989). Commercially available molecular modeling systems from Polygen Corporation, Waltham, Mass., include the CHARMm program, which performs energy minimization and molecular dynamics functions, and QUANTA program, which performs construction, graphic modeling and analysis of molecular structure. Such programs allow interactive construction, modification, and visualization of molecules. Other computer modeling programs are also available from BioDesign, Inc. (Pasadena, Calif.), Hypercube, Inc. (Cambridge, Ontario), and Allelix, Inc. (Mississauga, Ontario, Canada).

[0108] A template can be formed based on the established model. Various compounds can then be designed by linking various chemical groups or moieties to the template. Various moieties of the template can also be replaced. In addition, in the case of a peptide lead compound, the peptide or mimetics thereof can be cyclized, e.g., by linking the N-terminus and C-terminus together, to increase its stability. These rationally designed compounds are further tested. In this manner, pharmacologically acceptable and stable compounds with improved potency/efficacy and reduced side effects can be developed. The compounds identified in accordance with the present invention can be incorporated into a pharmaceutical formulation suitable for administration to an individual.

[0109] In addition, the structural models or atomic coordinates defining a three-dimensional structure of the target protein or protein complex can also be used in virtual screen to select compounds capable of activating TRPV2. Various methods of computer-based virtual screen using atomic coordinates are generally known in the art. For example, U.S. Pat. No. 5,798,247 (which is incorporated herein by reference) discloses a method of identifying a compound (specifically, an interleukin converting enzyme inhibitor) by determining binding interactions between an organic compound and binding sites of a binding cavity within the target protein. The binding sites are defined by atomic coordinates.

[0110] The compounds designed or selected based on rational drug design or virtual screen can be tested for their ability to modulate (interfere with or strengthen) the interaction between the interacting partners within the protein complexes of the present invention. In addition, the compounds can further be tested in TRPV2 channel conductivity assays or animal models as described supra.

[0111] Following the selection of desirable compounds according to the methods disclosed above, the methods of the present invention further provide for the manufacture of the selected compounds. The compounds can be manufactured for further experimental studies, or for therapeutic use. The compounds identified in the screening methods of the present invention can be made into therapeutically or prophylactically effective drugs for preventing or ameliorating diseases, disorders or symptoms caused by or associated with TRPV2, such as pain, or inflammation, etc.

Example 1

Expression of Rat and Human TRPV2 in HEK293 Cells

[0112] A cDNA fragment encoding the full-length rat TRPV2 was subcloned into pCI-neo (Promega, Madison, Wis.) mammalian expression vector. The expression construct was then transfected into HEK293 cells with FuGene6 transfection reagent (Roche, Indianapolis, Ind.) according to the vendor's protocol. Stable cell lines were selected by growth in the presence of 400 μg/ml G418. Single G418 resistant clones were isolated and purified. Stable expression of rat TRPV2 in these cells was confirmed by Western blot analysis with an anti-rat TRPV2 specific antibody (Chemicon, Temecula, Calif.), Ca^{2+} imaging assay (FLIPR) and whole cell patch clamp analyses.

[0113] A cDNA fragment encoding the full-length human TRPV2 was subcloned into pCI-neo or pcDNA3 mammalian expression vectors. The expression constructs were then transfected into HEK293 cells with FuGene6 transfection reagent (Roche, Indianapolis, Ind.) according to vendor's protocol. TRPV2-expressing HEK293 cells were cultured in DMEM supplemented with 10% fetal bovine serum, 100 units/ml penicillin, and 100 μg/ml streptomycin for 48-72 hr and either evaluated for transient expression and/or activity, or dosed with 400 μg/ml G418 to select for stably-transfected TRPV2-expressing cell clones. Cells were maintained at 37° C. and in 5% CO_2.

Example 2

TRPV2 is activated by Δ^9-tetrahydrocannabinol (Δ^9-THC)

[0114] To search for pharmacological activators of TRPV2, Δ^9-THC, a major psychoactive constituent of marijuana derived from *Cannabis*, was tested. The rat TRPV2-expressing HEK293 cells were seeded in a 384-well plate at a concentration of 5×10^3 cells/well and incubated overnight at 37° C. The following day, the cells were loaded with buffer and calcium dye 3 (Molecular Devices, Sunnyvale, Calif.) in a final volume of 50 μl and incubated for 30 minutes at 37° C./5% CO_2 followed by 30 additional minutes at room tem-

perature. The fluorescence intensity was measured by a fluorescent plate reader (FLIPR) before, during and after the addition of test compounds.

[0115] As shown in FIG. **4**A, addition of 100 μM Δ^9-THC solid line but not buffer (dotted line), caused a robust elevation of intracellular Ca^{2+} in rat TRPV2-expressing HEK293 cells. In contrast, no significant intracellular Ca^{2+} elevation was observed in untransfected HEK293 cells at the same concentration of Δ^9-THC (dashed line), suggesting that the elevation of intracellular Ca^{2+} was mediated by rat TRPV2. Activation of rat TRPV2 by Δ^9-THC was dose-dependent with an EC_{50} value of 15.7 uM and Hill slope of 1.04 (FIG. **4**B).

[0116] To further confirm the Δ^9-THC effect on TRPV2, whole-cell patch clamp studies were performed. The extracellular solution contained (in mM): NaCl, 132; CaCl, 1.8; KCl, 5.4; $MgCl_2$, 0.8; HEPES, 10; glucose, 10; pH=7.4. The intracellular solution used to fill recording pipettes contained (in mM): CsCl, 145; EGTA, 5; HEPES, 10; glucose, 5; pH=7.4. Recordings were performed using the conventional whole-cell patch clamp technique, 2-3 days after transient transfection of human TRPV2 into HEK293 cell or 1-2 days after plating HEK293 cells stably expressing rat TRPV2 onto glass coverslips. Currents were amplified by a patch clamp amplifier and filtered at 2 kHz (Axopatch 200B), sampled at 10 kHz using Digidata 1322A and acquired and analyzed with pClamp 9.0 (all instruments from Molecular Devices, CA). A 600 ms voltage ramp was given once every five seconds from −100 mV to +60 mV. The holding potential between voltage ramps was −100 mV. Extracellular solutions were applied to the cell at 0.5 ml/min via a gravity-fed perfusion system. All experiments were performed at 22° C.

[0117] As shown in FIG. **5**B, upon application of 100 μM Δ^9-THC, there was a significant increase of the whole-cell current amplitude (gray solid line) in HEK293 cells expressing rTRPV2 compared to control (black dotted line) at both hyperpolarized and depolarized membrane potentials. However, this effect was more pronounced at depolarized potentials. The same concentration of Δ^9-THC elicited no current above control level in untransfected HEK293 cells (data not shown). The Δ^9-THC-activated current had a reversal potential near 0 mV, indicating the relatively unselective (at least for the cations used in these experiments) nature of the channel. Similar effects induced by Δ^9-THC were also observed in human TRPV2 (FIG. **5**A). Furthermore, the Δ^9-THC-activated currents were significantly inhibited by 10 μM ruthenium red (RR), a non-selective TRP channel inhibitor (black line) in both rat and human TRPV2. Taken together, these results indicate that Δ^9-THC activates currents mediated by TRPV2 in these cells.

Example 3

TRPV2 is Activated by Other Cannabinoids

[0118] To further explore activation of TRPV2 by cannabinoids, several different classes of cannabinoids were tested in a FLIPR calcium mobilization assay using 100 μM compound concentrations (except for anandamide which was at 120 μM) as evaluated using rat TRPV2-expressing HEK293 cells. All data was normalized to that observed for 100 μM Δ^9-THC. The tested compounds included: the non-psychoactive constituents of marijuana (cannabidiol and cannabinol); synthetic analogs of THC (nabilone, CP 55,940, HU210, HU211, HU-308, HU331, 11-hydroxy-Δ9-THC, and O-1821); several endocannabinoids (anandamide, 2-arachidonoyl-glycerol (2-AG) and their analog palmitoylethanolamide (PEA)); a cannabinoid transport blocker (AM404); other synthetic cannabinoid receptor agonists (WIN55, 212-2, WIN55, 212-3, JWH015, JWH133, O-1918 and CAY10429); and the non-selective agonist, 2-APB The ability of these compounds to activate rat TRPV2 is shown in Table 1. The data suggest that TRPV2 could be activated by more than one class of cannabinoids.

TABLE 1

Activation of rat TRPV2 by Cannabinoids

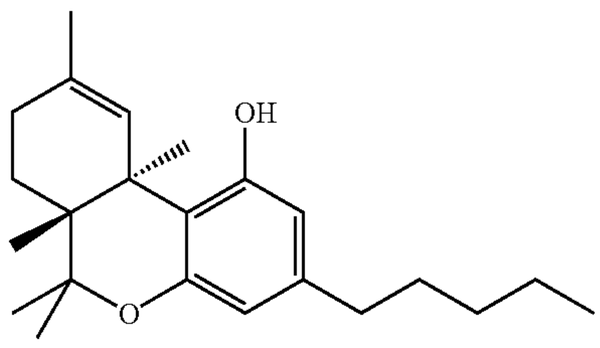
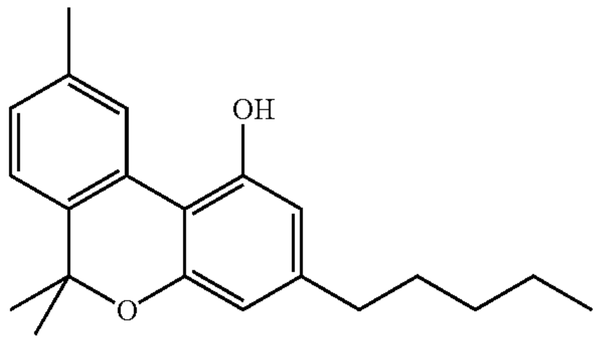
Compound	Compound Structure	% Response	EC_{50}
Δ^9-THC		100	15.5 uM
Cannabinol		68	77.7 uM

TABLE 1-continued

Activation of rat TRPV2 by Cannabinoids

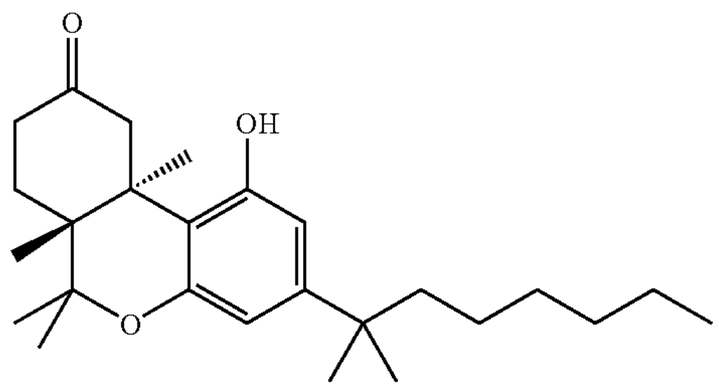
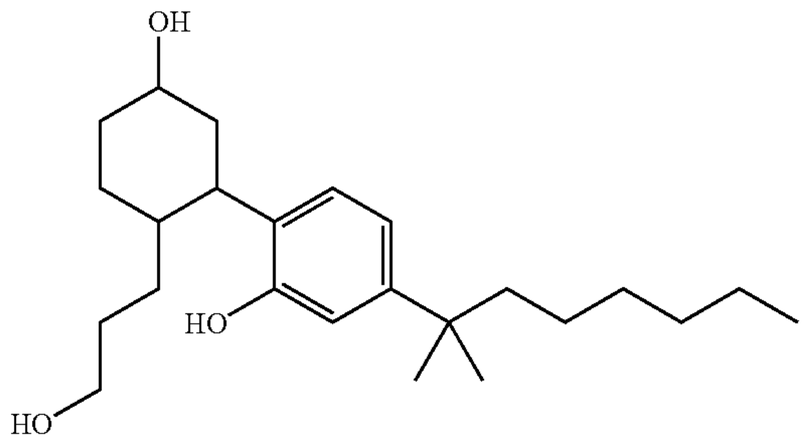
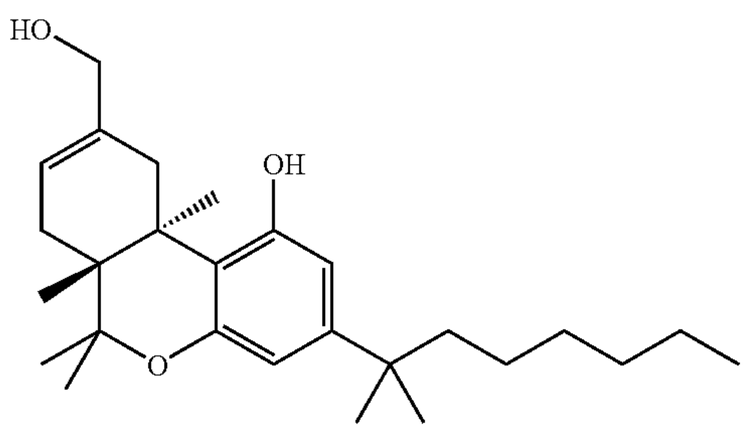
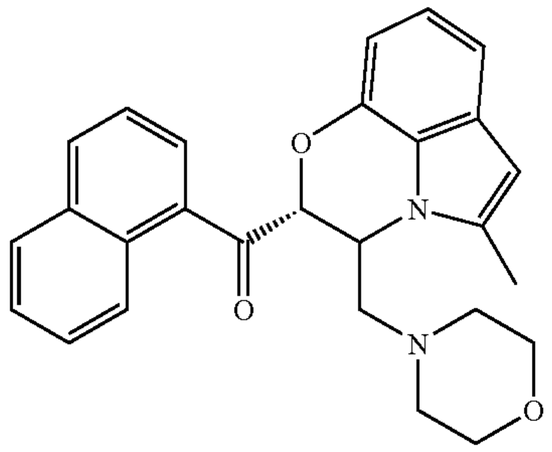
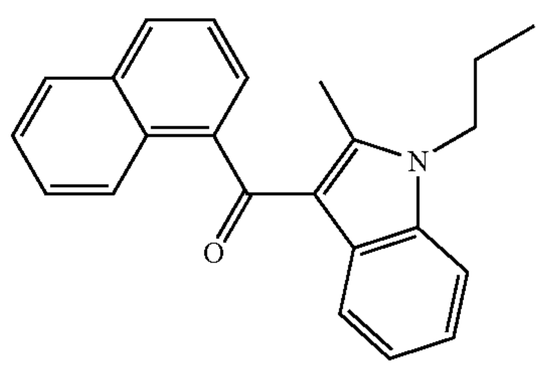
Compound	Compound Structure	% Response	EC_{50}
Nabilone		59	
CP55,940		43	
HU-210		39	
WIN-55,212-2		−2	
JWH015		14	

TABLE 1-continued

Activation of rat TRPV2 by Cannabinoids

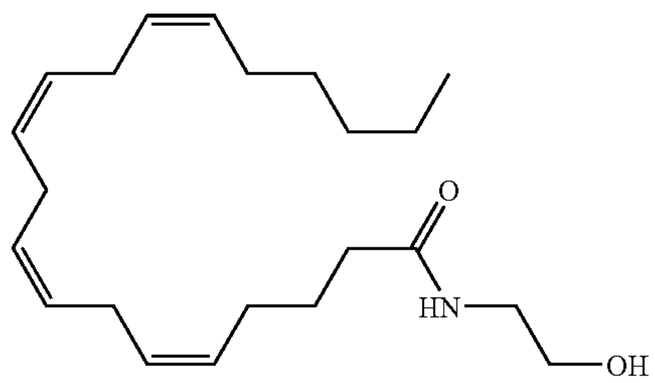
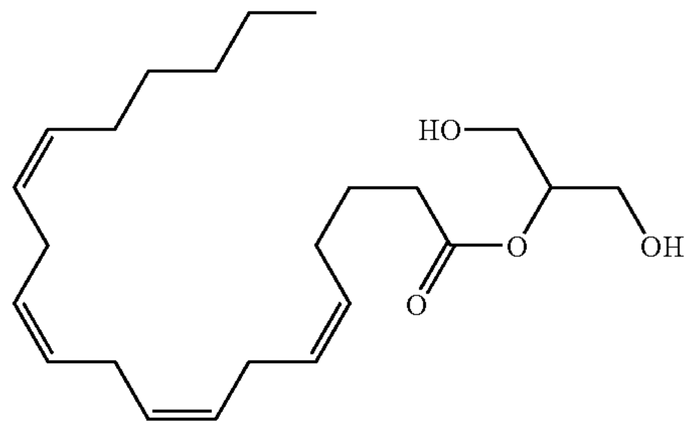
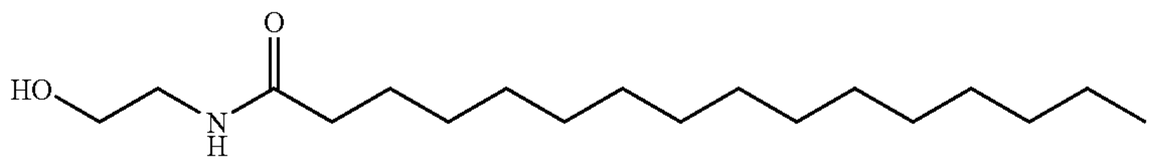
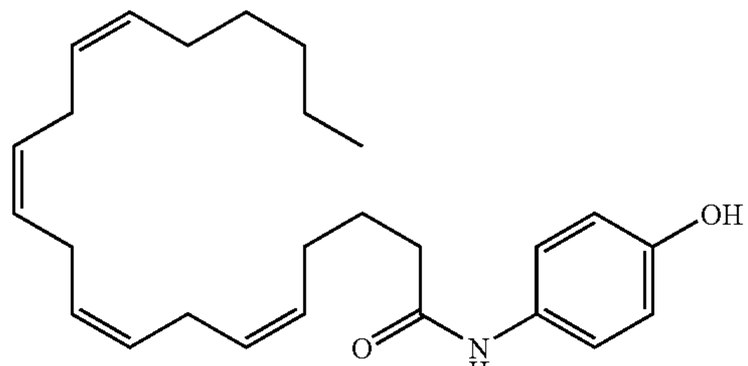
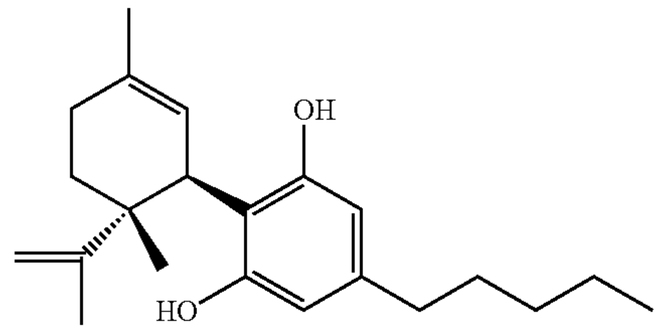
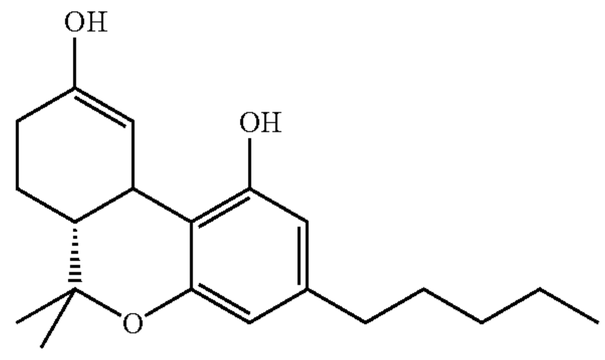
Compound	Compound Structure	% Response	EC_{50}
Anandamide		0	
2-AG		30	
PEA		5	
AM404		6	
Cannabidiol		163	3.7 uM
11-hydroxy-Δ^9-THC		58	

TABLE 1-continued

Activation of rat TRPV2 by Cannabinoids

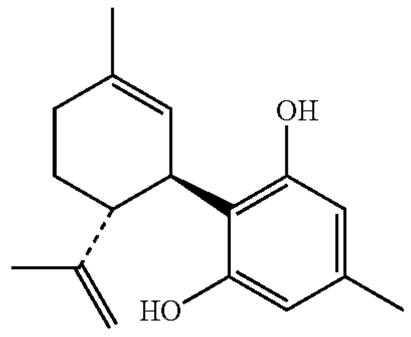
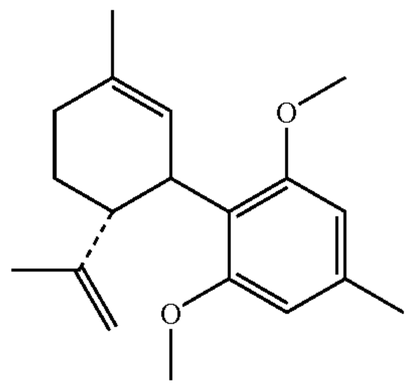
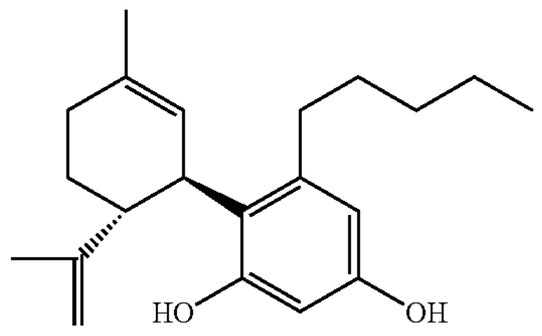
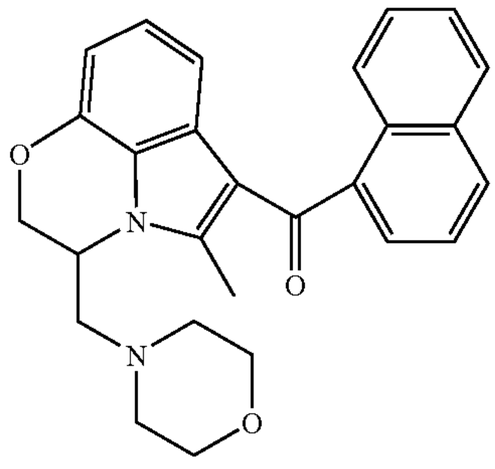
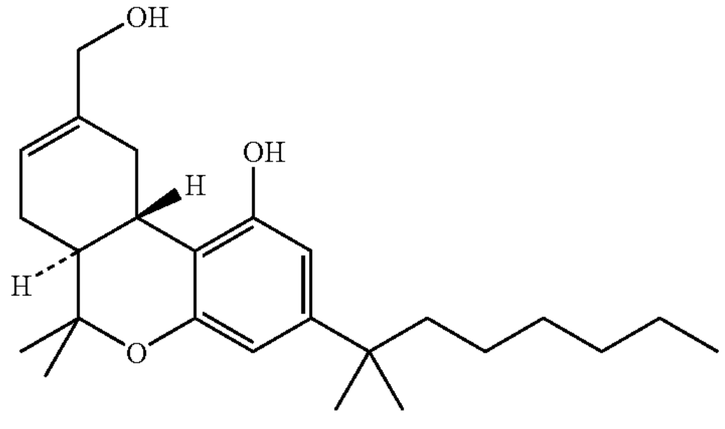
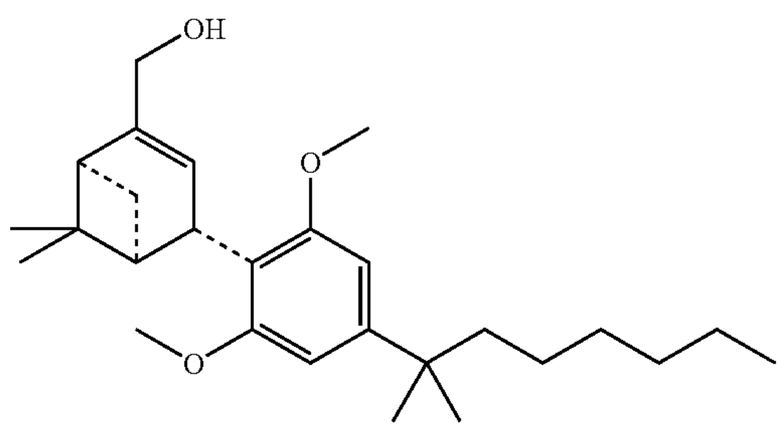
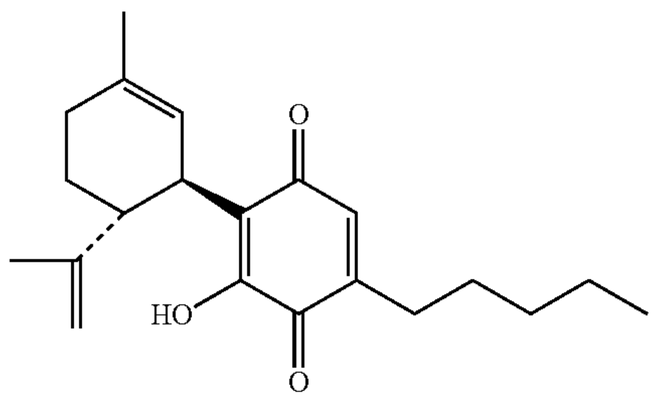
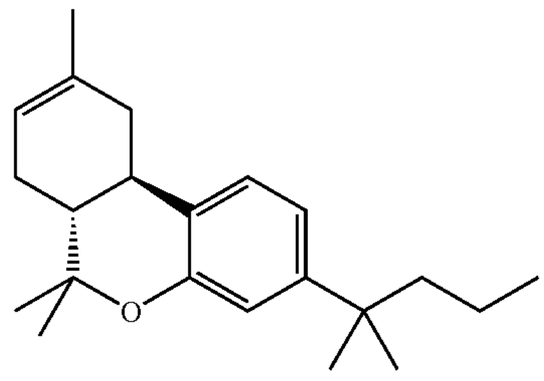
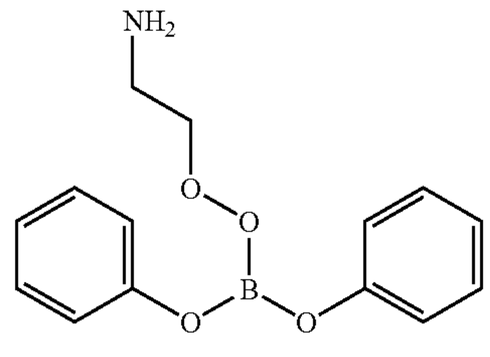
Compound	Compound Structure	% Response	EC_{50}
O-1821		95	~20 uM
O-1918		6	
CAY10429		0	
WIN 55,212-3		7	
HU-211		31	

TABLE 1-continued

Activation of rat TRPV2 by Cannabinoids

Compound	Compound Structure	% Response	EC_{50}
HU-308		10	
HU-331		47	~14 uM
JWH-133		5	
2-APB		102	8.0 uM

Example 4

Δ^9-THC Selectively Activates TRPV2

[0119] A selected number of cannabinoids were also tested against HEK293 cells expressing human TRPV1 and canine TRPM8 in the FLIRP assay. As summarized in Table 2, Δ^9-THC (240 μM) and cannabinol (600 μM) showed no significant activation of TRPV1, whereas anandamide, 2-AG and AM404 activated TRPV1, consistent with previous reports. None of these cannabinoids showed agonist effect against TRPM8.

TABLE 2

Activation of TRP channels by cannabinoids

	TRPV1	TRPV2	TRPM8
Δ^9-THC (240 μM)	−	+	−
Cannabinol (600 μM)	−	+	−
Anandamide (120 μM)	+	−	−
2-AG (120 μM)	+	+	−
AM404 (120 μM)	+	−	−

Example 5

Deletion Mutants of TRPV2 were Activated by Cannabinoids

[0120] TRPV2 deletion mutants were constructed and tested for activation by Δ^9-THC, 2-APB and high temperature stimulation. Methods of this Example can be used to construct and test any type of TRPV2 deletion mutants, including, but not limited to, mutants having one or more amino acid residues deleted at the N-terminal of the TRPV2, at the C-terminal of the TRPV2, and/or at any other location of the TRPV2.

[0121] DNA molecules encoding the deletion mutants were amplified by PCR using the rat TRPV2 cDNA as the template. For amino-terminal deletions, a series N-terminal forward primers encoding an initiating methionine in frame with sequences matching adjacent regions of the desired start at residues G21 (mutant N20, SEQ ID NO:11), P33 (N32, SEQ ID NO:12), A66 (N65, SEQ ID NO:13) and V84 (N83, SEQ ID NO:14) paired with a C-terminal reverse primer were used for PCR amplification. While for carboxyl-terminal deletions, a forward N-terminal primer paired with a series C-terminal reverse primers ending at residues R706 (C51, SEQ ID NO:7), P729 (C32, SEQ ID NO:8), P738 (C23, SEQ ID NO:9) and E750 (C11, SEQ ID NO: 10) with an in-frame stop codon at the terminal end of the open reading frame were used for amplification. After PCR amplification and purification, the DNA molecules encoding the deletion mutants were subcloned into the pCI-neo mammalian expression vector and the constructs were confirmed by DNA sequencing. The DNA molecules that encoded for the various TRPV2 deletion mutants comprised the nucleotide sequences of: SEQ ID NO:18 (N20), SEQ ID NO:19 (N32), SEQ ID NO:20 (N65), SEQ ID NO:21 (N83), SEQ ID NO:22 (C51), SEQ ID NO:23 (C32), SEQ ID NO:24 (C23), and SEQ ID NO:25 (C11).

[0122] The deletion mutant constructs were then transfected into HEK293 cells using Fugene 6 reagent (Roche) as per the manufacturer's instructions. At 24 hours post-transfection, the cells were harvested and replated in fresh DMEM medium supplemented with 10% fetal bovine serum, 100 units/ml penicillin, 100 μg/ml streptomycin and. The cells were distributed onto poly-D-Lysine coated 96- or 384-well plates at a density of approximately 40,000 and 10,000 cells per well, respectively. At approximately 48 hours post-transfection, the medium was removed from the assay plate and replaced with Calcium 3 Dye Buffer (Molecular Devices) using the protocol available from the manufacturer. Calcium mobilization was triggered using Δ^9-THC or 2-APB or elevated temperature buffer and measured using either FLIPR or FLEX STATION instruments.

[0123] It was found that deletion mutants of rat TRPV2 lacking the N-terminal 20, 33, 66, or lacking the C-terminal 11, 23, or 32 amino acid residues were still active in their responses to Δ^9-THC (FIG. **6**), 2-APB and an elevated temperature of about 53° C. (data not shown).

Example 6

Activation of TRPV2 Chimera

[0124] The domain-swapping chimeras between rat and human TRPV2s were also made and tested for activation by Δ^9-THC, 2-APB and high temperature stimulation. Methods of this Example can be used to construct and test any type of TRPV2 chimeras, including, but not limited to, the domain-swapping chimeras between TRPV2s from different animals, and the chimeras between TRPV2 and other TRPV channels such as TRPV1 and TRPV3.

[0125] Based on the predicted topology and primary sequence features of TRPV2, TRPV2 are divided into 3 major domains: 1) the amino-terminal intracellular domain; 2) the transmembrane domain; and 3) the carboxyl-terminal intracellular domain. For a chimera, each domain can be of rat (R) or human (H) origin. Three rat and human TRPV2 chimera were constructed and tested herein. RRH (SEQ ID NO:15) was a chimera comprising rat 1-392 aa, rat 393-646 aa, and human 647-764 aa. RHR (SEQ ID NO:16) was a chimera comprising rat 1-392, human 391-646, and rat 647-761. HRR (SEQ ID NO:17) was a chimera comprising human 1-390, rat 393-646, and rat 647-761.

[0126] DNA molecules encoding the three rat and human TRPV2 chimeras were obtained by fusion PCR. First, DNA molecules encoding the desired TRPV2 domains were amplified by PCR using the rat or human TRPV2 cDNA as the template with synthetic primer DNA containing in-frame sequence that overlapped with the other species domain to be linked. After PCR amplification and purification, DNA molecules encoding the desired TRPV2 domains from human and rat were combined and used as templates for fusion PCR with primer DNA matching the 5' and 3' end sequences of the coding sequence for the full length TRPV2 chimera. The DNA molecules that encoded the various TRPV2 chimeras comprised the nucleotide sequences of: SEQ ID NO: 26 (RRH), SEQ ID NO:27 (RHR), and SEQ ID NO:28 (HRR).

[0127] The DNA molecules encoding the TRPV2 chimera were then subcloned into the mammalian expression vector, pCI-neo and the resulting constructs confirmed by DNA sequencing. The chimeras were transiently expressed in HEK293 cells and their responses to a variety of stimulators were also tested as described in Example 5.

[0128] Chimera RHR was fully responsive to the addition of Δ^9-THC (FIG. **7**A),). Although the HEK cells expressing chimera RRH or HRR separately were poorly, or not active, respectively, the cells co-expressing both chimeras (RRH+HHR) were fully responsive to Δ^9-THC (FIG. **7**B. Similar responses by the above-listed chimeras to 2-APB stimulation were observed (data not shown). The gain of function study by coexpression of two inactive mutants suggests that a functional TRPV2 channel is a complex with multiple subunits and some of the critical functional domains act in trans rather than in cis.

SEQUENCE LISTING

<160> NUMBER OF SEQ ID NOS: 28

<210> SEQ ID NO 1
<211> LENGTH: 2295
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 1

atgacctcac cctccagctc tccagttttc aggttggaga cattagatgg aggccaagaa 60

gatggctctg aggcggacag aggaaagctg gattttggga gcgggctgcc tcccatggag 120

tcacagttcc agggcgagga ccggaaattc gcccctcaga taagagtcaa cctcaactac 180

cgaaagggaa caggtgccag tcagccggat ccaaaccgat ttgaccgaga tcggctcttc 240

aatgcggtct cccggggtgt ccccgaggat ctggctggac ttccagagta cctgagcaag 300

accagcaagt acctcaccga ctcggaatac acagagggct ccacaggtaa gacgtgcctg 360

atgaaggctg tgctgaacct taaggacgga gtcaatgcct gcattctgcc actgctgcag 420

atcgacaggg actctggcaa tcctcagccc ctggtaaatg cccagtgcac agatgactat 480

taccgaggcc acagcgctct gcacatcgcc attgagaaga ggagtctgca gtgtgtgaag 540

ctcctggtgg agaatggggc caatgtgcat gcccgggcct gcggccgctt cttccagaag 600

ggccaaggga cttgctttta tttcggtgag ctacccctct ctttggccgc ttgcaccaag 660

cagtgggatg tggtaagcta cctcctggag aacccacacc agcccgccag cctgcaggcc 720

actgactccc agggcaacac agtcctgcat gccctagtga tgatctcgga caactcagct 780

gagaacattg cactggtgac cagcatgtat gatgggctcc tccaagctgg ggcccgcctc 840

tgccctaccg tgcagcttga ggacatccgc aacctgcagg atctcacgcc tctgaagctg 900

gccgccaagg agggcaagat cgagattttc aggcacatcc tgcagcggga gttttcagga 960

ctgagccacc tttcccgaaa gttcaccgag tggtgctatg ggcctgtccg ggtgtcgctg 1020

tatgacctgg cttctgtgga cagctgtgag gagaactcag tgctggagat cattgccttt 1080

cattgcaaga gcccgcaccg acaccgaatg gtcgttttgg agcccctgaa caaactgctg 1140

caggcgaaat gggatctgct catccccaag ttcttcttaa acttcctgtg taatctgatc 1200

tacatgttca tcttcaccgc tgttgcctac catcagccta ccctgaagaa gcaggccgcc 1260

cctcacctga aagcggaggt tggaaactcc atgctgctga cgggccacat ccttatcctg 1320

ctaggggga tctacctcct cgtgggccag ctgtggtact tctggcggcg ccacgtgttc 1380

atctggatct cgttcataga cagctacttt gaaatcctct tcctgttcca ggccctgctc 1440

acagtggtgt cccaggtgct gtgtttcctg gccatcgagt ggtacctgcc cctgcttgtg 1500

tctgcgctgg tgctgggctg gctgaacctg ctttactata cacgtggctt ccagcacaca 1560

ggcatctaca gtgtcatgat ccagaaggtc atcctgcggg acctgctgcg cttccttctg 1620

atctacttag tcttcctttt cggcttcgct gtagccctgg tgagcctgag ccaggaggct 1680

tggcgccccg aagctcctac aggccccaat gccacagagt cagtgcagcc catggaggga 1740

caggaggacg agggcaacgg ggcccagtac aggggtatcc tggaagcctc cttggagctc 1800

ttcaaattca ccatcggcat gggcgagctg gccttccagg agcagctgca cttccgcggc 1860

atggtgctgc tgctgctgct ggcctacgtg ctgctcacct acatcctgct gctcaacatg 1920

-continued

ctcatcgccc tcatgagcga gaccgtcaac agtgtcgcca ctgacagctg gagcatctgg 1980

aagctgcaga aagccatctc tgtcctggag atggagaatg gctattggtg gtgcaggaag 2040

aagcagcggg caggtgtgat gctgaccgtt ggcactaagc cagatggcag ccccgatgag 2100

cgctggtgct tcagggtgga ggaggtgaac tgggcttcat gggagcagac gctgcctacg 2160

ctgtgtgagg acccgtcagg ggcaggtgtc cctcgaactc tcgagaaccc tgtcctggct 2220

tcccctccca aggaggatga ggatggtgcc tctgaggaaa actatgtgcc cgtccagctc 2280

ctccagtcca actga 2295

<210> SEQ ID NO 2
<211> LENGTH: 764
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 2

Met Thr Ser Pro Ser Ser Ser Pro Val Phe Arg Leu Glu Thr Leu Asp
1 5 10 15

Gly Gly Gln Glu Asp Gly Ser Glu Ala Asp Arg Gly Lys Leu Asp Phe
20 25 30

Gly Ser Gly Leu Pro Pro Met Glu Ser Gln Phe Gln Gly Glu Asp Arg
35 40 45

Lys Phe Ala Pro Gln Ile Arg Val Asn Leu Asn Tyr Arg Lys Gly Thr
50 55 60

Gly Ala Ser Gln Pro Asp Pro Asn Arg Phe Asp Arg Asp Arg Leu Phe
65 70 75 80

Asn Ala Val Ser Arg Gly Val Pro Glu Asp Leu Ala Gly Leu Pro Glu
85 90 95

Tyr Leu Ser Lys Thr Ser Lys Tyr Leu Thr Asp Ser Glu Tyr Thr Glu
100 105 110

Gly Ser Thr Gly Lys Thr Cys Leu Met Lys Ala Val Leu Asn Leu Lys
115 120 125

Asp Gly Val Asn Ala Cys Ile Leu Pro Leu Leu Gln Ile Asp Arg Asp
130 135 140

Ser Gly Asn Pro Gln Pro Leu Val Asn Ala Gln Cys Thr Asp Asp Tyr
145 150 155 160

Tyr Arg Gly His Ser Ala Leu His Ile Ala Ile Glu Lys Arg Ser Leu
165 170 175

Gln Cys Val Lys Leu Leu Val Glu Asn Gly Ala Asn Val His Ala Arg
180 185 190

Ala Cys Gly Arg Phe Phe Gln Lys Gly Gln Gly Thr Cys Phe Tyr Phe
195 200 205

Gly Glu Leu Pro Leu Ser Leu Ala Ala Cys Thr Lys Gln Trp Asp Val
210 215 220

Val Ser Tyr Leu Leu Glu Asn Pro His Gln Pro Ala Ser Leu Gln Ala
225 230 235 240

Thr Asp Ser Gln Gly Asn Thr Val Leu His Ala Leu Val Met Ile Ser
245 250 255

Asp Asn Ser Ala Glu Asn Ile Ala Leu Val Thr Ser Met Tyr Asp Gly
260 265 270

Leu Leu Gln Ala Gly Ala Arg Leu Cys Pro Thr Val Gln Leu Glu Asp
275 280 285

-continued

```
Ile Arg Asn Leu Gln Asp Leu Thr Pro Leu Lys Leu Ala Ala Lys Glu
    290                 295                 300

Gly Lys Ile Glu Ile Phe Arg His Ile Leu Gln Arg Glu Phe Ser Gly
305                 310                 315                 320

Leu Ser His Leu Ser Arg Lys Phe Thr Glu Trp Cys Tyr Gly Pro Val
                325                 330                 335

Arg Val Ser Leu Tyr Asp Leu Ala Ser Val Asp Ser Cys Glu Glu Asn
            340                 345                 350

Ser Val Leu Glu Ile Ile Ala Phe His Cys Lys Ser Pro His Arg His
        355                 360                 365

Arg Met Val Val Leu Glu Pro Leu Asn Lys Leu Leu Gln Ala Lys Trp
    370                 375                 380

Asp Leu Leu Ile Pro Lys Phe Phe Leu Asn Phe Leu Cys Asn Leu Ile
385                 390                 395                 400

Tyr Met Phe Ile Phe Thr Ala Val Ala Tyr His Gln Pro Thr Leu Lys
                405                 410                 415

Lys Gln Ala Ala Pro His Leu Lys Ala Glu Val Gly Asn Ser Met Leu
            420                 425                 430

Leu Thr Gly His Ile Leu Ile Leu Leu Gly Gly Ile Tyr Leu Leu Val
        435                 440                 445

Gly Gln Leu Trp Tyr Phe Trp Arg Arg His Val Phe Ile Trp Ile Ser
    450                 455                 460

Phe Ile Asp Ser Tyr Phe Glu Ile Leu Phe Leu Phe Gln Ala Leu Leu
465                 470                 475                 480

Thr Val Val Ser Gln Val Leu Cys Phe Leu Ala Ile Glu Trp Tyr Leu
                485                 490                 495

Pro Leu Leu Val Ser Ala Leu Val Leu Gly Trp Leu Asn Leu Leu Tyr
            500                 505                 510

Tyr Thr Arg Gly Phe Gln His Thr Gly Ile Tyr Ser Val Met Ile Gln
        515                 520                 525

Lys Val Ile Leu Arg Asp Leu Leu Arg Phe Leu Leu Ile Tyr Leu Val
    530                 535                 540

Phe Leu Phe Gly Phe Ala Val Ala Leu Val Ser Leu Ser Gln Glu Ala
545                 550                 555                 560

Trp Arg Pro Glu Ala Pro Thr Gly Pro Asn Ala Thr Glu Ser Val Gln
                565                 570                 575

Pro Met Glu Gly Gln Glu Asp Glu Gly Asn Gly Ala Gln Tyr Arg Gly
            580                 585                 590

Ile Leu Glu Ala Ser Leu Glu Leu Phe Lys Phe Thr Ile Gly Met Gly
        595                 600                 605

Glu Leu Ala Phe Gln Glu Gln Leu His Phe Arg Gly Met Val Leu Leu
    610                 615                 620

Leu Leu Leu Ala Tyr Val Leu Leu Thr Tyr Ile Leu Leu Leu Asn Met
625                 630                 635                 640

Leu Ile Ala Leu Met Ser Glu Thr Val Asn Ser Val Ala Thr Asp Ser
                645                 650                 655

Trp Ser Ile Trp Lys Leu Gln Lys Ala Ile Ser Val Leu Glu Met Glu
            660                 665                 670

Asn Gly Tyr Trp Trp Cys Arg Lys Lys Gln Arg Ala Gly Val Met Leu
        675                 680                 685

Thr Val Gly Thr Lys Pro Asp Gly Ser Pro Asp Glu Arg Trp Cys Phe
```

-continued

```
    690                 695                 700

Arg Val Glu Glu Val Asn Trp Ala Ser Trp Glu Gln Thr Leu Pro Thr
705                 710                 715                 720

Leu Cys Glu Asp Pro Ser Gly Ala Gly Val Pro Arg Thr Leu Glu Asn
                725                 730                 735

Pro Val Leu Ala Ser Pro Pro Lys Glu Asp Glu Asp Gly Ala Ser Glu
            740                 745                 750

Glu Asn Tyr Val Pro Val Gln Leu Leu Gln Ser Asn
        755                 760
```

<210> SEQ ID NO 3
<211> LENGTH: 2286
<212> TYPE: DNA
<213> ORGANISM: Rattus norvegicus

<400> SEQUENCE: 3

```
atgacttcag cctccagccc cccagctttc aggctggaga cttccgatgg agatgaagag     60

ggcaatgctg aggtgaacaa ggggaagcag gaaccgcccc ccatggagtc accattccag    120

agggaggacc ggaattcctc ccctcagatc aaagtgaacc tcaacttcat aaagagacct    180

cctaaaaaca cttctgctcc cagccagcag gagccagatc ggtttgaccg tgaccgactc    240

ttcagtgtgg tctcccgggg tgtccccgag gaactgactg gactgctaga atacctgcgc    300

tggaacagca agtacctcac tgactctgca tacacagaag gctccactgg aaagacgtgc    360

ctgatgaagg ctgtgctgaa ccttcaggat ggggtcaatg cctgcatcat gccgctgctg    420

cagattgaca aggattccgg caatcccaag cccctcgtca atgcccagtg catcgatgag    480

ttctaccaag gccacagtgc gctgcacatc gccatagaga agaggagcct gcagtgcgtg    540

aagctgctgg tagagaatgg agcggatgtt cacctccgag cctgtggccg cttcttccaa    600

aagcaccaag gaacttgttt ctattttgga gagctacctc tttctctggc tgcgtgcacc    660

aagcagtggg atgtggtgac ctacctcctg gagaacccac accagccggc cagcctggag    720

gccaccgact ccctgggcaa cacagtcctg catgctctgg taatgattgc agataactcg    780

cctgagaaca gtgccctggt gatccacatg tacgacgggc ttctacaaat gggggcgcgc    840

ctctgcccca ctgtgcagct tgaggaaatc tccaaccacc aaggcctcac acccctgaaa    900

ctagccgcca aggaaggcaa aatcgagatt ttcaggcaca ttctgcagcg ggaattctca    960

ggaccgtacc agccccttcc ccgaaagttt actgagtggt gttacggtcc tgtgcgggta   1020

tcgctgtacg acctgtcctc tgtggacagc tgggaaaaga actcggtgct ggagatcatc   1080

gcttttcatt gcaagagccc gaaccggcac cgcatggtgg ttttagaacc actgaacaag   1140

cttctgcagg agaaatggga tcggctcgtc tcaagattct tcttcaactt cgcctgctac   1200

ttggtctaca tgttcatctt caccgtcgtt gcctaccacc agccttccct ggatcagcca   1260

gccatccccc catcaaaagc gacttttggg gaatccatgc tgctgctggg ccacattctg   1320

atcctgcttg ggggtattta cctcttactg ggccagctgt ggtacttttg gcggcggcgc   1380

ctgttcatct ggatctcatt catggacagc tactttgaaa tcctctttct ccttcaggct   1440

ctgctcacag tgctgtccca ggtgctgcgc ttcatggaga ctgaatggta cctacccctg   1500

ctagtgttat ccctagtgct gggctggctg aacctgcttt actacacacg gggctttcag   1560

cacacaggca tctacagtgt catgatccag aaggtcatcc ttcgagacct gctccgtttc   1620
```

-continued

ctgctggtct acctggtctt ccttttcggc tttgctgtag ccctagtaag cttgagcaga 1680

gaggcccgaa gtcccaaagc ccctgaagat aacaactcca cagtgacgga acagcccacg 1740

gtgggccagg aggaggagcc agctccatat cggagcattc tggatgcctc cctagagctg 1800

ttcaagttca ccattggtat gggggagctg gctttccagg aacagctgcg ttttcgtggg 1860

gtggtcctgc tgttgctgtt ggcctacgtc cttctcacct acgtcctgct gctcaacatg 1920

ctcattgctc tcatgagcga aactgtcaac cacgttgctg acaacagctg gagcatctgg 1980

aagttgcaga aagccatctc tgtcttggag atggagaatg gttactggtg gtgccggagg 2040

aagaaacatc gtgaagggag gctgctgaaa gtcggcacca ggggggatgg tacccctgat 2100

gagcgctggt gcttcagggt ggaggaagta aattgggttg cttgggagaa gactcttccc 2160

accttatctg aggatccatc agggccaggc atcactggta ataaaaagaa cccaacctct 2220

aaaccgggga agaacagtgc ctcagaggaa gaccatctgc cccttcaggt cctccagtcc 2280

ccctga 2286

<210> SEQ ID NO 4
<211> LENGTH: 761
<212> TYPE: PRT
<213> ORGANISM: Rattus norvegicus

<400> SEQUENCE: 4

Met Thr Ser Ala Ser Ser Pro Pro Ala Phe Arg Leu Glu Thr Ser Asp
1 5 10 15

Gly Asp Glu Glu Gly Asn Ala Glu Val Asn Lys Gly Lys Gln Glu Pro
20 25 30

Pro Pro Met Glu Ser Pro Phe Gln Arg Glu Asp Arg Asn Ser Ser Pro
35 40 45

Gln Ile Lys Val Asn Leu Asn Phe Ile Lys Arg Pro Pro Lys Asn Thr
50 55 60

Ser Ala Pro Ser Gln Gln Glu Pro Asp Arg Phe Asp Arg Asp Arg Leu
65 70 75 80

Phe Ser Val Val Ser Arg Gly Val Pro Glu Glu Leu Thr Gly Leu Leu
85 90 95

Glu Tyr Leu Arg Trp Asn Ser Lys Tyr Leu Thr Asp Ser Ala Tyr Thr
100 105 110

Glu Gly Ser Thr Gly Lys Thr Cys Leu Met Lys Ala Val Leu Asn Leu
115 120 125

Gln Asp Gly Val Asn Ala Cys Ile Met Pro Leu Leu Gln Ile Asp Lys
130 135 140

Asp Ser Gly Asn Pro Lys Pro Leu Val Asn Ala Gln Cys Ile Asp Glu
145 150 155 160

Phe Tyr Gln Gly His Ser Ala Leu His Ile Ala Ile Glu Lys Arg Ser
165 170 175

Leu Gln Cys Val Lys Leu Leu Val Glu Asn Gly Ala Asp Val His Leu
180 185 190

Arg Ala Cys Gly Arg Phe Phe Gln Lys His Gln Gly Thr Cys Phe Tyr
195 200 205

Phe Gly Glu Leu Pro Leu Ser Leu Ala Ala Cys Thr Lys Gln Trp Asp
210 215 220

Val Val Thr Tyr Leu Leu Glu Asn Pro His Gln Pro Ala Ser Leu Glu
225 230 235 240

-continued

```
Ala Thr Asp Ser Leu Gly Asn Thr Val Leu His Ala Leu Val Met Ile
                245                 250                 255

Ala Asp Asn Ser Pro Glu Asn Ser Ala Leu Val Ile His Met Tyr Asp
            260                 265                 270

Gly Leu Leu Gln Met Gly Ala Arg Leu Cys Pro Thr Val Gln Leu Glu
        275                 280                 285

Glu Ile Ser Asn His Gln Gly Leu Thr Pro Leu Lys Leu Ala Ala Lys
    290                 295                 300

Glu Gly Lys Ile Glu Ile Phe Arg His Ile Leu Gln Arg Glu Phe Ser
305                 310                 315                 320

Gly Pro Tyr Gln Pro Leu Ser Arg Lys Phe Thr Glu Trp Cys Tyr Gly
                325                 330                 335

Pro Val Arg Val Ser Leu Tyr Asp Leu Ser Ser Val Asp Ser Trp Glu
            340                 345                 350

Lys Asn Ser Val Leu Glu Ile Ile Ala Phe His Cys Lys Ser Pro Asn
        355                 360                 365

Arg His Arg Met Val Val Leu Glu Pro Leu Asn Lys Leu Leu Gln Glu
    370                 375                 380

Lys Trp Asp Arg Leu Val Ser Arg Phe Phe Phe Asn Phe Ala Cys Tyr
385                 390                 395                 400

Leu Val Tyr Met Phe Ile Phe Thr Val Val Ala Tyr His Gln Pro Ser
                405                 410                 415

Leu Asp Gln Pro Ala Ile Pro Ser Ser Lys Ala Thr Phe Gly Glu Ser
            420                 425                 430

Met Leu Leu Leu Gly His Ile Leu Ile Leu Leu Gly Gly Ile Tyr Leu
        435                 440                 445

Leu Leu Gly Gln Leu Trp Tyr Phe Trp Arg Arg Arg Leu Phe Ile Trp
    450                 455                 460

Ile Ser Phe Met Asp Ser Tyr Phe Glu Ile Leu Phe Leu Leu Gln Ala
465                 470                 475                 480

Leu Leu Thr Val Leu Ser Gln Val Leu Arg Phe Met Glu Thr Glu Trp
                485                 490                 495

Tyr Leu Pro Leu Leu Val Leu Ser Leu Val Leu Gly Trp Leu Asn Leu
            500                 505                 510

Leu Tyr Tyr Thr Arg Gly Phe Gln His Thr Gly Ile Tyr Ser Val Met
        515                 520                 525

Ile Gln Lys Val Ile Leu Arg Asp Leu Leu Arg Phe Leu Leu Val Tyr
    530                 535                 540

Leu Val Phe Leu Phe Gly Phe Ala Val Ala Leu Val Ser Leu Ser Arg
545                 550                 555                 560

Glu Ala Arg Ser Pro Lys Ala Pro Glu Asp Asn Asn Ser Thr Val Thr
                565                 570                 575

Glu Gln Pro Thr Val Gly Gln Glu Glu Glu Pro Ala Pro Tyr Arg Ser
            580                 585                 590

Ile Leu Asp Ala Ser Leu Glu Leu Phe Lys Phe Thr Ile Gly Met Gly
        595                 600                 605

Glu Leu Ala Phe Gln Glu Gln Leu Arg Phe Arg Gly Val Val Leu Leu
    610                 615                 620

Leu Leu Leu Ala Tyr Val Leu Leu Thr Tyr Val Leu Leu Leu Asn Met
625                 630                 635                 640
```

-continued

Leu Ile Ala Leu Met Ser Glu Thr Val Asn His Val Ala Asp Asn Ser
645 650 655

Trp Ser Ile Trp Lys Leu Gln Lys Ala Ile Ser Val Leu Glu Met Glu
660 665 670

Asn Gly Tyr Trp Trp Cys Arg Arg Lys Lys His Arg Glu Gly Arg Leu
675 680 685

Leu Lys Val Gly Thr Arg Gly Asp Gly Thr Pro Asp Glu Arg Trp Cys
690 695 700

Phe Arg Val Glu Glu Val Asn Trp Val Ala Trp Glu Lys Thr Leu Pro
705 710 715 720

Thr Leu Ser Glu Asp Pro Ser Gly Pro Gly Ile Thr Gly Asn Lys Lys
725 730 735

Asn Pro Thr Ser Lys Pro Gly Lys Asn Ser Ala Ser Glu Glu Asp His
740 745 750

Leu Pro Leu Gln Val Leu Gln Ser Pro
755 760

<210> SEQ ID NO 5
<211> LENGTH: 2271
<212> TYPE: DNA
<213> ORGANISM: Mus musculus

<400> SEQUENCE: 5

atgacttcag cctccaaccc cccagctttt aggctggaga cgtccgatgg agatgaagaa 60

ggcagtgctg aggtgaacaa aggaaagaat gagccacccc ccatggagtc tcccttccag 120

ggagaggacc ggaacttctc ccctcagatt aaagtgaatc tcaactaccg aaagggactg 180

ggtcccagcc aacaggaccc aaatcggttt gaccgtgacc gactcttcag tgtggtctcc 240

cggggtgtcc ccgaggagct gactggactg ctagagtacc tgcgccggac cagcaagtac 300

ctcactgact cggcatacac agaaggctcc actggaaaga cgtgcctgat gaaggctgtg 360

ctgaaccttc aggatggggt caatgcctgt atcctgccgc tgctgcagat tgacagggat 420

tccggcaatc ctcagcccct tgtcaatgcc cagtgcaccg atgagttcta ccgaggccac 480

agtgcgctgc acatcgccat agagaagagg agcctgtggt gcgtgaagct gctggtagag 540

aatggagcga atgttcacat ccgagcctgt ggccgcttct tccaaaagca ccaaggaact 600

tgtttctatt ttggagagct acctctttct ctggcagcgt gcaccaagca gtgggatgtg 660

gtgacctacc tcctggagaa cccacaccag cctgccagcc tggaggccac cgactccctg 720

ggcaacacag tcctgcatgc tctggtaatg attgcagaca actcacctga gaacagtgcg 780

ctggtgatcc acatgtatga cagccttctc caaatggggg cccgcctctg ccccactgta 840

cagcttgagg atatctgcaa ccatcaaggc ttaacacccc tgaagttggc tgccaaggaa 900

ggtaaaattg agatcttcag gcacatcctg cagcgggagt tctcagggct gtaccagccc 960

ctttcccgaa agttcaccga gtggtgctac ggtcctgtcc gagtgtcact gtacgacctg 1020

tcctctgtgg acagttggga aaagaactcg gtcctggaaa tcatcgcttt ccattgcaag 1080

agcccgcacc ggcaccgcat ggtggtttta gagccactga acaagcttct gcaggagaaa 1140

tgggatcggc tcatcccaag attcttcttc aacttcgcct gttacttggt ctacatgatc 1200

atcttcacca tagttgccta ccaccagcct tccctggagc agccagccat tccctcatca 1260

aaagcgactt ttggggactc catgctgctg ttgggccaca ttctgatcct gcttgggggt 1320

-continued

atttacctct tactgggcca gctgtggtac ttttggcggc ggcgcctgtt catctggatc 1380

tcgttcatgg acagttactt tgaaatcctc ttccttgtcc aggcgctgct cacagtgctg 1440

tcccaggtgc tgcgcttcgt ggagactgaa tggtacctcc ccctgttagt gtcatcccta 1500

gtgctgggct ggctgaacct gctttattat acacgtggct ttcagcacac aggcatctac 1560

agtgtcatga tccaaaaggt cattctgcga gacctgctcc gcttcctgct ggtctaccta 1620

gtcttccttt tcggctttgc tgtagcccta gtaagcttga gccgggaggc ccgaagtccc 1680

aaagcccctg aaaatagcaa caccactgtg acggaaaagc ccacgctggg tcaggaggag 1740

gagccagtcc catatggggg cattctggat gcctccctag agctgttcaa gttcaccatt 1800

ggtatgggtg agctggcttt ccaggaacag ctgcgctttc gtggggtggt gctgctgttg 1860

ctgttggcct acgtcctcct cacctacgtc ctactgctca acatgctcat tgccctcatg 1920

agtgagactg tcaacagcgt tgccactgac agctggagca tctggaagtt gcagaaagcc 1980

atctctgtct tggagatgga gaatggttac tggtggtgca ggaggaaaag gcatcgcgca 2040

gggaggctgc tgaaagttgg caccaaaggg gatggtatac ctgatgagcg ctggtgcttc 2100

agggtggagg aagtaaactg ggctgcatgg gagaagaccc ttcccacctt atctgaggat 2160

ccatcagggg caggcatcac tggttataaa aagaacccaa cctctaaacc tgggaagaac 2220

agtgcctcag aggaagacca tctgcctctt caggtcctcc agtcccactg a 2271

<210> SEQ ID NO 6
<211> LENGTH: 756
<212> TYPE: PRT
<213> ORGANISM: Mus musculus

<400> SEQUENCE: 6

Met Thr Ser Ala Ser Asn Pro Pro Ala Phe Arg Leu Glu Thr Ser Asp
1 5 10 15

Gly Asp Glu Glu Gly Ser Ala Glu Val Asn Lys Gly Lys Asn Glu Pro
20 25 30

Pro Pro Met Glu Ser Pro Phe Gln Gly Glu Asp Arg Asn Phe Ser Pro
35 40 45

Gln Ile Lys Val Asn Leu Asn Tyr Arg Lys Gly Leu Gly Pro Ser Gln
50 55 60

Gln Asp Pro Asn Arg Phe Asp Arg Asp Arg Leu Phe Ser Val Val Ser
65 70 75 80

Arg Gly Val Pro Glu Glu Leu Thr Gly Leu Leu Glu Tyr Leu Arg Arg
85 90 95

Thr Ser Lys Tyr Leu Thr Asp Ser Ala Tyr Thr Glu Gly Ser Thr Gly
100 105 110

Lys Thr Cys Leu Met Lys Ala Val Leu Asn Leu Gln Asp Gly Val Asn
115 120 125

Ala Cys Ile Leu Pro Leu Leu Gln Ile Asp Arg Asp Ser Gly Asn Pro
130 135 140

Gln Pro Leu Val Asn Ala Gln Cys Thr Asp Glu Phe Tyr Arg Gly His
145 150 155 160

Ser Ala Leu His Ile Ala Ile Glu Lys Arg Ser Leu Trp Cys Val Lys
165 170 175

Leu Leu Val Glu Asn Gly Ala Asn Val His Ile Arg Ala Cys Gly Arg
180 185 190

-continued

```
Phe Phe Gln Lys His Gln Gly Thr Cys Phe Tyr Phe Gly Glu Leu Pro
        195                 200                 205

Leu Ser Leu Ala Ala Cys Thr Lys Gln Trp Asp Val Val Thr Tyr Leu
    210                 215                 220

Leu Glu Asn Pro His Gln Pro Ala Ser Leu Glu Ala Thr Asp Ser Leu
225                 230                 235                 240

Gly Asn Thr Val Leu His Ala Leu Val Met Ile Ala Asp Asn Ser Pro
                245                 250                 255

Glu Asn Ser Ala Leu Val Ile His Met Tyr Asp Ser Leu Leu Gln Met
            260                 265                 270

Gly Ala Arg Leu Cys Pro Thr Val Gln Leu Glu Asp Ile Cys Asn His
        275                 280                 285

Gln Gly Leu Thr Pro Leu Lys Leu Ala Ala Lys Glu Gly Lys Ile Glu
    290                 295                 300

Ile Phe Arg His Ile Leu Gln Arg Glu Phe Ser Gly Leu Tyr Gln Pro
305                 310                 315                 320

Leu Ser Arg Lys Phe Thr Glu Trp Cys Tyr Gly Pro Val Arg Val Ser
                325                 330                 335

Leu Tyr Asp Leu Ser Ser Val Asp Ser Trp Glu Lys Asn Ser Val Leu
            340                 345                 350

Glu Ile Ile Ala Phe His Cys Lys Ser Pro His Arg His Arg Met Val
        355                 360                 365

Val Leu Glu Pro Leu Asn Lys Leu Leu Gln Glu Lys Trp Asp Arg Leu
    370                 375                 380

Ile Pro Arg Phe Phe Phe Asn Phe Ala Cys Tyr Leu Val Tyr Met Ile
385                 390                 395                 400

Ile Phe Thr Ile Val Ala Tyr His Gln Pro Ser Leu Glu Gln Pro Ala
                405                 410                 415

Ile Pro Ser Ser Lys Ala Thr Phe Gly Asp Ser Met Leu Leu Leu Gly
            420                 425                 430

His Ile Leu Ile Leu Leu Gly Gly Ile Tyr Leu Leu Leu Gly Gln Leu
        435                 440                 445

Trp Tyr Phe Trp Arg Arg Arg Leu Phe Ile Trp Ile Ser Phe Met Asp
    450                 455                 460

Ser Tyr Phe Glu Ile Leu Phe Leu Val Gln Ala Leu Leu Thr Val Leu
465                 470                 475                 480

Ser Gln Val Leu Arg Phe Val Glu Thr Glu Trp Tyr Leu Pro Leu Leu
                485                 490                 495

Val Ser Ser Leu Val Leu Gly Trp Leu Asn Leu Leu Tyr Tyr Thr Arg
            500                 505                 510

Gly Phe Gln His Thr Gly Ile Tyr Ser Val Met Ile Gln Lys Val Ile
        515                 520                 525

Leu Arg Asp Leu Leu Arg Phe Leu Leu Val Tyr Leu Val Phe Leu Phe
    530                 535                 540

Gly Phe Ala Val Ala Leu Val Ser Leu Ser Arg Glu Ala Arg Ser Pro
545                 550                 555                 560

Lys Ala Pro Glu Asn Ser Asn Thr Thr Val Thr Glu Lys Pro Thr Leu
                565                 570                 575

Gly Gln Glu Glu Glu Pro Val Pro Tyr Gly Gly Ile Leu Asp Ala Ser
            580                 585                 590

Leu Glu Leu Phe Lys Phe Thr Ile Gly Met Gly Glu Leu Ala Phe Gln
```

-continued

595 600 605

Glu Gln Leu Arg Phe Arg Gly Val Val Leu Leu Leu Leu Ala Tyr
610 615 620

Val Leu Leu Thr Tyr Val Leu Leu Leu Asn Met Leu Ile Ala Leu Met
625 630 635 640

Ser Glu Thr Val Asn Ser Val Ala Thr Asp Ser Trp Ser Ile Trp Lys
645 650 655

Leu Gln Lys Ala Ile Ser Val Leu Glu Met Glu Asn Gly Tyr Trp Trp
660 665 670

Cys Arg Arg Lys Arg His Arg Ala Gly Arg Leu Leu Lys Val Gly Thr
675 680 685

Lys Gly Asp Gly Ile Pro Asp Glu Arg Trp Cys Phe Arg Val Glu Glu
690 695 700

Val Asn Trp Ala Ala Trp Glu Lys Thr Leu Pro Thr Leu Ser Glu Asp
705 710 715 720

Pro Ser Gly Ala Gly Ile Thr Gly Tyr Lys Lys Asn Pro Thr Ser Lys
725 730 735

Pro Gly Lys Asn Ser Ala Ser Glu Glu Asp His Leu Pro Leu Gln Val
740 745 750

Leu Gln Ser His
755

<210> SEQ ID NO 7
<211> LENGTH: 706
<212> TYPE: PRT
<213> ORGANISM: Rattus norvegicus

<400> SEQUENCE: 7

Met Thr Ser Ala Ser Ser Pro Pro Ala Phe Arg Leu Glu Thr Ser Asp
1 5 10 15

Gly Asp Glu Glu Gly Asn Ala Glu Val Asn Lys Gly Lys Gln Glu Pro
20 25 30

Pro Pro Met Glu Ser Pro Phe Gln Arg Glu Asp Arg Asn Ser Ser Pro
35 40 45

Gln Ile Lys Val Asn Leu Asn Phe Ile Lys Arg Pro Pro Lys Asn Thr
50 55 60

Ser Ala Pro Ser Gln Gln Glu Pro Asp Arg Phe Asp Arg Asp Arg Leu
65 70 75 80

Phe Ser Val Val Ser Arg Gly Val Pro Glu Glu Leu Thr Gly Leu Leu
85 90 95

Glu Tyr Leu Arg Trp Asn Ser Lys Tyr Leu Thr Asp Ser Ala Tyr Thr
100 105 110

Glu Gly Ser Thr Gly Lys Thr Cys Leu Met Lys Ala Val Leu Asn Leu
115 120 125

Gln Asp Gly Val Asn Ala Cys Ile Met Pro Leu Leu Gln Ile Asp Lys
130 135 140

Asp Ser Gly Asn Pro Lys Pro Leu Val Asn Ala Gln Cys Ile Asp Glu
145 150 155 160

Phe Tyr Gln Gly His Ser Ala Leu His Ile Ala Ile Glu Lys Arg Ser
165 170 175

Leu Gln Cys Val Lys Leu Leu Val Glu Asn Gly Ala Asp Val His Leu
180 185 190

-continued

```
Arg Ala Cys Gly Arg Phe Phe Gln Lys His Gln Gly Thr Cys Phe Tyr
        195                 200                 205

Phe Gly Glu Leu Pro Leu Ser Leu Ala Ala Cys Thr Lys Gln Trp Asp
    210                 215                 220

Val Val Thr Tyr Leu Leu Glu Asn Pro His Gln Pro Ala Ser Leu Glu
225                 230                 235                 240

Ala Thr Asp Ser Leu Gly Asn Thr Val Leu His Ala Leu Val Met Ile
                245                 250                 255

Ala Asp Asn Ser Pro Glu Asn Ser Ala Leu Val Ile His Met Tyr Asp
            260                 265                 270

Gly Leu Leu Gln Met Gly Ala Arg Leu Cys Pro Thr Val Gln Leu Glu
        275                 280                 285

Glu Ile Ser Asn His Gln Gly Leu Thr Pro Leu Lys Leu Ala Ala Lys
    290                 295                 300

Glu Gly Lys Ile Glu Ile Phe Arg His Ile Leu Gln Arg Glu Phe Ser
305                 310                 315                 320

Gly Pro Tyr Gln Pro Leu Ser Arg Lys Phe Thr Glu Trp Cys Tyr Gly
                325                 330                 335

Pro Val Arg Val Ser Leu Tyr Asp Leu Ser Ser Val Asp Ser Trp Glu
            340                 345                 350

Lys Asn Ser Val Leu Glu Ile Ile Ala Phe His Cys Lys Ser Pro Asn
        355                 360                 365

Arg His Arg Met Val Val Leu Glu Pro Leu Asn Lys Leu Leu Gln Glu
    370                 375                 380

Lys Trp Asp Arg Leu Val Ser Arg Phe Phe Phe Asn Phe Ala Cys Tyr
385                 390                 395                 400

Leu Val Tyr Met Phe Ile Phe Thr Val Val Ala Tyr His Gln Pro Ser
                405                 410                 415

Leu Asp Gln Pro Ala Ile Pro Ser Ser Lys Ala Thr Phe Gly Glu Ser
            420                 425                 430

Met Leu Leu Leu Gly His Ile Leu Ile Leu Leu Gly Gly Ile Tyr Leu
        435                 440                 445

Leu Leu Gly Gln Leu Trp Tyr Phe Trp Arg Arg Arg Leu Phe Ile Trp
    450                 455                 460

Ile Ser Phe Met Asp Ser Tyr Phe Glu Ile Leu Phe Leu Leu Gln Ala
465                 470                 475                 480

Leu Leu Thr Val Leu Ser Gln Val Leu Arg Phe Met Glu Thr Glu Trp
                485                 490                 495

Tyr Leu Pro Leu Leu Val Leu Ser Leu Val Leu Gly Trp Leu Asn Leu
            500                 505                 510

Leu Tyr Tyr Thr Arg Gly Phe Gln His Thr Gly Ile Tyr Ser Val Met
        515                 520                 525

Ile Gln Lys Val Ile Leu Arg Asp Leu Leu Arg Phe Leu Leu Val Tyr
    530                 535                 540

Leu Val Phe Leu Phe Gly Phe Ala Val Ala Leu Val Ser Leu Ser Arg
545                 550                 555                 560

Glu Ala Arg Ser Pro Lys Ala Pro Glu Asp Asn Asn Ser Thr Val Thr
                565                 570                 575

Glu Gln Pro Thr Val Gly Gln Glu Glu Glu Pro Ala Pro Tyr Arg Ser
            580                 585                 590

Ile Leu Asp Ala Ser Leu Glu Leu Phe Lys Phe Thr Ile Gly Met Gly
```

-continued

```
        595                 600                 605

Glu Leu Ala Phe Gln Glu Gln Leu Arg Phe Arg Gly Val Val Leu Leu
    610                 615                 620

Leu Leu Leu Ala Tyr Val Leu Leu Thr Tyr Val Leu Leu Leu Asn Met
625                 630                 635                 640

Leu Ile Ala Leu Met Ser Glu Thr Val Asn His Val Ala Asp Asn Ser
                645                 650                 655

Trp Ser Ile Trp Lys Leu Gln Lys Ala Ile Ser Val Leu Glu Met Glu
            660                 665                 670

Asn Gly Tyr Trp Trp Cys Arg Arg Lys Lys His Arg Glu Gly Arg Leu
        675                 680                 685

Leu Lys Val Gly Thr Arg Gly Asp Gly Thr Pro Asp Glu Arg Trp Cys
    690                 695                 700

Phe Arg
705


<210> SEQ ID NO 8
<211> LENGTH: 729
<212> TYPE: PRT
<213> ORGANISM: Rattus norvegicus

<400> SEQUENCE: 8

Met Thr Ser Ala Ser Ser Pro Pro Ala Phe Arg Leu Glu Thr Ser Asp
1               5                   10                  15

Gly Asp Glu Glu Gly Asn Ala Glu Val Asn Lys Gly Lys Gln Glu Pro
            20                  25                  30

Pro Pro Met Glu Ser Pro Phe Gln Arg Glu Asp Arg Asn Ser Ser Pro
        35                  40                  45

Gln Ile Lys Val Asn Leu Asn Phe Ile Lys Arg Pro Pro Lys Asn Thr
    50                  55                  60

Ser Ala Pro Ser Gln Gln Glu Pro Asp Arg Phe Asp Arg Asp Arg Leu
65                  70                  75                  80

Phe Ser Val Val Ser Arg Gly Val Pro Glu Glu Leu Thr Gly Leu Leu
                85                  90                  95

Glu Tyr Leu Arg Trp Asn Ser Lys Tyr Leu Thr Asp Ser Ala Tyr Thr
            100                 105                 110

Glu Gly Ser Thr Gly Lys Thr Cys Leu Met Lys Ala Val Leu Asn Leu
        115                 120                 125

Gln Asp Gly Val Asn Ala Cys Ile Met Pro Leu Leu Gln Ile Asp Lys
    130                 135                 140

Asp Ser Gly Asn Pro Lys Pro Leu Val Asn Ala Gln Cys Ile Asp Glu
145                 150                 155                 160

Phe Tyr Gln Gly His Ser Ala Leu His Ile Ala Ile Glu Lys Arg Ser
                165                 170                 175

Leu Gln Cys Val Lys Leu Leu Val Glu Asn Gly Ala Asp Val His Leu
            180                 185                 190

Arg Ala Cys Gly Arg Phe Phe Gln Lys His Gln Gly Thr Cys Phe Tyr
        195                 200                 205

Phe Gly Glu Leu Pro Leu Ser Leu Ala Ala Cys Thr Lys Gln Trp Asp
    210                 215                 220

Val Val Thr Tyr Leu Leu Glu Asn Pro His Gln Pro Ala Ser Leu Glu
225                 230                 235                 240
```

-continued

```
Ala Thr Asp Ser Leu Gly Asn Thr Val Leu His Ala Leu Val Met Ile
                245                 250                 255

Ala Asp Asn Ser Pro Glu Asn Ser Ala Leu Val Ile His Met Tyr Asp
            260                 265                 270

Gly Leu Leu Gln Met Gly Ala Arg Leu Cys Pro Thr Val Gln Leu Glu
        275                 280                 285

Glu Ile Ser Asn His Gln Gly Leu Thr Pro Leu Lys Leu Ala Ala Lys
    290                 295                 300

Glu Gly Lys Ile Glu Ile Phe Arg His Ile Leu Gln Arg Glu Phe Ser
305                 310                 315                 320

Gly Pro Tyr Gln Pro Leu Ser Arg Lys Phe Thr Glu Trp Cys Tyr Gly
                325                 330                 335

Pro Val Arg Val Ser Leu Tyr Asp Leu Ser Ser Val Asp Ser Trp Glu
            340                 345                 350

Lys Asn Ser Val Leu Glu Ile Ile Ala Phe His Cys Lys Ser Pro Asn
        355                 360                 365

Arg His Arg Met Val Val Leu Glu Pro Leu Asn Lys Leu Leu Gln Glu
    370                 375                 380

Lys Trp Asp Arg Leu Val Ser Arg Phe Phe Phe Asn Phe Ala Cys Tyr
385                 390                 395                 400

Leu Val Tyr Met Phe Ile Phe Thr Val Val Ala Tyr His Gln Pro Ser
                405                 410                 415

Leu Asp Gln Pro Ala Ile Pro Ser Ser Lys Ala Thr Phe Gly Glu Ser
            420                 425                 430

Met Leu Leu Leu Gly His Ile Leu Ile Leu Leu Gly Gly Ile Tyr Leu
        435                 440                 445

Leu Leu Gly Gln Leu Trp Tyr Phe Trp Arg Arg Arg Leu Phe Ile Trp
    450                 455                 460

Ile Ser Phe Met Asp Ser Tyr Phe Glu Ile Leu Phe Leu Leu Gln Ala
465                 470                 475                 480

Leu Leu Thr Val Leu Ser Gln Val Leu Arg Phe Met Glu Thr Glu Trp
                485                 490                 495

Tyr Leu Pro Leu Leu Val Leu Ser Leu Val Leu Gly Trp Leu Asn Leu
            500                 505                 510

Leu Tyr Tyr Thr Arg Gly Phe Gln His Thr Gly Ile Tyr Ser Val Met
        515                 520                 525

Ile Gln Lys Val Ile Leu Arg Asp Leu Leu Arg Phe Leu Leu Val Tyr
    530                 535                 540

Leu Val Phe Leu Phe Gly Phe Ala Val Ala Leu Val Ser Leu Ser Arg
545                 550                 555                 560

Glu Ala Arg Ser Pro Lys Ala Pro Glu Asp Asn Asn Ser Thr Val Thr
                565                 570                 575

Glu Gln Pro Thr Val Gly Gln Glu Glu Glu Pro Ala Pro Tyr Arg Ser
            580                 585                 590

Ile Leu Asp Ala Ser Leu Glu Leu Phe Lys Phe Thr Ile Gly Met Gly
        595                 600                 605

Glu Leu Ala Phe Gln Glu Gln Leu Arg Phe Arg Gly Val Val Leu Leu
    610                 615                 620

Leu Leu Leu Ala Tyr Val Leu Leu Thr Tyr Val Leu Leu Leu Asn Met
625                 630                 635                 640

Leu Ile Ala Leu Met Ser Glu Thr Val Asn His Val Ala Asp Asn Ser
```

-continued

```
                645                 650                 655

Trp Ser Ile Trp Lys Leu Gln Lys Ala Ile Ser Val Leu Glu Met Glu
            660                 665                 670

Asn Gly Tyr Trp Trp Cys Arg Arg Lys Lys His Arg Glu Gly Arg Leu
        675                 680                 685

Leu Lys Val Gly Thr Arg Gly Asp Gly Thr Pro Asp Glu Arg Trp Cys
    690                 695                 700

Phe Arg Val Glu Glu Val Asn Trp Val Ala Trp Glu Lys Thr Leu Pro
705                 710                 715                 720

Thr Leu Ser Glu Asp Pro Ser Gly Pro
                725
```

<210> SEQ ID NO 9
<211> LENGTH: 738
<212> TYPE: PRT
<213> ORGANISM: Rattus norvegicus

<400> SEQUENCE: 9

```
Met Thr Ser Ala Ser Ser Pro Pro Ala Phe Arg Leu Glu Thr Ser Asp
1               5                   10                  15

Gly Asp Glu Glu Gly Asn Ala Glu Val Asn Lys Gly Lys Gln Glu Pro
            20                  25                  30

Pro Pro Met Glu Ser Pro Phe Gln Arg Glu Asp Arg Asn Ser Ser Pro
        35                  40                  45

Gln Ile Lys Val Asn Leu Asn Phe Ile Lys Arg Pro Pro Lys Asn Thr
    50                  55                  60

Ser Ala Pro Ser Gln Gln Glu Pro Asp Arg Phe Asp Arg Asp Arg Leu
65                  70                  75                  80

Phe Ser Val Val Ser Arg Gly Val Pro Glu Glu Leu Thr Gly Leu Leu
                85                  90                  95

Glu Tyr Leu Arg Trp Asn Ser Lys Tyr Leu Thr Asp Ser Ala Tyr Thr
            100                 105                 110

Glu Gly Ser Thr Gly Lys Thr Cys Leu Met Lys Ala Val Leu Asn Leu
        115                 120                 125

Gln Asp Gly Val Asn Ala Cys Ile Met Pro Leu Leu Gln Ile Asp Lys
    130                 135                 140

Asp Ser Gly Asn Pro Lys Pro Leu Val Asn Ala Gln Cys Ile Asp Glu
145                 150                 155                 160

Phe Tyr Gln Gly His Ser Ala Leu His Ile Ala Ile Glu Lys Arg Ser
                165                 170                 175

Leu Gln Cys Val Lys Leu Leu Val Glu Asn Gly Ala Asp Val His Leu
            180                 185                 190

Arg Ala Cys Gly Arg Phe Phe Gln Lys His Gln Gly Thr Cys Phe Tyr
        195                 200                 205

Phe Gly Glu Leu Pro Leu Ser Leu Ala Ala Cys Thr Lys Gln Trp Asp
    210                 215                 220

Val Val Thr Tyr Leu Leu Glu Asn Pro His Gln Pro Ala Ser Leu Glu
225                 230                 235                 240

Ala Thr Asp Ser Leu Gly Asn Thr Val Leu His Ala Leu Val Met Ile
                245                 250                 255

Ala Asp Asn Ser Pro Glu Asn Ser Ala Leu Val Ile His Met Tyr Asp
            260                 265                 270
```

-continued

```
Gly Leu Leu Gln Met Gly Ala Arg Leu Cys Pro Thr Val Gln Leu Glu
        275                 280                 285

Glu Ile Ser Asn His Gln Gly Leu Thr Pro Leu Lys Leu Ala Ala Lys
    290                 295                 300

Glu Gly Lys Ile Glu Ile Phe Arg His Ile Leu Gln Arg Glu Phe Ser
305                 310                 315                 320

Gly Pro Tyr Gln Pro Leu Ser Arg Lys Phe Thr Glu Trp Cys Tyr Gly
                325                 330                 335

Pro Val Arg Val Ser Leu Tyr Asp Leu Ser Ser Val Asp Ser Trp Glu
            340                 345                 350

Lys Asn Ser Val Leu Glu Ile Ile Ala Phe His Cys Lys Ser Pro Asn
        355                 360                 365

Arg His Arg Met Val Val Leu Glu Pro Leu Asn Lys Leu Leu Gln Glu
    370                 375                 380

Lys Trp Asp Arg Leu Val Ser Arg Phe Phe Phe Asn Phe Ala Cys Tyr
385                 390                 395                 400

Leu Val Tyr Met Phe Ile Phe Thr Val Val Ala Tyr His Gln Pro Ser
                405                 410                 415

Leu Asp Gln Pro Ala Ile Pro Ser Ser Lys Ala Thr Phe Gly Glu Ser
            420                 425                 430

Met Leu Leu Leu Gly His Ile Leu Ile Leu Leu Gly Gly Ile Tyr Leu
        435                 440                 445

Leu Leu Gly Gln Leu Trp Tyr Phe Trp Arg Arg Arg Leu Phe Ile Trp
    450                 455                 460

Ile Ser Phe Met Asp Ser Tyr Phe Glu Ile Leu Phe Leu Leu Gln Ala
465                 470                 475                 480

Leu Leu Thr Val Leu Ser Gln Val Leu Arg Phe Met Glu Thr Glu Trp
                485                 490                 495

Tyr Leu Pro Leu Leu Val Leu Ser Leu Val Leu Gly Trp Leu Asn Leu
            500                 505                 510

Leu Tyr Tyr Thr Arg Gly Phe Gln His Thr Gly Ile Tyr Ser Val Met
        515                 520                 525

Ile Gln Lys Val Ile Leu Arg Asp Leu Leu Arg Phe Leu Leu Val Tyr
    530                 535                 540

Leu Val Phe Leu Phe Gly Phe Ala Val Ala Leu Val Ser Leu Ser Arg
545                 550                 555                 560

Glu Ala Arg Ser Pro Lys Ala Pro Glu Asp Asn Asn Ser Thr Val Thr
                565                 570                 575

Glu Gln Pro Thr Val Gly Gln Glu Glu Glu Pro Ala Pro Tyr Arg Ser
            580                 585                 590

Ile Leu Asp Ala Ser Leu Glu Leu Phe Lys Phe Thr Ile Gly Met Gly
        595                 600                 605

Glu Leu Ala Phe Gln Glu Gln Leu Arg Phe Arg Gly Val Val Leu Leu
    610                 615                 620

Leu Leu Leu Ala Tyr Val Leu Leu Thr Tyr Val Leu Leu Leu Asn Met
625                 630                 635                 640

Leu Ile Ala Leu Met Ser Glu Thr Val Asn His Val Ala Asp Asn Ser
                645                 650                 655

Trp Ser Ile Trp Lys Leu Gln Lys Ala Ile Ser Val Leu Glu Met Glu
            660                 665                 670

Asn Gly Tyr Trp Trp Cys Arg Arg Lys Lys His Arg Glu Gly Arg Leu
```

-continued

```
        675                 680                 685

Leu Lys Val Gly Thr Arg Gly Asp Gly Thr Pro Asp Glu Arg Trp Cys
    690                 695                 700

Phe Arg Val Glu Glu Val Asn Trp Val Ala Trp Glu Lys Thr Leu Pro
705                 710                 715                 720

Thr Leu Ser Glu Asp Pro Ser Gly Pro Gly Ile Thr Gly Asn Lys Lys
                725                 730                 735

Asn Pro
```

<210> SEQ ID NO 10
<211> LENGTH: 750
<212> TYPE: PRT
<213> ORGANISM: Rattus norvegicus

<400> SEQUENCE: 10

```
Met Thr Ser Ala Ser Ser Pro Pro Ala Phe Arg Leu Glu Thr Ser Asp
1               5                   10                  15

Gly Asp Glu Glu Gly Asn Ala Glu Val Asn Lys Gly Lys Gln Glu Pro
            20                  25                  30

Pro Pro Met Glu Ser Pro Phe Gln Arg Glu Asp Arg Asn Ser Ser Pro
        35                  40                  45

Gln Ile Lys Val Asn Leu Asn Phe Ile Lys Arg Pro Pro Lys Asn Thr
    50                  55                  60

Ser Ala Pro Ser Gln Gln Glu Pro Asp Arg Phe Asp Arg Asp Arg Leu
65                  70                  75                  80

Phe Ser Val Val Ser Arg Gly Val Pro Glu Glu Leu Thr Gly Leu Leu
                85                  90                  95

Glu Tyr Leu Arg Trp Asn Ser Lys Tyr Leu Thr Asp Ser Ala Tyr Thr
            100                 105                 110

Glu Gly Ser Thr Gly Lys Thr Cys Leu Met Lys Ala Val Leu Asn Leu
        115                 120                 125

Gln Asp Gly Val Asn Ala Cys Ile Met Pro Leu Leu Gln Ile Asp Lys
    130                 135                 140

Asp Ser Gly Asn Pro Lys Pro Leu Val Asn Ala Gln Cys Ile Asp Glu
145                 150                 155                 160

Phe Tyr Gln Gly His Ser Ala Leu His Ile Ala Ile Glu Lys Arg Ser
                165                 170                 175

Leu Gln Cys Val Lys Leu Leu Val Glu Asn Gly Ala Asp Val His Leu
            180                 185                 190

Arg Ala Cys Gly Arg Phe Phe Gln Lys His Gln Gly Thr Cys Phe Tyr
        195                 200                 205

Phe Gly Glu Leu Pro Leu Ser Leu Ala Ala Cys Thr Lys Gln Trp Asp
    210                 215                 220

Val Val Thr Tyr Leu Leu Glu Asn Pro His Gln Pro Ala Ser Leu Glu
225                 230                 235                 240

Ala Thr Asp Ser Leu Gly Asn Thr Val Leu His Ala Leu Val Met Ile
                245                 250                 255

Ala Asp Asn Ser Pro Glu Asn Ser Ala Leu Val Ile His Met Tyr Asp
            260                 265                 270

Gly Leu Leu Gln Met Gly Ala Arg Leu Cys Pro Thr Val Gln Leu Glu
        275                 280                 285

Glu Ile Ser Asn His Gln Gly Leu Thr Pro Leu Lys Leu Ala Ala Lys
```

-continued

```
    290                 295                 300

Glu Gly Lys Ile Glu Ile Phe Arg His Ile Leu Gln Arg Glu Phe Ser
305                 310                 315                 320

Gly Pro Tyr Gln Pro Leu Ser Arg Lys Phe Thr Glu Trp Cys Tyr Gly
                325                 330                 335

Pro Val Arg Val Ser Leu Tyr Asp Leu Ser Ser Val Asp Ser Trp Glu
            340                 345                 350

Lys Asn Ser Val Leu Glu Ile Ile Ala Phe His Cys Lys Ser Pro Asn
        355                 360                 365

Arg His Arg Met Val Val Leu Glu Pro Leu Asn Lys Leu Leu Gln Glu
    370                 375                 380

Lys Trp Asp Arg Leu Val Ser Arg Phe Phe Phe Asn Phe Ala Cys Tyr
385                 390                 395                 400

Leu Val Tyr Met Phe Ile Phe Thr Val Val Ala Tyr His Gln Pro Ser
                405                 410                 415

Leu Asp Gln Pro Ala Ile Pro Ser Ser Lys Ala Thr Phe Gly Glu Ser
            420                 425                 430

Met Leu Leu Leu Gly His Ile Leu Ile Leu Leu Gly Gly Ile Tyr Leu
        435                 440                 445

Leu Leu Gly Gln Leu Trp Tyr Phe Trp Arg Arg Arg Leu Phe Ile Trp
    450                 455                 460

Ile Ser Phe Met Asp Ser Tyr Phe Glu Ile Leu Phe Leu Leu Gln Ala
465                 470                 475                 480

Leu Leu Thr Val Leu Ser Gln Val Leu Arg Phe Met Glu Thr Glu Trp
                485                 490                 495

Tyr Leu Pro Leu Leu Val Leu Ser Leu Val Leu Gly Trp Leu Asn Leu
            500                 505                 510

Leu Tyr Tyr Thr Arg Gly Phe Gln His Thr Gly Ile Tyr Ser Val Met
        515                 520                 525

Ile Gln Lys Val Ile Leu Arg Asp Leu Leu Arg Phe Leu Leu Val Tyr
    530                 535                 540

Leu Val Phe Leu Phe Gly Phe Ala Val Ala Leu Val Ser Leu Ser Arg
545                 550                 555                 560

Glu Ala Arg Ser Pro Lys Ala Pro Glu Asp Asn Asn Ser Thr Val Thr
                565                 570                 575

Glu Gln Pro Thr Val Gly Gln Glu Glu Glu Pro Ala Pro Tyr Arg Ser
            580                 585                 590

Ile Leu Asp Ala Ser Leu Glu Leu Phe Lys Phe Thr Ile Gly Met Gly
        595                 600                 605

Glu Leu Ala Phe Gln Glu Gln Leu Arg Phe Arg Gly Val Val Leu Leu
    610                 615                 620

Leu Leu Leu Ala Tyr Val Leu Leu Thr Tyr Val Leu Leu Leu Asn Met
625                 630                 635                 640

Leu Ile Ala Leu Met Ser Glu Thr Val Asn His Val Ala Asp Asn Ser
                645                 650                 655

Trp Ser Ile Trp Lys Leu Gln Lys Ala Ile Ser Val Leu Glu Met Glu
            660                 665                 670

Asn Gly Tyr Trp Trp Cys Arg Arg Lys Lys His Arg Glu Gly Arg Leu
        675                 680                 685

Leu Lys Val Gly Thr Arg Gly Asp Gly Thr Pro Asp Glu Arg Trp Cys
    690                 695                 700
```

-continued

```
Phe Arg Val Glu Glu Val Asn Trp Val Ala Trp Glu Lys Thr Leu Pro
705                 710                 715                 720

Thr Leu Ser Glu Asp Pro Ser Gly Pro Gly Ile Thr Gly Asn Lys Lys
                725                 730                 735

Asn Pro Thr Ser Lys Pro Gly Lys Asn Ser Ala Ser Glu Glu
            740                 745                 750


<210> SEQ ID NO 11
<211> LENGTH: 741
<212> TYPE: PRT
<213> ORGANISM: Rattus norvegicus
<400> SEQUENCE: 11

Gly Asn Ala Glu Val Asn Lys Gly Lys Gln Glu Pro Pro Pro Met Glu
1               5                   10                  15

Ser Pro Phe Gln Arg Glu Asp Arg Asn Ser Ser Pro Gln Ile Lys Val
            20                  25                  30

Asn Leu Asn Phe Ile Lys Arg Pro Pro Lys Asn Thr Ser Ala Pro Ser
        35                  40                  45

Gln Gln Glu Pro Asp Arg Phe Asp Arg Asp Arg Leu Phe Ser Val Val
    50                  55                  60

Ser Arg Gly Val Pro Glu Glu Leu Thr Gly Leu Leu Glu Tyr Leu Arg
65                  70                  75                  80

Trp Asn Ser Lys Tyr Leu Thr Asp Ser Ala Tyr Thr Glu Gly Ser Thr
                85                  90                  95

Gly Lys Thr Cys Leu Met Lys Ala Val Leu Asn Leu Gln Asp Gly Val
            100                 105                 110

Asn Ala Cys Ile Met Pro Leu Leu Gln Ile Asp Lys Asp Ser Gly Asn
        115                 120                 125

Pro Lys Pro Leu Val Asn Ala Gln Cys Ile Asp Glu Phe Tyr Gln Gly
    130                 135                 140

His Ser Ala Leu His Ile Ala Ile Glu Lys Arg Ser Leu Gln Cys Val
145                 150                 155                 160

Lys Leu Leu Val Glu Asn Gly Ala Asp Val His Leu Arg Ala Cys Gly
                165                 170                 175

Arg Phe Phe Gln Lys His Gln Gly Thr Cys Phe Tyr Phe Gly Glu Leu
            180                 185                 190

Pro Leu Ser Leu Ala Ala Cys Thr Lys Gln Trp Asp Val Val Thr Tyr
        195                 200                 205

Leu Leu Glu Asn Pro His Gln Pro Ala Ser Leu Glu Ala Thr Asp Ser
    210                 215                 220

Leu Gly Asn Thr Val Leu His Ala Leu Val Met Ile Ala Asp Asn Ser
225                 230                 235                 240

Pro Glu Asn Ser Ala Leu Val Ile His Met Tyr Asp Gly Leu Leu Gln
                245                 250                 255

Met Gly Ala Arg Leu Cys Pro Thr Val Gln Leu Glu Glu Ile Ser Asn
            260                 265                 270

His Gln Gly Leu Thr Pro Leu Lys Leu Ala Ala Lys Glu Gly Lys Ile
        275                 280                 285

Glu Ile Phe Arg His Ile Leu Gln Arg Glu Phe Ser Gly Pro Tyr Gln
    290                 295                 300

Pro Leu Ser Arg Lys Phe Thr Glu Trp Cys Tyr Gly Pro Val Arg Val
```

-continued

```
305                 310                 315                 320

Ser Leu Tyr Asp Leu Ser Ser Val Asp Ser Trp Glu Lys Asn Ser Val
                325                 330                 335

Leu Glu Ile Ile Ala Phe His Cys Lys Ser Pro Asn Arg His Arg Met
            340                 345                 350

Val Val Leu Glu Pro Leu Asn Lys Leu Leu Gln Glu Lys Trp Asp Arg
        355                 360                 365

Leu Val Ser Arg Phe Phe Phe Asn Phe Ala Cys Tyr Leu Val Tyr Met
    370                 375                 380

Phe Ile Phe Thr Val Val Ala Tyr His Gln Pro Ser Leu Asp Gln Pro
385                 390                 395                 400

Ala Ile Pro Ser Ser Lys Ala Thr Phe Gly Glu Ser Met Leu Leu Leu
                405                 410                 415

Gly His Ile Leu Ile Leu Leu Gly Gly Ile Tyr Leu Leu Leu Gly Gln
            420                 425                 430

Leu Trp Tyr Phe Trp Arg Arg Arg Leu Phe Ile Trp Ile Ser Phe Met
        435                 440                 445

Asp Ser Tyr Phe Glu Ile Leu Phe Leu Leu Gln Ala Leu Leu Thr Val
    450                 455                 460

Leu Ser Gln Val Leu Arg Phe Met Glu Thr Glu Trp Tyr Leu Pro Leu
465                 470                 475                 480

Leu Val Leu Ser Leu Val Leu Gly Trp Leu Asn Leu Leu Tyr Tyr Thr
                485                 490                 495

Arg Gly Phe Gln His Thr Gly Ile Tyr Ser Val Met Ile Gln Lys Val
            500                 505                 510

Ile Leu Arg Asp Leu Leu Arg Phe Leu Leu Val Tyr Leu Val Phe Leu
        515                 520                 525

Phe Gly Phe Ala Val Ala Leu Val Ser Leu Ser Arg Glu Ala Arg Ser
    530                 535                 540

Pro Lys Ala Pro Glu Asp Asn Asn Ser Thr Val Thr Glu Gln Pro Thr
545                 550                 555                 560

Val Gly Gln Glu Glu Glu Pro Ala Pro Tyr Arg Ser Ile Leu Asp Ala
                565                 570                 575

Ser Leu Glu Leu Phe Lys Phe Thr Ile Gly Met Gly Glu Leu Ala Phe
            580                 585                 590

Gln Glu Gln Leu Arg Phe Arg Gly Val Val Leu Leu Leu Leu Leu Ala
        595                 600                 605

Tyr Val Leu Leu Thr Tyr Val Leu Leu Leu Asn Met Leu Ile Ala Leu
    610                 615                 620

Met Ser Glu Thr Val Asn His Val Ala Asp Asn Ser Trp Ser Ile Trp
625                 630                 635                 640

Lys Leu Gln Lys Ala Ile Ser Val Leu Glu Met Glu Asn Gly Tyr Trp
                645                 650                 655

Trp Cys Arg Arg Lys Lys His Arg Glu Gly Arg Leu Leu Lys Val Gly
            660                 665                 670

Thr Arg Gly Asp Gly Thr Pro Asp Glu Arg Trp Cys Phe Arg Val Glu
        675                 680                 685

Glu Val Asn Trp Val Ala Trp Glu Lys Thr Leu Pro Thr Leu Ser Glu
    690                 695                 700

Asp Pro Ser Gly Pro Gly Ile Thr Gly Asn Lys Lys Asn Pro Thr Ser
705                 710                 715                 720
```

-continued

Lys Pro Gly Lys Asn Ser Ala Ser Glu Glu Asp His Leu Pro Leu Gln
725 730 735

Val Leu Gln Ser Pro
740

<210> SEQ ID NO 12
<211> LENGTH: 728
<212> TYPE: PRT
<213> ORGANISM: Rattus norvegicus

<400> SEQUENCE: 12

Pro Pro Met Glu Ser Pro Phe Gln Arg Glu Asp Arg Asn Ser Ser Pro
1 5 10 15

Gln Ile Lys Val Asn Leu Asn Phe Ile Lys Arg Pro Pro Lys Asn Thr
20 25 30

Ser Ala Pro Ser Gln Gln Glu Pro Asp Arg Phe Asp Arg Asp Arg Leu
35 40 45

Phe Ser Val Val Ser Arg Gly Val Pro Glu Glu Leu Thr Gly Leu Leu
50 55 60

Glu Tyr Leu Arg Trp Asn Ser Lys Tyr Leu Thr Asp Ser Ala Tyr Thr
65 70 75 80

Glu Gly Ser Thr Gly Lys Thr Cys Leu Met Lys Ala Val Leu Asn Leu
85 90 95

Gln Asp Gly Val Asn Ala Cys Ile Met Pro Leu Leu Gln Ile Asp Lys
100 105 110

Asp Ser Gly Asn Pro Lys Pro Leu Val Asn Ala Gln Cys Ile Asp Glu
115 120 125

Phe Tyr Gln Gly His Ser Ala Leu His Ile Ala Ile Glu Lys Arg Ser
130 135 140

Leu Gln Cys Val Lys Leu Leu Val Glu Asn Gly Ala Asp Val His Leu
145 150 155 160

Arg Ala Cys Gly Arg Phe Phe Gln Lys His Gln Gly Thr Cys Phe Tyr
165 170 175

Phe Gly Glu Leu Pro Leu Ser Leu Ala Ala Cys Thr Lys Gln Trp Asp
180 185 190

Val Val Thr Tyr Leu Leu Glu Asn Pro His Gln Pro Ala Ser Leu Glu
195 200 205

Ala Thr Asp Ser Leu Gly Asn Thr Val Leu His Ala Leu Val Met Ile
210 215 220

Ala Asp Asn Ser Pro Glu Asn Ser Ala Leu Val Ile His Met Tyr Asp
225 230 235 240

Gly Leu Leu Gln Met Gly Ala Arg Leu Cys Pro Thr Val Gln Leu Glu
245 250 255

Glu Ile Ser Asn His Gln Gly Leu Thr Pro Leu Lys Leu Ala Ala Lys
260 265 270

Glu Gly Lys Ile Glu Ile Phe Arg His Ile Leu Gln Arg Glu Phe Ser
275 280 285

Gly Pro Tyr Gln Pro Leu Ser Arg Lys Phe Thr Glu Trp Cys Tyr Gly
290 295 300

Pro Val Arg Val Ser Leu Tyr Asp Leu Ser Ser Val Asp Ser Trp Glu
305 310 315 320

Lys Asn Ser Val Leu Glu Ile Ile Ala Phe His Cys Lys Ser Pro Asn

-continued

```
                325                 330                 335

Arg His Arg Met Val Val Leu Glu Pro Leu Asn Lys Leu Leu Gln Glu
            340                 345                 350

Lys Trp Asp Arg Leu Val Ser Arg Phe Phe Phe Asn Phe Ala Cys Tyr
        355                 360                 365

Leu Val Tyr Met Phe Ile Phe Thr Val Val Ala Tyr His Gln Pro Ser
    370                 375                 380

Leu Asp Gln Pro Ala Ile Pro Ser Ser Lys Ala Thr Phe Gly Glu Ser
385                 390                 395                 400

Met Leu Leu Leu Gly His Ile Leu Ile Leu Leu Gly Gly Ile Tyr Leu
                405                 410                 415

Leu Leu Gly Gln Leu Trp Tyr Phe Trp Arg Arg Arg Leu Phe Ile Trp
            420                 425                 430

Ile Ser Phe Met Asp Ser Tyr Phe Glu Ile Leu Phe Leu Leu Gln Ala
        435                 440                 445

Leu Leu Thr Val Leu Ser Gln Val Leu Arg Phe Met Glu Thr Glu Trp
    450                 455                 460

Tyr Leu Pro Leu Leu Val Leu Ser Leu Val Leu Gly Trp Leu Asn Leu
465                 470                 475                 480

Leu Tyr Tyr Thr Arg Gly Phe Gln His Thr Gly Ile Tyr Ser Val Met
                485                 490                 495

Ile Gln Lys Val Ile Leu Arg Asp Leu Leu Arg Phe Leu Leu Val Tyr
            500                 505                 510

Leu Val Phe Leu Phe Gly Phe Ala Val Ala Leu Val Ser Leu Ser Arg
        515                 520                 525

Glu Ala Arg Ser Pro Lys Ala Pro Glu Asp Asn Asn Ser Thr Val Thr
    530                 535                 540

Glu Gln Pro Thr Val Gly Gln Glu Glu Glu Pro Ala Pro Tyr Arg Ser
545                 550                 555                 560

Ile Leu Asp Ala Ser Leu Glu Leu Phe Lys Phe Thr Ile Gly Met Gly
                565                 570                 575

Glu Leu Ala Phe Gln Glu Gln Leu Arg Phe Arg Gly Val Val Leu Leu
            580                 585                 590

Leu Leu Leu Ala Tyr Val Leu Leu Thr Tyr Val Leu Leu Leu Asn Met
        595                 600                 605

Leu Ile Ala Leu Met Ser Glu Thr Val Asn His Val Ala Asp Asn Ser
    610                 615                 620

Trp Ser Ile Trp Lys Leu Gln Lys Ala Ile Ser Val Leu Glu Met Glu
625                 630                 635                 640

Asn Gly Tyr Trp Trp Cys Arg Arg Lys Lys His Arg Glu Gly Arg Leu
                645                 650                 655

Leu Lys Val Gly Thr Arg Gly Asp Gly Thr Pro Asp Glu Arg Trp Cys
            660                 665                 670

Phe Arg Val Glu Glu Val Asn Trp Val Ala Trp Glu Lys Thr Leu Pro
        675                 680                 685

Thr Leu Ser Glu Asp Pro Ser Gly Pro Gly Ile Thr Gly Asn Lys Lys
    690                 695                 700

Asn Pro Thr Ser Lys Pro Gly Lys Asn Ser Ala Ser Glu Glu Asp His
705                 710                 715                 720

Leu Pro Leu Gln Val Leu Gln Ser
                725
```

-continued

<210> SEQ ID NO 13
<211> LENGTH: 696
<212> TYPE: PRT
<213> ORGANISM: Rattus norvegicus

<400> SEQUENCE: 13

Ala Pro Ser Gln Gln Glu Pro Asp Arg Phe Asp Arg Asp Arg Leu Phe
1 5 10 15

Ser Val Val Ser Arg Gly Val Pro Glu Glu Leu Thr Gly Leu Leu Glu
20 25 30

Tyr Leu Arg Trp Asn Ser Lys Tyr Leu Thr Asp Ser Ala Tyr Thr Glu
35 40 45

Gly Ser Thr Gly Lys Thr Cys Leu Met Lys Ala Val Leu Asn Leu Gln
50 55 60

Asp Gly Val Asn Ala Cys Ile Met Pro Leu Leu Gln Ile Asp Lys Asp
65 70 75 80

Ser Gly Asn Pro Lys Pro Leu Val Asn Ala Gln Cys Ile Asp Glu Phe
85 90 95

Tyr Gln Gly His Ser Ala Leu His Ile Ala Ile Glu Lys Arg Ser Leu
100 105 110

Gln Cys Val Lys Leu Leu Val Glu Asn Gly Ala Asp Val His Leu Arg
115 120 125

Ala Cys Gly Arg Phe Phe Gln Lys His Gln Gly Thr Cys Phe Tyr Phe
130 135 140

Gly Glu Leu Pro Leu Ser Leu Ala Ala Cys Thr Lys Gln Trp Asp Val
145 150 155 160

Val Thr Tyr Leu Leu Glu Asn Pro His Gln Pro Ala Ser Leu Glu Ala
165 170 175

Thr Asp Ser Leu Gly Asn Thr Val Leu His Ala Leu Val Met Ile Ala
180 185 190

Asp Asn Ser Pro Glu Asn Ser Ala Leu Val Ile His Met Tyr Asp Gly
195 200 205

Leu Leu Gln Met Gly Ala Arg Leu Cys Pro Thr Val Gln Leu Glu Glu
210 215 220

Ile Ser Asn His Gln Gly Leu Thr Pro Leu Lys Leu Ala Ala Lys Glu
225 230 235 240

Gly Lys Ile Glu Ile Phe Arg His Ile Leu Gln Arg Glu Phe Ser Gly
245 250 255

Pro Tyr Gln Pro Leu Ser Arg Lys Phe Thr Glu Trp Cys Tyr Gly Pro
260 265 270

Val Arg Val Ser Leu Tyr Asp Leu Ser Ser Val Asp Ser Trp Glu Lys
275 280 285

Asn Ser Val Leu Glu Ile Ile Ala Phe His Cys Lys Ser Pro Asn Arg
290 295 300

His Arg Met Val Val Leu Glu Pro Leu Asn Lys Leu Leu Gln Glu Lys
305 310 315 320

Trp Asp Arg Leu Val Ser Arg Phe Phe Phe Asn Phe Ala Cys Tyr Leu
325 330 335

Val Tyr Met Phe Ile Phe Thr Val Val Ala Tyr His Gln Pro Ser Leu
340 345 350

Asp Gln Pro Ala Ile Pro Ser Ser Lys Ala Thr Phe Gly Glu Ser Met

-continued

```
        355                 360                 365

Leu Leu Leu Gly His Ile Leu Ile Leu Leu Gly Gly Ile Tyr Leu Leu
    370                 375                 380

Leu Gly Gln Leu Trp Tyr Phe Trp Arg Arg Arg Leu Phe Ile Trp Ile
385                 390                 395                 400

Ser Phe Met Asp Ser Tyr Phe Glu Ile Leu Phe Leu Leu Gln Ala Leu
                405                 410                 415

Leu Thr Val Leu Ser Gln Val Leu Arg Phe Met Glu Thr Glu Trp Tyr
            420                 425                 430

Leu Pro Leu Leu Val Leu Ser Leu Val Leu Gly Trp Leu Asn Leu Leu
        435                 440                 445

Tyr Tyr Thr Arg Gly Phe Gln His Thr Gly Ile Tyr Ser Val Met Ile
    450                 455                 460

Gln Lys Val Ile Leu Arg Asp Leu Leu Arg Phe Leu Leu Val Tyr Leu
465                 470                 475                 480

Val Phe Leu Phe Gly Phe Ala Val Ala Leu Val Ser Leu Ser Arg Glu
                485                 490                 495

Ala Arg Ser Pro Lys Ala Pro Glu Asp Asn Asn Ser Thr Val Thr Glu
            500                 505                 510

Gln Pro Thr Val Gly Gln Glu Glu Glu Pro Ala Pro Tyr Arg Ser Ile
        515                 520                 525

Leu Asp Ala Ser Leu Glu Leu Phe Lys Phe Thr Ile Gly Met Gly Glu
    530                 535                 540

Leu Ala Phe Gln Glu Gln Leu Arg Phe Arg Gly Val Val Leu Leu Leu
545                 550                 555                 560

Leu Leu Ala Tyr Val Leu Leu Thr Tyr Val Leu Leu Leu Asn Met Leu
                565                 570                 575

Ile Ala Leu Met Ser Glu Thr Val Asn His Val Ala Asp Asn Ser Trp
            580                 585                 590

Ser Ile Trp Lys Leu Gln Lys Ala Ile Ser Val Leu Glu Met Glu Asn
        595                 600                 605

Gly Tyr Trp Trp Cys Arg Arg Lys Lys His Arg Glu Gly Arg Leu Leu
    610                 615                 620

Lys Val Gly Thr Arg Gly Asp Gly Thr Pro Asp Glu Arg Trp Cys Phe
625                 630                 635                 640

Arg Val Glu Glu Val Asn Trp Val Ala Trp Glu Lys Thr Leu Pro Thr
                645                 650                 655

Leu Ser Glu Asp Pro Ser Gly Pro Gly Ile Thr Gly Asn Lys Lys Asn
            660                 665                 670

Pro Thr Ser Lys Pro Gly Lys Asn Ser Ala Ser Glu Glu Asp His Leu
        675                 680                 685

Pro Leu Gln Val Leu Gln Ser Pro
    690                 695


<210> SEQ ID NO 14
<211> LENGTH: 678
<212> TYPE: PRT
<213> ORGANISM: Rattus norvegicus

<400> SEQUENCE: 14

Val Ser Arg Gly Val Pro Glu Glu Leu Thr Gly Leu Leu Glu Tyr Leu
1               5                   10                  15
```

-continued

```
Arg Trp Asn Ser Lys Tyr Leu Thr Asp Ser Ala Tyr Thr Glu Gly Ser
            20                  25                  30

Thr Gly Lys Thr Cys Leu Met Lys Ala Val Leu Asn Leu Gln Asp Gly
        35                  40                  45

Val Asn Ala Cys Ile Met Pro Leu Leu Gln Ile Asp Lys Asp Ser Gly
    50                  55                  60

Asn Pro Lys Pro Leu Val Asn Ala Gln Cys Ile Asp Glu Phe Tyr Gln
65                  70                  75                  80

Gly His Ser Ala Leu His Ile Ala Ile Glu Lys Arg Ser Leu Gln Cys
                85                  90                  95

Val Lys Leu Leu Val Glu Asn Gly Ala Asp Val His Leu Arg Ala Cys
            100                 105                 110

Gly Arg Phe Phe Gln Lys His Gln Gly Thr Cys Phe Tyr Phe Gly Glu
        115                 120                 125

Leu Pro Leu Ser Leu Ala Ala Cys Thr Lys Gln Trp Asp Val Val Thr
    130                 135                 140

Tyr Leu Leu Glu Asn Pro His Gln Pro Ala Ser Leu Glu Ala Thr Asp
145                 150                 155                 160

Ser Leu Gly Asn Thr Val Leu His Ala Leu Val Met Ile Ala Asp Asn
                165                 170                 175

Ser Pro Glu Asn Ser Ala Leu Val Ile His Met Tyr Asp Gly Leu Leu
            180                 185                 190

Gln Met Gly Ala Arg Leu Cys Pro Thr Val Gln Leu Glu Glu Ile Ser
        195                 200                 205

Asn His Gln Gly Leu Thr Pro Leu Lys Leu Ala Ala Lys Glu Gly Lys
    210                 215                 220

Ile Glu Ile Phe Arg His Ile Leu Gln Arg Glu Phe Ser Gly Pro Tyr
225                 230                 235                 240

Gln Pro Leu Ser Arg Lys Phe Thr Glu Trp Cys Tyr Gly Pro Val Arg
                245                 250                 255

Val Ser Leu Tyr Asp Leu Ser Ser Val Asp Ser Trp Glu Lys Asn Ser
            260                 265                 270

Val Leu Glu Ile Ile Ala Phe His Cys Lys Ser Pro Asn Arg His Arg
        275                 280                 285

Met Val Val Leu Glu Pro Leu Asn Lys Leu Leu Gln Glu Lys Trp Asp
    290                 295                 300

Arg Leu Val Ser Arg Phe Phe Phe Asn Phe Ala Cys Tyr Leu Val Tyr
305                 310                 315                 320

Met Phe Ile Phe Thr Val Val Ala Tyr His Gln Pro Ser Leu Asp Gln
                325                 330                 335

Pro Ala Ile Pro Ser Ser Lys Ala Thr Phe Gly Glu Ser Met Leu Leu
            340                 345                 350

Leu Gly His Ile Leu Ile Leu Leu Gly Gly Ile Tyr Leu Leu Leu Gly
        355                 360                 365

Gln Leu Trp Tyr Phe Trp Arg Arg Arg Leu Phe Ile Trp Ile Ser Phe
    370                 375                 380

Met Asp Ser Tyr Phe Glu Ile Leu Phe Leu Leu Gln Ala Leu Leu Thr
385                 390                 395                 400

Val Leu Ser Gln Val Leu Arg Phe Met Glu Thr Glu Trp Tyr Leu Pro
                405                 410                 415

Leu Leu Val Leu Ser Leu Val Leu Gly Trp Leu Asn Leu Leu Tyr Tyr
```

-continued

```
            420                 425                 430

Thr Arg Gly Phe Gln His Thr Gly Ile Tyr Ser Val Met Ile Gln Lys
        435                 440                 445

Val Ile Leu Arg Asp Leu Leu Arg Phe Leu Leu Val Tyr Leu Val Phe
    450                 455                 460

Leu Phe Gly Phe Ala Val Ala Leu Val Ser Leu Ser Arg Glu Ala Arg
465                 470                 475                 480

Ser Pro Lys Ala Pro Glu Asp Asn Asn Ser Thr Val Thr Glu Gln Pro
                485                 490                 495

Thr Val Gly Gln Glu Glu Glu Pro Ala Pro Tyr Arg Ser Ile Leu Asp
            500                 505                 510

Ala Ser Leu Glu Leu Phe Lys Phe Thr Ile Gly Met Gly Glu Leu Ala
        515                 520                 525

Phe Gln Glu Gln Leu Arg Phe Arg Gly Val Val Leu Leu Leu Leu Leu
    530                 535                 540

Ala Tyr Val Leu Leu Thr Tyr Val Leu Leu Leu Asn Met Leu Ile Ala
545                 550                 555                 560

Leu Met Ser Glu Thr Val Asn His Val Ala Asp Asn Ser Trp Ser Ile
                565                 570                 575

Trp Lys Leu Gln Lys Ala Ile Ser Val Leu Glu Met Glu Asn Gly Tyr
            580                 585                 590

Trp Trp Cys Arg Arg Lys Lys His Arg Glu Gly Arg Leu Leu Lys Val
        595                 600                 605

Gly Thr Arg Gly Asp Gly Thr Pro Asp Glu Arg Trp Cys Phe Arg Val
    610                 615                 620

Glu Glu Val Asn Trp Val Ala Trp Glu Lys Thr Leu Pro Thr Leu Ser
625                 630                 635                 640

Glu Asp Pro Ser Gly Pro Gly Ile Thr Gly Asn Lys Lys Asn Pro Thr
                645                 650                 655

Ser Lys Pro Gly Lys Asn Ser Ala Ser Glu Glu Asp His Leu Pro Leu
            660                 665                 670

Gln Val Leu Gln Ser Pro
        675
```

<210> SEQ ID NO 15
<211> LENGTH: 764
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide

<400> SEQUENCE: 15

```
Met Thr Ser Ala Ser Ser Pro Pro Ala Phe Arg Leu Glu Thr Ser Asp
1               5                   10                  15

Gly Asp Glu Glu Gly Asn Ala Glu Val Asn Lys Gly Lys Gln Glu Pro
            20                  25                  30

Pro Pro Met Glu Ser Pro Phe Gln Arg Glu Asp Arg Asn Ser Ser Pro
        35                  40                  45

Gln Ile Lys Val Asn Leu Asn Phe Ile Lys Arg Pro Pro Lys Asn Thr
    50                  55                  60

Ser Ala Pro Ser Gln Gln Glu Pro Asp Arg Phe Asp Arg Asp Arg Leu
65                  70                  75                  80
```

-continued

```
Phe Ser Val Val Ser Arg Gly Val Pro Glu Glu Leu Thr Gly Leu Leu
                85                  90                  95

Glu Tyr Leu Arg Trp Asn Ser Lys Tyr Leu Thr Asp Ser Ala Tyr Thr
            100                 105                 110

Glu Gly Ser Thr Gly Lys Thr Cys Leu Met Lys Ala Val Leu Asn Leu
        115                 120                 125

Gln Asp Gly Val Asn Ala Cys Ile Met Pro Leu Leu Gln Ile Asp Lys
    130                 135                 140

Asp Ser Gly Asn Pro Lys Pro Leu Val Asn Ala Gln Cys Ile Asp Glu
145                 150                 155                 160

Phe Tyr Gln Gly His Ser Ala Leu His Ile Ala Ile Glu Lys Arg Ser
                165                 170                 175

Leu Gln Cys Val Lys Leu Leu Val Glu Asn Gly Ala Asp Val His Leu
            180                 185                 190

Arg Ala Cys Gly Arg Phe Phe Gln Lys His Gln Gly Thr Cys Phe Tyr
        195                 200                 205

Phe Gly Glu Leu Pro Leu Ser Leu Ala Ala Cys Thr Lys Gln Trp Asp
    210                 215                 220

Val Val Thr Tyr Leu Leu Glu Asn Pro His Gln Pro Ala Ser Leu Glu
225                 230                 235                 240

Ala Thr Asp Ser Leu Gly Asn Thr Val Leu His Ala Leu Val Met Ile
                245                 250                 255

Ala Asp Asn Ser Pro Glu Asn Ser Ala Leu Val Ile His Met Tyr Asp
            260                 265                 270

Gly Leu Leu Gln Met Gly Ala Arg Leu Cys Pro Thr Val Gln Leu Glu
        275                 280                 285

Glu Ile Ser Asn His Gln Gly Leu Thr Pro Leu Lys Leu Ala Ala Lys
    290                 295                 300

Glu Gly Lys Ile Glu Ile Phe Arg His Ile Leu Gln Arg Glu Phe Ser
305                 310                 315                 320

Gly Pro Tyr Gln Pro Leu Ser Arg Lys Phe Thr Glu Trp Cys Tyr Gly
                325                 330                 335

Pro Val Arg Val Ser Leu Tyr Asp Leu Ser Ser Val Asp Ser Trp Glu
            340                 345                 350

Lys Asn Ser Val Leu Glu Ile Ile Ala Phe His Cys Lys Ser Pro Asn
        355                 360                 365

Arg His Arg Met Val Val Leu Glu Pro Leu Asn Lys Leu Leu Gln Glu
    370                 375                 380

Lys Trp Asp Arg Leu Val Ser Arg Phe Phe Phe Asn Phe Ala Cys Tyr
385                 390                 395                 400

Leu Val Tyr Met Phe Ile Phe Thr Val Val Ala Tyr His Gln Pro Ser
                405                 410                 415

Leu Asp Gln Pro Ala Ile Pro Ser Ser Lys Ala Thr Phe Gly Glu Ser
            420                 425                 430

Met Leu Leu Leu Gly His Ile Leu Ile Leu Leu Gly Gly Ile Tyr Leu
        435                 440                 445

Leu Leu Gly Gln Leu Trp Tyr Phe Trp Arg Arg Arg Leu Phe Ile Trp
    450                 455                 460

Ile Ser Phe Met Asp Ser Tyr Phe Glu Ile Leu Phe Leu Leu Gln Ala
465                 470                 475                 480

Leu Leu Thr Val Leu Ser Gln Val Leu Arg Phe Met Glu Thr Glu Trp
```

-continued

```
                485                 490                 495

Tyr Leu Pro Leu Leu Val Leu Ser Leu Val Leu Gly Trp Leu Asn Leu
            500                 505                 510

Leu Tyr Tyr Thr Arg Gly Phe Gln His Thr Gly Ile Tyr Ser Val Met
        515                 520                 525

Ile Gln Lys Val Ile Leu Arg Asp Leu Leu Arg Phe Leu Leu Val Tyr
    530                 535                 540

Leu Val Phe Leu Phe Gly Phe Ala Val Ala Leu Val Ser Leu Ser Arg
545                 550                 555                 560

Glu Ala Arg Ser Pro Lys Ala Pro Glu Asp Asn Asn Ser Thr Val Thr
                565                 570                 575

Glu Gln Pro Thr Val Gly Gln Glu Glu Glu Pro Ala Pro Tyr Arg Ser
            580                 585                 590

Ile Leu Asp Ala Ser Leu Glu Leu Phe Lys Phe Thr Ile Gly Met Gly
        595                 600                 605

Glu Leu Ala Phe Gln Glu Gln Leu Arg Phe Arg Gly Val Val Leu Leu
    610                 615                 620

Leu Leu Leu Ala Tyr Val Leu Leu Thr Tyr Val Leu Leu Leu Asn Met
625                 630                 635                 640

Leu Ile Ala Leu Met Ser Glu Thr Val Asn Ser Val Ala Thr Asp Ser
                645                 650                 655

Trp Ser Ile Trp Lys Leu Gln Lys Ala Ile Ser Val Leu Glu Met Glu
            660                 665                 670

Asn Gly Tyr Trp Trp Cys Arg Lys Lys Gln Arg Ala Gly Val Met Leu
        675                 680                 685

Thr Val Gly Thr Lys Pro Asp Gly Ser Pro Asp Glu Arg Trp Cys Phe
    690                 695                 700

Arg Val Glu Glu Val Asn Trp Ala Ser Trp Glu Gln Thr Leu Pro Thr
705                 710                 715                 720

Leu Cys Glu Asp Pro Ser Gly Ala Gly Val Pro Arg Thr Leu Glu Asn
                725                 730                 735

Pro Val Leu Ala Ser Pro Pro Lys Glu Asp Glu Asp Gly Ala Ser Glu
            740                 745                 750

Glu Asn Tyr Val Pro Val Gln Leu Leu Gln Ser Asn
        755                 760


<210> SEQ ID NO 16
<211> LENGTH: 763
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      polypeptide

<400> SEQUENCE: 16

Met Thr Ser Ala Ser Ser Pro Pro Ala Phe Arg Leu Glu Thr Ser Asp
1               5                   10                  15

Gly Asp Glu Glu Gly Asn Ala Glu Val Asn Lys Gly Lys Gln Glu Pro
            20                  25                  30

Pro Pro Met Glu Ser Pro Phe Gln Arg Glu Asp Arg Asn Ser Ser Pro
        35                  40                  45

Gln Ile Lys Val Asn Leu Asn Phe Ile Lys Arg Pro Pro Lys Asn Thr
    50                  55                  60
```

-continued

```
Ser Ala Pro Ser Gln Gln Glu Pro Asp Arg Phe Asp Arg Asp Arg Leu
65                  70                  75                  80

Phe Ser Val Val Ser Arg Gly Val Pro Glu Glu Leu Thr Gly Leu Leu
                85                  90                  95

Glu Tyr Leu Arg Trp Asn Ser Lys Tyr Leu Thr Asp Ser Ala Tyr Thr
            100                 105                 110

Glu Gly Ser Thr Gly Lys Thr Cys Leu Met Lys Ala Val Leu Asn Leu
        115                 120                 125

Gln Asp Gly Val Asn Ala Cys Ile Met Pro Leu Leu Gln Ile Asp Lys
    130                 135                 140

Asp Ser Gly Asn Pro Lys Pro Leu Val Asn Ala Gln Cys Ile Asp Glu
145                 150                 155                 160

Phe Tyr Gln Gly His Ser Ala Leu His Ile Ala Ile Glu Lys Arg Ser
                165                 170                 175

Leu Gln Cys Val Lys Leu Leu Val Glu Asn Gly Ala Asp Val His Leu
            180                 185                 190

Arg Ala Cys Gly Arg Phe Phe Gln Lys His Gln Gly Thr Cys Phe Tyr
        195                 200                 205

Phe Gly Glu Leu Pro Leu Ser Leu Ala Ala Cys Thr Lys Gln Trp Asp
    210                 215                 220

Val Val Thr Tyr Leu Leu Glu Asn Pro His Gln Pro Ala Ser Leu Glu
225                 230                 235                 240

Ala Thr Asp Ser Leu Gly Asn Thr Val Leu His Ala Leu Val Met Ile
                245                 250                 255

Ala Asp Asn Ser Pro Glu Asn Ser Ala Leu Val Ile His Met Tyr Asp
            260                 265                 270

Gly Leu Leu Gln Met Gly Ala Arg Leu Cys Pro Thr Val Gln Leu Glu
        275                 280                 285

Glu Ile Ser Asn His Gln Gly Leu Thr Pro Leu Lys Leu Ala Ala Lys
    290                 295                 300

Glu Gly Lys Ile Glu Ile Phe Arg His Ile Leu Gln Arg Glu Phe Ser
305                 310                 315                 320

Gly Pro Tyr Gln Pro Leu Ser Arg Lys Phe Thr Glu Trp Cys Tyr Gly
                325                 330                 335

Pro Val Arg Val Ser Leu Tyr Asp Leu Ser Ser Val Asp Ser Trp Glu
            340                 345                 350

Lys Asn Ser Val Leu Glu Ile Ile Ala Phe His Cys Lys Ser Pro Asn
        355                 360                 365

Arg His Arg Met Val Val Leu Glu Pro Leu Asn Lys Leu Leu Gln Glu
    370                 375                 380

Lys Trp Asp Arg Leu Val Ser Arg Phe Phe Leu Asn Phe Leu Cys Asn
385                 390                 395                 400

Leu Ile Tyr Met Phe Ile Phe Thr Ala Val Ala Tyr His Gln Pro Thr
                405                 410                 415

Leu Lys Lys Gln Ala Ala Pro His Leu Lys Ala Glu Val Gly Asn Ser
            420                 425                 430

Met Leu Leu Thr Gly His Ile Leu Ile Leu Leu Gly Gly Ile Tyr Leu
        435                 440                 445

Leu Val Gly Gln Leu Trp Tyr Phe Trp Arg Arg His Val Phe Ile Trp
    450                 455                 460

Ile Ser Phe Ile Asp Ser Tyr Phe Glu Ile Leu Phe Leu Phe Gln Ala
```

-continued

```
465                 470                 475                 480

Leu Leu Thr Val Val Ser Gln Val Leu Cys Phe Leu Ala Ile Glu Trp
                485                 490                 495

Tyr Leu Pro Leu Leu Val Ser Ala Leu Val Leu Gly Trp Leu Asn Leu
            500                 505                 510

Leu Tyr Tyr Thr Arg Gly Phe Gln His Thr Gly Ile Tyr Ser Val Met
        515                 520                 525

Ile Gln Lys Val Ile Leu Arg Asp Leu Leu Arg Phe Leu Leu Ile Tyr
    530                 535                 540

Leu Val Phe Leu Phe Gly Phe Ala Val Ala Leu Val Ser Leu Ser Gln
545                 550                 555                 560

Glu Ala Trp Arg Pro Glu Ala Pro Thr Gly Pro Asn Ala Thr Glu Ser
                565                 570                 575

Val Gln Pro Met Glu Gly Gln Glu Asp Glu Gly Asn Gly Ala Gln Tyr
            580                 585                 590

Arg Gly Ile Leu Glu Ala Ser Leu Glu Leu Phe Lys Phe Thr Ile Gly
        595                 600                 605

Met Gly Glu Leu Ala Phe Gln Glu Gln Leu His Phe Arg Gly Met Val
    610                 615                 620

Leu Leu Leu Leu Leu Ala Tyr Val Leu Leu Thr Tyr Ile Leu Leu Leu
625                 630                 635                 640

Asn Met Leu Ile Ala Leu Met Ser Glu Thr Val Asn His Val Ala Asp
                645                 650                 655

Asn Ser Trp Ser Ile Trp Lys Leu Gln Lys Ala Ile Ser Val Leu Glu
            660                 665                 670

Met Glu Asn Gly Tyr Trp Trp Cys Arg Arg Lys Lys His Arg Glu Gly
        675                 680                 685

Arg Leu Leu Lys Val Gly Thr Arg Gly Asp Gly Thr Pro Asp Glu Arg
    690                 695                 700

Trp Cys Phe Arg Val Glu Glu Val Asn Trp Val Ala Trp Glu Lys Thr
705                 710                 715                 720

Leu Pro Thr Leu Ser Glu Asp Pro Ser Gly Pro Gly Ile Thr Gly Asn
                725                 730                 735

Lys Lys Asn Pro Thr Ser Lys Pro Gly Lys Asn Ser Ala Ser Glu Glu
            740                 745                 750

Asp His Leu Pro Leu Gln Val Leu Gln Ser Pro
        755                 760
```

<210> SEQ ID NO 17
<211> LENGTH: 759
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide

<400> SEQUENCE: 17

```
Met Thr Ser Pro Ser Ser Ser Pro Val Phe Arg Leu Glu Thr Leu Asp
1               5                   10                  15

Gly Gly Gln Glu Asp Gly Ser Glu Ala Asp Arg Gly Lys Leu Asp Phe
            20                  25                  30

Gly Ser Gly Leu Pro Pro Met Glu Ser Gln Phe Gln Gly Glu Asp Arg
        35                  40                  45
```

-continued

```
Lys Phe Ala Pro Gln Ile Arg Val Asn Leu Asn Tyr Arg Lys Gly Thr
    50                  55                  60

Gly Ala Ser Gln Pro Asp Pro Asn Arg Phe Asp Arg Asp Arg Leu Phe
65                  70                  75                  80

Asn Ala Val Ser Arg Gly Val Pro Glu Asp Leu Ala Gly Leu Pro Glu
                85                  90                  95

Tyr Leu Ser Lys Thr Ser Lys Tyr Leu Thr Asp Ser Glu Tyr Thr Glu
            100                 105                 110

Gly Ser Thr Gly Lys Thr Cys Leu Met Lys Ala Val Leu Asn Leu Lys
        115                 120                 125

Asp Gly Val Asn Ala Cys Ile Leu Pro Leu Leu Gln Ile Asp Arg Asp
    130                 135                 140

Ser Gly Asn Pro Gln Pro Leu Val Asn Ala Gln Cys Thr Asp Asp Tyr
145                 150                 155                 160

Tyr Arg Gly His Ser Ala Leu His Ile Ala Ile Glu Lys Arg Ser Leu
                165                 170                 175

Gln Cys Val Lys Leu Leu Val Glu Asn Gly Ala Asn Val His Ala Arg
            180                 185                 190

Ala Cys Gly Arg Phe Phe Gln Lys Gly Gln Gly Thr Cys Phe Tyr Phe
        195                 200                 205

Gly Glu Leu Pro Leu Ser Leu Ala Ala Cys Thr Lys Gln Trp Asp Val
    210                 215                 220

Val Ser Tyr Leu Leu Glu Asn Pro His Gln Pro Ala Ser Leu Gln Ala
225                 230                 235                 240

Thr Asp Ser Gln Gly Asn Thr Val Leu His Ala Leu Val Met Ile Ser
                245                 250                 255

Asp Asn Ser Ala Glu Asn Ile Ala Leu Val Thr Ser Met Tyr Asp Gly
            260                 265                 270

Leu Leu Gln Ala Gly Ala Arg Leu Cys Pro Thr Val Gln Leu Glu Asp
        275                 280                 285

Ile Arg Asn Leu Gln Asp Leu Thr Pro Leu Lys Leu Ala Ala Lys Glu
    290                 295                 300

Gly Lys Ile Glu Ile Phe Arg His Ile Leu Gln Arg Glu Phe Ser Gly
305                 310                 315                 320

Leu Ser His Leu Ser Arg Lys Phe Thr Glu Trp Cys Tyr Gly Pro Val
                325                 330                 335

Arg Val Ser Leu Tyr Asp Leu Ala Ser Val Asp Ser Cys Glu Glu Asn
            340                 345                 350

Ser Val Leu Glu Ile Ile Ala Phe His Cys Lys Ser Pro His Arg His
        355                 360                 365

Arg Met Val Val Leu Glu Pro Leu Asn Lys Leu Leu Gln Ala Lys Trp
    370                 375                 380

Asp Leu Leu Ile Pro Lys Phe Phe Phe Asn Phe Ala Cys Tyr Leu Val
385                 390                 395                 400

Tyr Met Phe Ile Phe Thr Val Val Ala Tyr His Gln Pro Ser Leu Asp
                405                 410                 415

Gln Pro Ala Ile Pro Ser Ser Lys Ala Thr Phe Gly Glu Ser Met Leu
            420                 425                 430

Leu Leu Gly His Ile Leu Ile Leu Leu Gly Gly Ile Tyr Leu Leu Leu
        435                 440                 445

Gly Gln Leu Trp Tyr Phe Trp Arg Arg Arg Leu Phe Ile Trp Ile Ser
```

-continued

```
    450                 455                 460

Phe Met Asp Ser Tyr Phe Glu Ile Leu Phe Leu Leu Gln Ala Leu Leu
465                 470                 475                 480

Thr Val Leu Ser Gln Val Leu Arg Phe Met Glu Thr Glu Trp Tyr Leu
                485                 490                 495

Pro Leu Leu Val Leu Ser Leu Val Leu Gly Trp Leu Asn Leu Leu Tyr
            500                 505                 510

Tyr Thr Arg Gly Phe Gln His Thr Gly Ile Tyr Ser Val Met Ile Gln
        515                 520                 525

Lys Val Ile Leu Arg Asp Leu Leu Arg Phe Leu Leu Val Tyr Leu Val
    530                 535                 540

Phe Leu Phe Gly Phe Ala Val Ala Leu Val Ser Leu Ser Arg Glu Ala
545                 550                 555                 560

Arg Ser Pro Lys Ala Pro Glu Asp Asn Asn Ser Thr Val Thr Glu Gln
                565                 570                 575

Pro Thr Val Gly Gln Glu Glu Glu Pro Ala Pro Tyr Arg Ser Ile Leu
            580                 585                 590

Asp Ala Ser Leu Glu Leu Phe Lys Phe Thr Ile Gly Met Gly Glu Leu
        595                 600                 605

Ala Phe Gln Glu Gln Leu Arg Phe Arg Gly Val Val Leu Leu Leu Leu
    610                 615                 620

Leu Ala Tyr Val Leu Leu Thr Tyr Val Leu Leu Leu Asn Met Leu Ile
625                 630                 635                 640

Ala Leu Met Ser Glu Thr Val Asn His Val Ala Asp Asn Ser Trp Ser
                645                 650                 655

Ile Trp Lys Leu Gln Lys Ala Ile Ser Val Leu Glu Met Glu Asn Gly
            660                 665                 670

Tyr Trp Trp Cys Arg Arg Lys Lys His Arg Glu Gly Arg Leu Leu Lys
        675                 680                 685

Val Gly Thr Arg Gly Asp Gly Thr Pro Asp Glu Arg Trp Cys Phe Arg
    690                 695                 700

Val Glu Glu Val Asn Trp Val Ala Trp Glu Lys Thr Leu Pro Thr Leu
705                 710                 715                 720

Ser Glu Asp Pro Ser Gly Pro Gly Ile Thr Gly Asn Lys Lys Asn Pro
                725                 730                 735

Thr Ser Lys Pro Gly Lys Asn Ser Ala Ser Glu Glu Asp His Leu Pro
            740                 745                 750

Leu Gln Val Leu Gln Ser Pro
        755


<210> SEQ ID NO 18
<211> LENGTH: 2226
<212> TYPE: DNA
<213> ORGANISM: Rattus norvegicus

<400> SEQUENCE: 18

ggcaatgctg aggtgaacaa ggggaagcag gaaccgcccc ccatggagtc accattccag     60

agggaggacc ggaattcctc ccctcagatc aaagtgaacc tcaacttcat aaagagacct    120

cctaaaaaca cttctgctcc cagccagcag gagccagatc ggtttgaccg tgaccgactc    180

ttcagtgtgg tctcccgggg tgtccccgag gaactgactg gactgctaga atacctgcgc    240

tggaacagca agtacctcac tgactctgca tacacagaag gctccactgg aaagacgtgc    300
```

-continued

ctgatgaagg ctgtgctgaa ccttcaggat ggggtcaatg cctgcatcat gccgctgctg 360

cagattgaca aggattccgg caatcccaag cccctcgtca atgcccagtg catcgatgag 420

ttctaccaag gccacagtgc gctgcacatc gccatagaga agaggagcct gcagtgcgtg 480

aagctgctgg tagagaatgg agcggatgtt cacctccgag cctgtggccg cttcttccaa 540

aagcaccaag gaacttgttt ctattttgga gagctacctc tttctctggc tgcgtgcacc 600

aagcagtggg atgtggtgac ctacctcctg gagaacccac accagccggc cagcctggag 660

gccaccgact ccctgggcaa cacagtcctg catgctctgg taatgattgc agataactcg 720

cctgagaaca gtgccctggt gatccacatg tacgacgggc ttctacaaat gggggcgcgc 780

ctctgcccca ctgtgcagct tgaggaaatc tccaaccacc aaggcctcac acccctgaaa 840

ctagccgcca aggaaggcaa aatcgagatt ttcaggcaca ttctgcagcg ggaattctca 900

ggaccgtacc agccccttc ccgaaagttt actgagtggt gttacggtcc tgtgcgggta 960

tcgctgtacg acctgtcctc tgtggacagc tgggaaaaga actcggtgct ggagatcatc 1020

gcttttcatt gcaagagccc gaaccggcac cgcatggtgg ttttagaacc actgaacaag 1080

cttctgcagg agaaatggga tcggctcgtc tcaagattct tcttcaactt cgcctgctac 1140

ttggtctaca tgttcatctt caccgtcgtt gcctaccacc agccttccct ggatcagcca 1200

gccatcccct catcaaaagc gacttttggg gaatccatgc tgctgctggg ccacattctg 1260

atcctgcttg ggggtattta cctcttactg ggccagctgt ggtacttttg gcggcggcgc 1320

ctgttcatct ggatctcatt catggacagc tactttgaaa tcctctttct ccttcaggct 1380

ctgctcacag tgctgtccca ggtgctgcgc ttcatggaga ctgaatggta cctacccctg 1440

ctagtgttat ccctagtgct gggctggctg aacctgcttt actacacacg gggctttcag 1500

cacacaggca tctacagtgt catgatccag aaggtcatcc ttcgagacct gctccgtttc 1560

ctgctggtct acctggtctt ccttttcggc tttgctgtag ccctagtaag cttgagcaga 1620

gaggcccgaa gtcccaaagc ccctgaagat aacaactcca cagtgacgga acagcccacg 1680

gtgggccagg aggaggagcc agctccatat cggagcattc tggatgcctc cctagagctg 1740

ttcaagttca ccattggtat gggggagctg gctttccagg aacagctgcg ttttcgtggg 1800

gtggtcctgc tgttgctgtt ggcctacgtc cttctcacct acgtcctgct gctcaacatg 1860

ctcattgctc tcatgagcga aactgtcaac cacgttgctg acaacagctg gagcatctgg 1920

aagttgcaga aagccatctc tgtcttggag atggagaatg gttactggtg gtgccggagg 1980

aagaaacatc gtgaagggag gctgctgaaa gtcggcacca gggggggatgg tacccctgat 2040

gagcgctggt gcttcagggt ggaggaagta aattgggttg cttgggagaa gactcttccc 2100

accttatctg aggatccatc agggccaggc atcactggta ataaaaagaa cccaacctct 2160

aaaccgggga agaacagtgc ctcagaggaa gaccatctgc cccttcaggt cctccagtcc 2220

ccctga 2226

<210> SEQ ID NO 19
<211> LENGTH: 2190
<212> TYPE: DNA
<213> ORGANISM: Rattus norvegicus

<400> SEQUENCE: 19

ccccccatgg agtcaccatt ccagagggag gaccggaatt cctcccctca gatcaaagtg 60

-continued

aacctcaact tcataaagag acctcctaaa aacacttctg ctcccagcca gcaggagcca 120

gatcggtttg accgtgaccg actcttcagt gtggtctccc ggggtgtccc cgaggaactg 180

actggactgc tagaatacct gcgctggaac agcaagtacc tcactgactc tgcatacaca 240

gaaggctcca ctggaaagac gtgcctgatg aaggctgtgc tgaaccttca ggatggggtc 300

aatgcctgca tcatgccgct gctgcagatt gacaaggatt ccggcaatcc caagcccctc 360

gtcaatgccc agtgcatcga tgagttctac caaggccaca gtgcgctgca catcgccata 420

gagaagagga gcctgcagtg cgtgaagctg ctggtagaga atggagcgga tgttcacctc 480

cgagcctgtg gccgcttctt ccaaaagcac caaggaactt gtttctattt tggagagcta 540

cctctttctc tggctgcgtg caccaagcag tgggatgtgg tgacctacct cctggagaac 600

ccacaccagc cggccagcct ggaggccacc gactccctgg gcaacacagt cctgcatgct 660

ctggtaatga ttgcagataa ctcgcctgag aacagtgccc tggtgatcca catgtacgac 720

gggcttctac aaatgggggc gcgcctctgc cccactgtgc agcttgagga aatctccaac 780

caccaaggcc tcacacccct gaaactagcc gccaaggaag gcaaaatcga gattttcagg 840

cacattctgc agcgggaatt ctcaggaccg taccagcccc tttcccgaaa gtttactgag 900

tggtgttacg gtcctgtgcg ggtatcgctg tacgacctgt cctctgtgga cagctgggaa 960

aagaactcgg tgctggagat catcgctttt cattgcaaga gcccgaaccg gcaccgcatg 1020

gtggttttag aaccactgaa caagcttctg caggagaaat gggatcggct cgtctcaaga 1080

ttcttcttca acttcgcctg ctacttggtc tacatgttca tcttcaccgt cgttgcctac 1140

caccagcctt ccctggatca gccagccatc ccctcatcaa aagcgacttt tggggaatcc 1200

atgctgctgc tgggccacat tctgatcctg cttgggggta tttacctctt actgggccag 1260

ctgtggtact tttggcggcg gcgcctgttc atctggatct cattcatgga cagctacttt 1320

gaaatcctct ttctccttca ggctctgctc acagtgctgt cccaggtgct gcgcttcatg 1380

gagactgaat ggtacctacc cctgctagtg ttatccctag tgctgggctg gctgaacctg 1440

ctttactaca cacggggctt tcagcacaca ggcatctaca gtgtcatgat ccagaaggtc 1500

atccttcgag acctgctccg tttcctgctg gtctacctgg tcttcctttt cggctttgct 1560

gtagccctag taagcttgag cagagaggcc cgaagtccca aagcccctga agataacaac 1620

tccacagtga cggaacagcc cacggtgggc caggaggagg agccagctcc atatcggagc 1680

attctggatg cctccctaga gctgttcaag ttcaccattg gtatggggga gctggctttc 1740

caggaacagc tgcgttttcg tggggtggtc ctgctgttgc tgttggccta cgtccttctc 1800

acctacgtcc tgctgctcaa catgctcatt gctctcatga gcgaaactgt caaccacgtt 1860

gctgacaaca gctggagcat ctggaagttg cagaaagcca tctctgtctt ggagatggag 1920

aatggttact ggtggtgccg gaggaagaaa catcgtgaag ggaggctgct gaaagtcggc 1980

accaggggggg atggtacccc tgatgagcgc tggtgcttca gggtggagga agtaaattgg 2040

gttgcttggg agaagactct tcccacctta tctgaggatc catcagggcc aggcatcact 2100

ggtaataaaa agaacccaac ctctaaaccg gggaagaaca gtgcctcaga ggaagaccat 2160

ctgcccttc aggtcctcca gtccccctga 2190

<210> SEQ ID NO 20
<211> LENGTH: 2091

-continued

<212> TYPE: DNA
<213> ORGANISM: Rattus norvegicus

<400> SEQUENCE: 20

ttcagtgtgg tctcccgggg tgtccccgag gaactgactg gactgctaga atacctgcgc 60

tggaacagca agtacctcac tgactctgca tacacagaag gctccactgg aaagacgtgc 120

ctgatgaagg ctgtgctgaa ccttcaggat ggggtcaatg cctgcatcat gccgctgctg 180

cagattgaca aggattccgg caatcccaag cccctcgtca atgcccagtg catcgatgag 240

ttctaccaag gccacagtgc gctgcacatc gccatagaga agaggagcct gcagtgcgtg 300

aagctgctgg tagagaatgg agcggatgtt cacctccgag cctgtggccg cttcttccaa 360

aagcaccaag gaacttgttt ctattttgga gagctacctc tttctctggc tgcgtgcacc 420

aagcagtggg atgtggtgac ctacctcctg gagaacccac accagccggc cagcctggag 480

gccaccgact ccctgggcaa cacagtcctg catgctctgg taatgattgc agataactcg 540

cctgagaaca gtgccctggt gatccacatg tacgacgggc ttctacaaat gggggcgcgc 600

ctctgcccca ctgtgcagct tgaggaaatc tccaaccacc aaggcctcac acccctgaaa 660

ctagccgcca aggaaggcaa aatcgagatt ttcaggcaca ttctgcagcg ggaattctca 720

ggaccgtacc agccccttc ccgaaagttt actgagtggt gttacggtcc tgtgcgggta 780

tcgctgtacg acctgtcctc tgtggacagc tgggaaaaga actcggtgct ggagatcatc 840

gcttttcatt gcaagagccc gaaccggcac cgcatggtgg ttttagaacc actgaacaag 900

cttctgcagg agaaatggga tcggctcgtc tcaagattct tcttcaactt cgcctgctac 960

ttggtctaca tgttcatctt caccgtcgtt gcctaccacc agccttccct ggatcagcca 1020

gccatccccc catcaaaagc gacttttggg gaatccatgc tgctgctggg ccacattctg 1080

atcctgcttg ggggtattta cctcttactg ggccagctgt ggtacttttg gcggcggcgc 1140

ctgttcatct ggatctcatt catggacagc tactttgaaa tcctctttct ccttcaggct 1200

ctgctcacag tgctgtccca ggtgctgcgc ttcatggaga ctgaatggta cctacccctg 1260

ctagtgttat ccctagtgct gggctggctg aacctgcttt actacacacg gggctttcag 1320

cacacaggca tctacagtgt catgatccag aaggtcatcc ttcgagacct gctccgtttc 1380

ctgctggtct acctggtctt ccttttcggc tttgctgtag ccctagtaag cttgagcaga 1440

gaggcccgaa gtcccaaagc ccctgaagat aacaactcca cagtgacgga acagcccacg 1500

gtgggccagg aggaggagcc agctccatat cggagcattc tggatgcctc cctagagctg 1560

ttcaagttca ccattggtat gggggagctg gctttccagg aacagctgcg ttttcgtggg 1620

gtggtcctgc tgttgctgtt ggcctacgtc cttctcacct acgtcctgct gctcaacatg 1680

ctcattgctc tcatgagcga aactgtcaac cacgttgctg acaacagctg gagcatctgg 1740

aagttgcaga aagccatctc tgtcttggag atggagaatg gttactggtg gtgccggagg 1800

aagaaacatc gtgaagggag gctgctgaaa gtcggcacca ggggggatgg taccctgat 1860

gagcgctggt gcttcagggt ggaggaagta aattgggttg cttgggagaa gactcttccc 1920

accttatctg aggatccatc agggccaggc atcactggta ataaaaagaa cccaacctct 1980

aaaccgggga agaacagtgc ctcagaggaa gaccatctgc cccttcaggt cctccagtcc 2040

ccctgagctc ccagccagca ggagccagat cggtttgacc gtgaccgact c 2091

-continued

<210> SEQ ID NO 21
<211> LENGTH: 2037
<212> TYPE: DNA
<213> ORGANISM: Rattus norvegicus

<400> SEQUENCE: 21

gaatacctgc gctggaacag caagtacctc actgactctg catacacaga aggctccact 60

ggaaagacgt gcctgatgaa ggctgtgctg aaccttcagg atggggtcaa tgcctgcatc 120

atgccgctgc tgcagattga caaggattcc ggcaatccca agcccctcgt caatgcccag 180

tgcatcgatg agttctacca aggccacagt gcgctgcaca tcgccataga gaagaggagc 240

ctgcagtgcg tgaagctgct ggtagagaat ggagcggatg ttcacctccg agcctgtggc 300

cgcttcttcc aaaagcacca aggaacttgt ttctattttg gagagctacc tctttctctg 360

gctgcgtgca ccaagcagtg ggatgtggtg acctacctcc tggagaaccc acaccagccg 420

gccagcctgg aggccaccga ctccctgggc aacacagtcc tgcatgctct ggtaatgatt 480

gcagataact cgcctgagaa cagtgccctg gtgatccaca tgtacgacgg gcttctacaa 540

atgggggcgc gcctctgccc cactgtgcag cttgaggaaa tctccaacca ccaaggcctc 600

acacccctga aactagccgc caaggaaggc aaaatcgaga ttttcaggca cattctgcag 660

cgggaattct caggaccgta ccagcccctt tcccgaaagt ttactgagtg gtgttacggt 720

cctgtgcggg tatcgctgta cgacctgtcc tctgtggaca gctgggaaaa gaactcggtg 780

ctggagatca tcgcttttca ttgcaagagc ccgaaccggc accgcatggt ggttttagaa 840

ccactgaaca agcttctgca ggagaaatgg gatcggctcg tctcaagatt cttcttcaac 900

ttcgcctgct acttggtcta catgttcatc ttcaccgtcg ttgcctacca ccagccttcc 960

ctggatcagc cagccatccc ctcatcaaaa gcgacttttg gggaatccat gctgctgctg 1020

ggccacattc tgatcctgct tgggggtatt tacctcttac tgggccagct gtggtacttt 1080

tggcggcggc gcctgttcat ctggatctca ttcatggaca gctactttga aatcctcttt 1140

ctccttcagg ctctgctcac agtgctgtcc caggtgctgc gcttcatgga gactgaatgg 1200

tacctacccc tgctagtgtt atccctagtg ctgggctggc tgaacctgct ttactacaca 1260

cggggctttc agcacacagg catctacagt gtcatgatcc agaaggtcat ccttcgagac 1320

ctgctccgtt tcctgctggt ctacctggtc ttccttttcg gctttgctgt agccctagta 1380

agcttgagca gagaggcccg aagtcccaaa gcccctgaag ataacaactc cacagtgacg 1440

gaacagccca cggtgggcca ggaggaggag ccagctccat atcggagcat tctggatgcc 1500

tccctagagc tgttcaagtt caccattggt atgggggagc tggctttcca ggaacagctg 1560

cgttttcgtg gggtggtcct gctgttgctg ttggcctacg tccttctcac ctacgtcctg 1620

ctgctcaaca tgctcattgc tctcatgagc gaaactgtca accacgttgc tgacaacagc 1680

tggagcatct ggaagttgca gaaagccatc tctgtcttgg agatggagaa tggttactgg 1740

tggtgccgga ggaagaaaca tcgtgaaggg aggctgctga aagtcggcac caggggggat 1800

ggtacccctg atgagcgctg gtgcttcagg gtggaggaag taaattgggt tgcttgggag 1860

aagactcttc ccaccttatc tgaggatcca tcagggccag gcatcactgg taataaaaag 1920

aacccaacct ctaaaccggg gaagaacagt gcctcagagg aagaccatct gccccttcag 1980

gtcctccagt ccccctgagt ctcccggggt gtccccgagg aactgactgg actgcta 2037

-continued

<210> SEQ ID NO 22
<211> LENGTH: 2118
<212> TYPE: DNA
<213> ORGANISM: Rattus norvegicus

<400> SEQUENCE: 22

gaatacctgc gctggaacag caagtacctc actgactctg catacacaga aggctccact 60

ggaaagacgt gcctgatgaa ggctgtgctg aaccttcagg atggggtcaa tgcctgcatc 120

atgccgctgc tgcagattga caaggattcc ggcaatccca agcccctcgt caatgcccag 180

tgcatcgatg agttctacca aggccacagt gcgctgcaca tcgccataga gaagaggagc 240

ctgcagtgcg tgaagctgct ggtagagaat ggagcggatg ttcacctccg agcctgtggc 300

cgcttcttcc aaaagcacca aggaacttgt ttctattttg gagagctacc tctttctctg 360

gctgcgtgca ccaagcagtg ggatgtggtg acctacctcc tggagaaccc acaccagccg 420

gccagcctgg aggccaccga ctccctgggc aacacagtcc tgcatgctct ggtaatgatt 480

gcagataact cgcctgagaa cagtgccctg gtgatccaca tgtacgacgg gcttctacaa 540

atgggggcgc gcctctgccc cactgtgcag cttgaggaaa tctccaacca ccaaggcctc 600

acacccctga aactagccgc caaggaaggc aaaatcgaga ttttcaggca cattctgcag 660

cgggaattct caggaccgta ccagcccctt tcccgaaagt ttactgagtg gtgttacggt 720

cctgtgcggg tatcgctgta cgacctgtcc tctgtggaca gctgggaaaa gaactcggtg 780

ctggagatca tcgcttttca ttgcaagagc ccgaaccggc accgcatggt ggttttagaa 840

ccactgaaca agcttctgca ggagaaatgg gatcggctcg tctcaagatt cttcttcaac 900

ttcgcctgct acttggtcta catgttcatc ttcaccgtcg ttgcctacca ccagccttcc 960

ctggatcagc cagccatccc ctcatcaaaa gcgacttttg gggaatccat gctgctgctg 1020

ggccacattc tgatcctgct tgggggtatt tacctcttac tgggccagct gtggtacttt 1080

tggcggcggc gcctgttcat ctggatctca ttcatggaca gctactttga aatcctcttt 1140

ctccttcagg ctctgctcac agtgctgtcc caggtgctgc gcttcatgga gactgaatgg 1200

tacctacccc tgctagtgtt atccctagtg ctgggctggc tgaacctgct ttactacaca 1260

cggggctttc agcacacagg catctacagt gtcatgatcc agaaggtcat ccttcgagac 1320

ctgctccgtt tcctgctggt ctacctggtc ttccttttcg gctttgctgt agccctagta 1380

agcttgagca gagaggcccg aagtcccaaa gcccctgaag ataacaactc cacagtgacg 1440

gaacagccca cggtgggcca ggaggaggag ccagctccat atcggagcat tctggatgcc 1500

tccctagagc tgttcaagtt caccattggt atgggggagc tggctttcca ggaacagctg 1560

cgttttcgtg gggtggtcct gctgttgctg ttggcctacg tccttctcac ctacgtcctg 1620

ctgctcaaca tgatgacttc agcctccagc cccccagctt tcaggctgga gacttccgat 1680

ggagatgaag agggcaatgc tgaggtgaac aaggggaagc aggaaccgcc ccccatggag 1740

tcaccattcc agagggagga ccggaattcc tcccctcaga tcaaagtgaa cctcaacttc 1800

ataaagagac ctcctaaaaa cacttctgct cccagccagc aggagccaga tcggtttgac 1860

cgtgaccgac tcttcagtgt ggtctcccgg ggtgtccccg aggaactgac tggactgcta 1920

ctcattgctc tcatgagcga aactgtcaac cacgttgctg acaacagctg gagcatctgg 1980

aagttgcaga aagccatctc tgtcttggag atggagaatg gttactggtg gtgccggagg 2040

aagaaacatc gtgaagggag gctgctgaaa gtcggcacca ggggggatgg tacccctgat 2100

-continued

gagcgctggt gcttcagg 2118

<210> SEQ ID NO 23
<211> LENGTH: 2187
<212> TYPE: DNA
<213> ORGANISM: Rattus norvegicus

<400> SEQUENCE: 23

gaatacctgc gctggaacag caagtacctc actgactctg catacacaga aggctccact 60

ggaaagacgt gcctgatgaa ggctgtgctg aaccttcagg atggggtcaa tgcctgcatc 120

atgccgctgc tgcagattga caaggattcc ggcaatccca agcccctcgt caatgcccag 180

tgcatcgatg agttctacca aggccacagt gcgctgcaca tcgccataga gaagaggagc 240

ctgcagtgcg tgaagctgct ggtagagaat ggagcggatg ttcacctccg agcctgtggc 300

cgcttcttcc aaaagcacca aggaacttgt ttctattttg gagagctacc tctttctctg 360

gctgcgtgca ccaagcagtg ggatgtggtg acctacctcc tggagaaccc acaccagccg 420

gccagcctgg aggccaccga ctccctgggc aacacagtcc tgcatgctct ggtaatgatt 480

gcagataact cgcctgagaa cagtgccctg gtgatccaca tgtacgacgg gcttctacaa 540

atgggggcgc gcctctgccc cactgtgcag cttgaggaaa tctccaacca ccaaggcctc 600

acacccctga aactagccgc caaggaaggc aaaatcgaga ttttcaggca cattctgcag 660

cgggaattct caggaccgta ccagcccctt tcccgaaagt ttactgagtg gtgttacggt 720

cctgtgcggg tatcgctgta cgacctgtcc tctgtggaca gctgggaaaa gaactcggtg 780

ctggagatca tcgcttttca ttgcaagagc ccgaaccggc accgcatggt ggttttagaa 840

ccactgaaca agcttctgca ggagaaatgg gatcggctcg tctcaagatt cttcttcaac 900

ttcgcctgct acttggtcta catgttcatc ttcaccgtcg ttgcctacca ccagccttcc 960

ctggatcagc cagccatccc ctcatcaaaa gcgacttttg gggaatccat gctgctgctg 1020

ggccacattc tgatcctgct tgggggtatt tacctcttac tgggccagct gtggtacttt 1080

tggcggcggc gcctgttcat ctggatctca ttcatggaca gctactttga aatcctcttt 1140

ctccttcagg ctctgctcac agtgctgtcc caggtgctgc gcttcatgga gactgaatgg 1200

tacctacccc tgctagtgtt atccctagtg ctgggctggc tgaacctgct ttactacaca 1260

cggggctttc agcacacagg catctacagt gtcatgatcc agaaggtcat ccttcgagac 1320

ctgctccgtt tcctgctggt ctacctggtc ttccttttcg gctttgctgt agccctagta 1380

agcttgagca gagaggcccg aagtcccaaa gcccctgaag ataacaactc cacagtgacg 1440

gaacagccca cggtgggcca ggaggaggag ccagctccat atcggagcat tctggatgcc 1500

tccctagagc tgttcaagtt caccattggt atgggggagc tggctttcca ggaacagctg 1560

cgttttcgtg gggtggtcct gctgttgctg ttggcctacg tccttctcac ctacgtcctg 1620

ctgctcaaca tgatgacttc agcctccagc cccccagctt tcaggctgga gacttccgat 1680

ggagatgaag agggcaatgc tgaggtgaac aaggggaagc aggaaccgcc ccccatggag 1740

tcaccattcc agagggagga ccggaattcc tcccctcaga tcaaagtgaa cctcaacttc 1800

ataaagagac ctcctaaaaa cacttctgct cccagccagc aggagccaga tcggtttgac 1860

cgtgaccgac tcttcagtgt ggtctcccgg ggtgtccccg aggaactgac tggactgcta 1920

ctcattgctc tcatgagcga aactgtcaac cacgttgctg acaacagctg gagcatctgg 1980

-continued

aagttgcaga aagccatctc tgtcttggag atggagaatg gttactggtg gtgccggagg 2040

aagaaacatc gtgaagggag gctgctgaaa gtcggcacca gggggggatgg tacccctgat 2100

gagcgctggt gcttcagggt ggaggaagta aattgggttg cttgggagaa gactcttccc 2160

accttatctg aggatccatc agggcca 2187

<210> SEQ ID NO 24
<211> LENGTH: 2214
<212> TYPE: DNA
<213> ORGANISM: Rattus norvegicus

<400> SEQUENCE: 24

gaatacctgc gctggaacag caagtacctc actgactctg catacacaga aggctccact 60

ggaaagacgt gcctgatgaa ggctgtgctg aaccttcagg atggggtcaa tgcctgcatc 120

atgccgctgc tgcagattga caaggattcc ggcaatccca agcccctcgt caatgcccag 180

tgcatcgatg agttctacca aggccacagt gcgctgcaca tcgccataga gaagaggagc 240

ctgcagtgcg tgaagctgct ggtagagaat ggagcggatg ttcacctccg agcctgtggc 300

cgcttcttcc aaaagcacca aggaacttgt ttctattttg gagagctacc tctttctctg 360

gctgcgtgca ccaagcagtg ggatgtggtg acctacctcc tggagaaccc acaccagccg 420

gccagcctgg aggccaccga ctccctgggc aacacagtcc tgcatgctct ggtaatgatt 480

gcagataact cgcctgagaa cagtgccctg gtgatccaca tgtacgacgg gcttctacaa 540

atgggggcgc gcctctgccc cactgtgcag cttgaggaaa tctccaacca ccaaggcctc 600

acacccctga aactagccgc caaggaaggc aaaatcgaga ttttcaggca cattctgcag 660

cgggaattct caggaccgta ccagcccctt tcccgaaagt ttactgagtg gtgttacggt 720

cctgtgcggg tatcgctgta cgacctgtcc tctgtggaca gctgggaaaa gaactcggtg 780

ctggagatca tcgcttttca ttgcaagagc ccgaaccggc accgcatggt ggttttagaa 840

ccactgaaca agcttctgca ggagaaatgg gatcggctcg tctcaagatt cttcttcaac 900

ttcgcctgct acttggtcta catgttcatc ttcaccgtcg ttgcctacca ccagccttcc 960

ctggatcagc cagccatccc ctcatcaaaa gcgacttttg gggaatccat gctgctgctg 1020

ggccacattc tgatcctgct tgggggtatt tacctcttac tgggccagct gtggtacttt 1080

tggcggcggc gcctgttcat ctggatctca ttcatggaca gctactttga aatcctcttt 1140

ctccttcagg ctctgctcac agtgctgtcc caggtgctgc gcttcatgga gactgaatgg 1200

tacctacccc tgctagtgtt atccctagtg ctgggctggc tgaacctgct ttactacaca 1260

cggggctttc agcacacagg catctacagt gtcatgatcc agaaggtcat ccttcgagac 1320

ctgctccgtt tcctgctggt ctacctggtc ttccttttcg gctttgctgt agccctagta 1380

agcttgagca gagaggcccg aagtcccaaa gcccctgaag ataacaactc cacagtgacg 1440

gaacagccca cggtgggcca ggaggaggag ccagctccat atcggagcat tctggatgcc 1500

tccctagagc tgttcaagtt caccattggt atgggggagc tggctttcca ggaacagctg 1560

cgttttcgtg gggtggtcct gctgttgctg ttggcctacg tccttctcac ctacgtcctg 1620

ctgctcaaca tgatgacttc agcctccagc cccccagctt tcaggctgga gacttccgat 1680

ggagatgaag agggcaatgc tgaggtgaac aaggggaagc aggaaccgcc ccccatggag 1740

tcaccattcc agagggagga ccggaattcc tcccctcaga tcaaagtgaa cctcaacttc 1800

-continued

ataaagagac ctcctaaaaa cacttctgct cccagccagc aggagccaga tcggtttgac 1860

cgtgaccgac tcttcagtgt ggtctcccgg ggtgtccccg aggaactgac tggactgcta 1920

ctcattgctc tcatgagcga aactgtcaac cacgttgctg acaacagctg gagcatctgg 1980

aagttgcaga aagccatctc tgtcttggag atggagaatg gttactggtg gtgccggagg 2040

aagaaacatc gtgaagggag gctgctgaaa gtcggcacca gggggggatgg tacccctgat 2100

gagcgctggt gcttcagggt ggaggaagta aattgggttg cttgggagaa gactcttccc 2160

accttatctg aggatccatc agggccaggc atcactggta ataaaaagaa ccca 2214

<210> SEQ ID NO 25
<211> LENGTH: 2250
<212> TYPE: DNA
<213> ORGANISM: Rattus norvegicus

<400> SEQUENCE: 25

gaatacctgc gctggaacag caagtacctc actgactctg catacacaga aggctccact 60

ggaaagacgt gcctgatgaa ggctgtgctg aaccttcagg atggggtcaa tgcctgcatc 120

atgccgctgc tgcagattga caaggattcc ggcaatccca agcccctcgt caatgcccag 180

tgcatcgatg agttctacca aggccacagt gcgctgcaca tcgccataga gaagaggagc 240

ctgcagtgcg tgaagctgct ggtagagaat ggagcggatg ttcacctccg agcctgtggc 300

cgcttcttcc aaaagcacca aggaacttgt ttctattttg gagagctacc tctttctctg 360

gctgcgtgca ccaagcagtg ggatgtggtg acctacctcc tggagaaccc acaccagccg 420

gccagcctgg aggccaccga ctccctgggc aacacagtcc tgcatgctct ggtaatgatt 480

gcagataact cgcctgagaa cagtgccctg gtgatccaca tgtacgacgg gcttctacaa 540

atgggggcgc gcctctgccc cactgtgcag cttgaggaaa tctccaacca ccaaggcctc 600

acacccctga aactagccgc caaggaaggc aaaatcgaga ttttcaggca cattctgcag 660

cgggaattct caggaccgta ccagcccctt tcccgaaagt ttactgagtg gtgttacggt 720

cctgtgcggg tatcgctgta cgacctgtcc tctgtggaca gctgggaaaa gaactcggtg 780

ctggagatca tcgcttttca ttgcaagagc ccgaaccggc accgcatggt ggttttagaa 840

ccactgaaca agcttctgca ggagaaatgg gatcggctcg tctcaagatt cttcttcaac 900

ttcgcctgct acttggtcta catgttcatc ttcaccgtcg ttgcctacca ccagccttcc 960

ctggatcagc cagccatccc ctcatcaaaa gcgacttttg gggaatccat gctgctgctg 1020

ggccacattc tgatcctgct tgggggtatt tacctcttac tgggccagct gtggtacttt 1080

tggcggcggc gcctgttcat ctggatctca ttcatggaca gctactttga aatcctcttt 1140

ctccttcagg ctctgctcac agtgctgtcc caggtgctgc gcttcatgga gactgaatgg 1200

tacctacccc tgctagtgtt atccctagtg ctgggctggc tgaacctgct ttactacaca 1260

cggggctttc agcacacagg catctacagt gtcatgatcc agaaggtcat ccttcgagac 1320

ctgctccgtt tcctgctggt ctacctggtc ttccttttcg gctttgctgt agccctagta 1380

agcttgagca gagaggcccg aagtcccaaa gcccctgaag ataacaactc cacagtgacg 1440

gaacagccca cggtgggcca ggaggaggag ccagctccat atcggagcat tctggatgcc 1500

tccctagagc tgttcaagtt caccattggt atgggggagc tggctttcca ggaacagctg 1560

cgttttcgtg gggtggtcct gctgttgctg ttggcctacg tccttctcac ctacgtcctg 1620

-continued

ctgctcaaca tgatgacttc agcctccagc cccccagctt tcaggctgga gacttccgat 1680

ggagatgaag agggcaatgc tgaggtgaac aaggggaagc aggaaccgcc ccccatggag 1740

tcaccattcc agagggagga ccggaattcc tcccctcaga tcaaagtgaa cctcaacttc 1800

ataaagagac ctcctaaaaa cacttctgct cccagccagc aggagccaga tcggtttgac 1860

cgtgaccgac tcttcagtgt ggtctcccgg ggtgtccccg aggaactgac tggactgcta 1920

ctcattgctc tcatgagcga aactgtcaac cacgttgctg acaacagctg gagcatctgg 1980

aagttgcaga aagccatctc tgtcttggag atggagaatg gttactggtg gtgccggagg 2040

aagaaacatc gtgaagggag gctgctgaaa gtcggcacca gggggggatgg tacccctgat 2100

gagcgctggt gcttcagggt ggaggaagta aattgggttg cttgggagaa gactcttccc 2160

accttatctg aggatccatc agggccaggc atcactggta ataaaaagaa cccaacctct 2220

aaaccgggga agaacagtgc ctcagaggaa 2250

<210> SEQ ID NO 26
<211> LENGTH: 2295
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide

<400> SEQUENCE: 26

atgacttcag cctccagccc cccagctttc aggctggaga cttccgatgg agatgaagag 60

ggcaatgctg aggtgaacaa ggggaagcag gaaccgcccc ccatggagtc accattccag 120

agggaggacc ggaattcctc ccctcagatc aaagtgaacc tcaacttcat aaagagacct 180

cctaaaaaca cttctgctcc cagccagcag gagccagatc ggtttgaccg tgaccgactc 240

ttcagtgtgg tctcccgggg tgtccccgag gaactgactg gactgctaga atacctgcgc 300

tggaacagca agtacctcac tgactctgca tacacagaag gctccactgg aaagacgtgc 360

ctgatgaagg ctgtgctgaa ccttcaggat ggggtcaatg cctgcatcat gccgctgctg 420

cagattgaca aggattccgg caatcccaag cccctcgtca atgcccagtg catcgatgag 480

ttctaccaag gccacagtgc gctgcacatc gccatagaga agaggagcct gcagtgcgtg 540

aagctgctgg tagagaatgg agcggatgtt cacctccgag cctgtggccg cttcttccaa 600

aagcaccaag gaacttgttt ctattttgga gagctacctc tttctctggc tgcgtgcacc 660

aagcagtggg atgtggtgac ctacctcctg gagaacccac accagccggc cagcctggag 720

gccaccgact ccctgggcaa cacagtcctg catgctctgg taatgattgc agataactcg 780

cctgagaaca gtgccctggt gatccacatg tacgacgggc ttctacaaat gggggcgcgc 840

ctctgcccca ctgtgcagct tgaggaaatc tccaaccacc aaggcctcac acccctgaaa 900

ctagccgcca aggaaggcaa aatcgagatt ttcaggcaca ttctgcagcg ggaattctca 960

ggaccgtacc agccccttcc ccgaaagttt actgagtggt gttacggtcc tgtgcgggta 1020

tcgctgtacg acctgtcctc tgtggacagc tgggaaaaga actcggtgct ggagatcatc 1080

gcttttcatt gcaagagccc gaaccggcac cgcatggtgg ttttagaacc actgaacaag 1140

cttctgcagg agaaatggga tcggctcgtc tcaagattct tcttcaactt cgcctgctac 1200

ttggtctaca tgttcatctt caccgtcgtt gcctaccacc agccttccct ggatcagcca 1260

-continued

gccatcccct catcaaaagc gacttttggg gaatccatgc tgctgctggg ccacattctg 1320

atcctgcttg ggggtattta cctcttactg ggccagctgt ggtacttttg gcggcggcgc 1380

ctgttcatct ggatctcatt catggacagc tactttgaaa tcctctttct ccttcaggct 1440

ctgctcacag tgctgtccca ggtgctgcgc ttcatggaga ctgaatggta cctacccctg 1500

ctagtgttat ccctagtgct gggctggctg aacctgcttt actacacacg gggctttcag 1560

cacacaggca tctacagtgt catgatccag aaggtcatcc ttcgagacct gctccgtttc 1620

ctgctggtct acctggtctt ccttttcggc tttgctgtag ccctagtaag cttgagcaga 1680

gaggcccgaa gtcccaaagc ccctgaagat aacaactcca cagtgacgga acagcccacg 1740

gtgggccagg aggaggagcc agctccatat cggagcattc tggatgcctc cctagagctg 1800

ttcaagttca ccattggtat gggggagctg gctttccagg aacagctgcg ttttcgtggg 1860

gtggtcctgc tgttgctgtt ggcctacgtc cttctcacct acgtcctgct gctcaacatg 1920

ctcattgctc tcatgagcga gaccgtcaac agtgtcgcca ctgacagctg gagcatctgg 1980

aagctgcaga aagccatctc tgtcctggag atggagaatg gctattggtg gtgcaggaag 2040

aagcagcggg caggtgtgat gctgaccgtt ggcactaagc cagatggcag ccccgatgag 2100

cgctggtgct tcagggtgga ggaggtgaac tgggcttcat gggagcagac gctgcctacg 2160

ctgtgtgagg acccgtcagg ggcaggtgtc cctcgaactc tcgagaaccc tgtcctggct 2220

tcccctccca aggaggatga ggatggtgcc tctgaggaaa actatgtgcc cgtccagctc 2280

ctccagtcca actga 2295

<210> SEQ ID NO 27
<211> LENGTH: 2292
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide

<400> SEQUENCE: 27

atgacttcag cctccagccc cccagctttc aggctggaga cttccgatgg agatgaagag 60

ggcaatgctg aggtgaacaa ggggaagcag gaaccgcccc ccatggagtc accattccag 120

agggaggacc ggaattcctc ccctcagatc aaagtgaacc tcaacttcat aaagagacct 180

cctaaaaaca cttctgctcc cagccagcag gagccagatc ggtttgaccg tgaccgactc 240

ttcagtgtgg tctcccgggg tgtccccgag gaactgactg gactgctaga atacctgcgc 300

tggaacagca agtacctcac tgactctgca tacacagaag gctccactgg aaagacgtgc 360

ctgatgaagg ctgtgctgaa ccttcaggat ggggtcaatg cctgcatcat gccgctgctg 420

cagattgaca aggattccgg caatcccaag cccctcgtca atgcccagtg catcgatgag 480

ttctaccaag gccacagtgc gctgcacatc gccatagaga agaggagcct gcagtgcgtg 540

aagctgctgg tagagaatgg agcggatgtt cacctccgag cctgtggccg cttcttccaa 600

aagcaccaag gaacttgttt ctattttgga gagctacctc tttctctggc tgcgtgcacc 660

aagcagtggg atgtggtgac ctacctcctg gagaacccac accagccggc cagcctggag 720

gccaccgact ccctgggcaa cacagtcctg catgctctgg taatgattgc agataactcg 780

cctgagaaca gtgccctggt gatccacatg tacgacgggc ttctacaaat gggggcgcgc 840

ctctgcccca ctgtgcagct tgaggaaatc tccaaccacc aaggcctcac acccctgaaa 900

-continued

ctagccgcca aggaaggcaa aatcgagatt ttcaggcaca ttctgcagcg ggaattctca 960

ggaccgtacc agccccttc ccgaaagttt actgagtggt gttacggtcc tgtgcgggta 1020

tcgctgtacg acctgtcctc tgtggacagc tgggaaaaga actcggtgct ggagatcatc 1080

gcttttcatt gcaagagccc gaaccggcac cgcatggtgg ttttagaacc actgaacaag 1140

cttctgcagg agaaatggga tcggctcgtc tcaagattct tcttaaactt cctgtgtaat 1200

ctgatctaca tgttcatctt caccgctgtt gcctaccatc agcctaccct gaagaagcag 1260

gccgcccctc acctgaaagc ggaggttgga aactccatgc tgctgacggg ccacatcctt 1320

atcctgctag gggggatcta cctcctcgtg ggccagctgt ggtacttctg gcggcgccac 1380

gtgttcatct ggatctcgtt catagacagc tactttgaaa tcctcttcct gttccaggcc 1440

ctgctcacag tggtgtccca ggtgctgtgt ttcctggcca tcgagtggta cctgcccctg 1500

cttgtgtctg cgctggtgct gggctggctg aacctgcttt actatacacg tggcttccag 1560

cacacaggca tctacagtgt catgatccag aaggtcatcc tgcgggacct gctgcgcttc 1620

cttctgatct acttagtctt ccttttcggc ttcgctgtag ccctggtgag cctgagccag 1680

gaggcttggc gccccgaagc tcctacaggc cccaatgcca cagagtcagt gcagcccatg 1740

gagggacagg aggacgaggg caacggggcc cagtacaggg gtatcctgga agcctccttg 1800

gagctcttca aattcaccat cggcatgggc gagctggcct tccaggagca gctgcacttc 1860

cgcggcatgg tgctgctgct gctgctggcc tacgtgctgc tcacctacat cctgctgctc 1920

aacatgctca tcgccctcat gagcgaaact gtcaaccacg ttgctgacaa cagctggagc 1980

atctggaagt tgcagaaagc catctctgtc ttggagatgg agaatggtta ctggtggtgc 2040

cggaggaaga aacatcgtga agggaggctg ctgaaagtcg gcaccagggg ggatggtacc 2100

cctgatgagc gctggtgctt cagggtggag gaagtaaatt gggttgcttg ggagaagact 2160

cttcccacct tatctgagga tccatcaggg ccaggcatca ctggtaataa aaagaaccca 2220

acctctaaac cggggaagaa cagtgcctca gaggaagacc atctgcccct tcaggtcctc 2280

cagtcccct ga 2292

<210> SEQ ID NO 28
<211> LENGTH: 2280
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide

<400> SEQUENCE: 28

atgacctcac cctccagctc tccagttttc aggttggaga cattagatgg aggccaagaa 60

gatggctctg aggcggacag aggaaagctg gattttggga gcgggctgcc tcccatggag 120

tcacagttcc agggcgagga ccggaaattc gcccctcaga taagagtcaa cctcaactac 180

cgaaagggaa caggtgccag tcagccggat ccaaaccgat ttgaccgaga tcggctcttc 240

aatgcggtct cccggggtgt ccccgaggat ctggctggac ttccagagta cctgagcaag 300

accagcaagt acctcaccga ctcggaatac acagagggct ccacaggtaa gacgtgcctg 360

atgaaggctg tgctgaacct taaggacgga gtcaatgcct gcattctgcc actgctgcag 420

atcgacaggg actctggcaa tcctcagccc ctggtaaatg cccagtgcac agatgactat 480

-continued

taccgaggcc acagcgctct gcacatcgcc attgagaaga ggagtctgca gtgtgtgaag 540

ctcctggtgg agaatggggc caatgtgcat gcccgggcct gcggccgctt cttccagaag 600

ggccaaggga cttgctttta tttcggtgag ctacccctct ctttggccgc ttgcaccaag 660

cagtgggatg tggtaagcta cctcctggag aacccacacc agcccgccag cctgcaggcc 720

actgactccc agggcaacac agtcctgcat gccctagtga tgatctcgga caactcagct 780

gagaacattg cactggtgac cagcatgtat gatgggctcc tccaagctgg ggcccgcctc 840

tgccctaccg tgcagcttga ggacatccgc aacctgcagg atctcacgcc tctgaagctg 900

gccgccaagg agggcaagat cgagattttc aggcacatcc tgcagcggga gttttcagga 960

ctgagccacc tttcccgaaa gttcaccgag tggtgctatg ggcctgtccg ggtgtcgctg 1020

tatgacctgg cttctgtgga cagctgtgag gagaactcag tgctggagat cattgccttt 1080

cattgcaaga gcccgcaccg acaccgaatg gtcgttttgg agcccctgaa caaactgctg 1140

caggcgaaat gggatctgct catccccaag ttcttcttca acttcgcctg ctacttggtc 1200

tacatgttca tcttcaccgt cgttgcctac caccagcctt ccctggatca gccagccatc 1260

ccctcatcaa aagcgacttt tggggaatcc atgctgctgc tgggccacat tctgatcctg 1320

cttgggggta tttacctctt actgggccag ctgtggtact tttggcggcg gcgcctgttc 1380

atctggatct cattcatgga cagctacttt gaaatcctct ttctccttca ggctctgctc 1440

acagtgctgt cccaggtgct gcgcttcatg gagactgaat ggtacctacc cctgctagtg 1500

ttatccctag tgctgggctg gctgaacctg ctttactaca cacggggctt tcagcacaca 1560

ggcatctaca gtgtcatgat ccagaaggtc atccttcgag acctgctccg tttcctgctg 1620

gtctacctgg tcttcctttt cggctttgct gtagccctag taagcttgag cagagaggcc 1680

cgaagtccca aagcccctga agataacaac tccacagtga cggaacagcc cacggtgggc 1740

caggaggagg agccagctcc atatcggagc attctggatg cctccctaga gctgttcaag 1800

ttcaccattg gtatggggga gctggctttc caggaacagc tgcgttttcg tggggtggtc 1860

ctgctgttgc tgttggccta cgtccttctc acctacgtcc tgctgctcaa catgctcatt 1920

gctctcatga gcgaaactgt caaccacgtt gctgacaaca gctggagcat ctggaagttg 1980

cagaaagcca tctctgtctt ggagatggag aatggttact ggtggtgccg gaggaagaaa 2040

catcgtgaag ggaggctgct gaaagtcggc accaggggggg atggtacccc tgatgagcgc 2100

tggtgcttca gggtggagga agtaaattgg gttgcttggg agaagactct tcccacctta 2160

tctgaggatc catcagggcc aggcatcact ggtaataaaa agaacccaac ctctaaaccg 2220

gggaagaaca gtgcctcaga ggaagaccat ctgccccttc aggtcctcca gtccccctga 2280

1-18. (canceled)

19. A method for identifying a compound that increases the biological activity of TRPV2, comprising the steps of

a. obtaining atomic coordinates defining a three-dimensional structure of a complex comprising a TRPV2 interacting with a cannabinoid that is capable of activating the TRPV2;

b. elucidating a structural relationship between the TRPV2 and the interacting cannabinoid;

c. designing a structural analog of the cannabinoid based on the structural relationship;

d. synthesizing the structural analog;

e. determining the extent to which the structural analog alters the biological activity of the TRPV2, thereby identifying the compound that increases the biological activity of TRPV2.

20. The method of claim **19**, wherein the biological activity of the TRPV2 is determined as calcium-influx into a cell expressing the TRPV2.

21. The method of claim **19**, wherein the biological activity of the TRPV2 is measured by a method of patch clamp.

22. The method of claim **19**, wherein the biological activity of the TRPV2 is measured by a CA mobilization assay.

23. The method of claim **19**, wherein the biological activity of the TRPV2 is determined as its binding affinity to the cannabinoid that is capable of activating the TRPV2 activity.

24. A method of increasing the biological activity of a TRPV2, comprising the step of contacting the TRPV2 with a cannabinoid that is capable of activating the TRPV2 activity.

25. The method of claim **24**, wherein the TRPV2 is associated with an isolated membrane.

26. The method of claim **24**, wherein the TRPV2 is present in a cell.

27. The method of claim **26**, wherein the cell is a neuron.

28. The method of claim **24**, wherein the cannabinoid is selected from the group consisting of Δ^9-tetrahydrocannabinol, 11-hydroxy-Δ^9-tetrahydrocannabinol, cannabinol, cannabidiol, O-1821, nabilone, CP55940, 2-AG, and HU210, HU211, HU308, and HU331.

29. A method for stimulating noxious thermo-sensation in a subject, comprising administering to the subject a pharmaceutical composition comprising an effective amount of cannabinoid that is capable of activating the TRPV2 activity, thereby stimulating the noxious thermo-sensation in the subject.

30. The method of claim **29**, wherein the subject is a human.

31. The method of claim **29**, wherein the cannabinoid is selected from the group consisting of Δ^9-tetrahydrocannabinol, 11-hydroxy-Δ^9-tetrahydrocannabinol, cannabinol, cannabidiol, O-1821, nabilone, CP55940, 2-AG, and HU210, HU211, HU308, and HU331.

32. An isolated polypeptide consisting essentially of an amino acid sequence of SEQ ID NO: 7, SEQ ID NO: 8, SEQ ID NO: 9, SEQ ID NO:10, SEQ ID NO:11, SEQ ID NO:12, SEQ ID NO:13, SEQ ID NO:14, SEQ ID NO:15, SEQ ID NO:16, or SEQ ID NO:17.

33. An isolated nucleic acid molecule that encodes a polypeptide consisting essentially of an amino acid sequence of SEQ ID NO: 7, SEQ ID NO: 8, SEQ ID NO: 9, SEQ ID NO:10, SEQ ID NO:11, SEQ ID NO:12, SEQ ID NO:13, SEQ ID NO:14, SEQ ID NO:15, SEQ ID NO:16, or SEQ ID NO:17.

34. The isolated nucleic acid molecule of claim **33** consisting essentially of a nucleotide sequence of SEQ ID NO:18, SEQ ID NO:19, SEQ ID NO: 20, SEQ ID NO: 21, SEQ ID NO: 22, SEQ ID NO: 23, SEQ ID NO: 24, SEQ ID NO: 25, SEQ ID NO:26, SEQ ID NO:27, or SEQ ID NO:28.

35. An expression vector comprising nucleotide sequence that encodes a polypeptide consisting essentially of an amino acid sequence of SEQ ID NO: 7, SEQ ID NO: 8, SEQ ID NO: 9, SEQ ID NO:10, SEQ ID NO:11, SEQ ID NO:12, SEQ ID NO:13, SEQ ID NO:14, SEQ ID NO:15, SEQ ID NO:16, or SEQ ID NO:17.

36. A recombinant cell comprising an expression vector of claim **35**.

37. A method of producing a polypeptide consisting essentially of an amino acid sequence of SEQ ID NO: 7, SEQ ID NO: 8, SEQ ID NO: 9, SEQ ID NO:10, SEQ ID NO:11, SEQ ID NO:12, SEQ ID NO:13, SEQ ID NO:14, SEQ ID NO:15, SEQ ID NO:16, or SEQ ID NO:17, comprising the step of growing a cell of claim **36** under a condition whereby the polypeptide is produced by the cell.

* * * * *