Title: 3-AZABICYCLO [3.1.0] HEXANE DERIVATIVES AS VANILLOID RECEPTOR LIGANDS

Abstract: The present invention relates to 3-azabicyclo [3.1.0] hexane derivatives, which can be used as vanilloid receptor ligands, methods of treating diseases, conditions and/or disorders modulated by vanilloid receptors with them, and processes for preparing them.
3-AZABICYCLO [3.1.01 HEXANE DERIVATIVES AS VANILLOID RECEPTOR LIGANDS

This application claims the benefit of Indian Patent Application No. 1727/MUM/2007, filed on September 10, 2007, which is hereby incorporated by reference.

Field of the Invention

The present invention relates to 3-azabicyclo [3.1.0] hexane derivatives, which can be used as vanilloid receptor ligands, methods of treating diseases, conditions and/or disorders modulated by vanilloid receptors with them, and processes for preparing them.

Background of the Invention

Pain is the most common symptom for which patients seek medical advice and treatment. Pain can be acute or chronic. While acute pain is usually self-limiting, chronic pain persists for 3 months or longer and can lead to significant changes in a patient's personality, lifestyle, functional ability and overall quality of life (K. M. Foley, Pain, in Cecil Textbook of Medicine 100-107, J. C. Bennett and F. Plum eds., 20th ed., 1996). The sensation of pain can be triggered by any number of physical or chemical stimuli and the sensory neurons which mediate the response to these harmful stimuli are known as "nociceptors". Nociceptors are primary sensory afferent (C and Aδ fibers) neurons that are activated by a wide variety of noxious stimuli including chemical, mechanical, thermal, and proton (pH <6) modalities.

Moreover, chronic pain can be classified as either nociceptive or neuropathic. Nociceptive pain includes tissue injury-induced pain and inflammatory pain such as that associated with arthritis. Neuropathic pain is caused by damage to the sensory nerves of the peripheral or central nervous system and is maintained by aberrant somatosensory processing. There is a large body of evidence relating activity at vanilloid receptors (VR1) (V. Di Marzo et al., Current Opinion in Neurobiology 12: 372-379, 2002) to pain processing.

The lipophillic vanilloid, Capsaicin (8-methyl-N-vanillyl-6-nonenamides; CAP) is known to stimulate pain pathways through the release of a variety of sensory afferent neurotransmitters via a specific cell surface capsaicin receptor, cloned as the first vanilloid receptor (VR1 now known as TRPV1) (Caterina MJ, et al, Science , Apr 14; 288 (5464): 306-13, 2000). Capsaicin is the main pungent component in hot pepper. Hot pepper has been used historically not only as a spice, but also as a traditional medicine in the treatment of gastric disorders orally, and applied locally for the relief of pain and inflammation. CAP has
a wide spectrum of biological actions and not only exhibits effects on the cardiovascular and respiratory systems, but also induces pain and irritancy on local application. CAP, however, after such induction of pain induces desensitization, both to CAP itself and also to other noxious stimuli, thereby stopping the pain. The intradermal administration of capsaicin is characterized by an initial burning or hot sensation followed by a prolonged period of analgesia. The analgesic component of VR1 receptor activation is thought to be mediated by a capsaicin-induced desensitization of the primary sensory afferent terminal. Based on this property, CAP and its analogues such as olvanil, nuvanil, DA-5018, SDZ-249482, and resiniferatoxin are either used or are under development as analgesic agents or therapeutic agents for urinary incontinence or skin disorders (Wrigglesworth and Walpole, Drugs of the Future, 23: pp 531-538, 1998).

VR1 is widely expressed in non-neuronal tissues in various organ systems, and the functional roles of VR1 in various systems are not properly understood at this time. An increasing number of animal studies have revealed the possible involvement of VR1 receptors in a number of pathologies. Based on this information VR1 is now being considered as a molecular target for various indications such as migraine, arthralgia, diabetic neuropathy, neurodegeneration, neurotic skin disorder, stroke, cardiac pain arising from an ischemic myocardium, Huntington's disease, memory deficits, restricted brain function, amyotrophic lateral sclerosis (ALS), dementia, urinary bladder hypersensitiveness, urinary incontinence, vulvodynia, pruritic conditions such as uremic pruritus, irritable bowel syndrome including gastro-esophageal reflux disease, enteritis, ileitis, stomach-duodenal ulcer, inflammatory bowel disease including Crohn's disease, celiac disease and inflammatory diseases such as pancreatitis, and in respiratory disorders such as allergic and non-allergic rhinitis, asthma or chronic obstructive pulmonary disease, irritation of skin, eye or mucous membrane, dermatitis, and in non specific disorders such as fervescence, retinopathy, muscle spasms, emesis, dyskinesias and depression. Specifically VR1 antagonists are likely to be useful in multiple sub-types of pain such as acute, chronic, neuropathic pain or post-operative pain, as well as in pain due to neuralgia (e.g., post herpetic neuralgia, trigeminal neuralgia, and in pain due to diabetic neuropathy, dental pain as well as cancer pain. Additionally, VR1 antagonists will also prove useful in the treatment of inflammatory pain conditions such as arthritic or osteoarthritis. VR1 antagonists hold potential benefit in diabetes, obesity, urticaria, actinic keratosis, keratocanthoma, alopecia, Meniere's disease, tinnitus, hyperacusis and anxiety disorders.
One class of natural and synthetic compounds that modulate the function of vanilloid Receptor (VR1) have been characterized by the presence of a vanillyl (4-hydroxy 3-methoxybenzyl) group or a functionally equivalent group and the same have been widely studied and is extensively reviewed by Szallasi and Blumberg (The Am. Soc. for Pharmacology and Experimental Therapeutics, Vol. 51, No. 2, 1999).

Various vanilloid agonists and antagonists have been developed for the treatment of pain; the agonists work through desensitizing the receptor while antagonists block its stimulation by (patho) physiological ligands. The first antagonist Capsazepine was developed by Novartis.

There are other VR1 antagonists, which are at the preclinical stage, for example, Amore Pacific's PAC-20030, Neurogen's BCTC, Abbott's A-425619 and Amgen's AMG-9810.

According to the following patent publications, 3-azabicyclo[3.1.0]hexane groups may be incorporated into certain compounds useful as sorbitol dehydrogenase inhibitors, modulators of CCR5 chemokine receptors, NK-3 receptor antagonists, and AKT protein kinase inhibitors.


There still exists a need for safe and more effective vanilloid receptor modulators useful in the treatment of diseases, conditions, and/or disorders modulated by vanilloid receptors, including acute and chronic pain and neuropathic pain.
Summary of the Invention

Accordingly, in one aspect, the present invention relates to VR1 receptor ligands of general formula (I):

![Formula (I)](image)

a prodrug thereof, a pharmaceutically acceptable salt thereof, an N-oxide thereof, an ester thereof, a solvate thereof, a tautomer thereof, a stereoisomer thereof or a polymorph thereof,

wherein:

R₁ and R₃ are independently selected from hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted cycloalkenyl, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heteroarylalkyl, substituted or unsubstituted heterocyclic or substituted or unsubstituted heterocyclylalkyl;

each occurrence of R² and R₂' are independently selected from hydrogen, nitro, cyano, formyl, acetyl, halogen, -OR⁷, -SR⁷, substituted or unsubstituted alkyl, fully or partially substituted haloalkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted cycloalkenyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted cycloalkenyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heteroarylalkyl, substituted or unsubstituted heterocyclic group, substituted or unsubstituted heterocyclylalkyl, -C(O)R⁵, -C(O)OR⁵, -C(O)NR⁵R⁶, -NR⁵R⁶, -S(O)ₘR⁵, or -S(O)ₙNR⁵R⁶;

each occurrence of R⁵ and R⁶ may be same or different and are independently selected from hydrogen, nitro, halo, cyano, -ORₐ, -SRₐ, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted cycloalkenyl, substituted or unsubstituted cycloalkenylalkyl, substituted or unsubstituted cycloalkylalkyl.
cycloalkenyl, substituted or unsubstituted cycloalkenylalkyl, substituted or unsubstituted aryl,
substituted or unsubstituted arylalkyl, substituted or unsubstituted heteroaryl, substituted or
unsubstituted heteroarylalkyl, substituted or unsubstituted heterocyclic group, substituted or
unsubstituted heterocyclylalkyl, -C(O)R₈, -C(O)OR³, -C(O)NR₄R₅, -S(O)ₙR₆, -S(O)ₙNR₇R₈,
or -NR₉R₁₀; or

R⁵ and R⁶ are joined, together with the nitrogen to which they are attached, to form
substituted or unsubstituted 3 to 7 membered saturated or unsaturated cyclic ring, which
optionally includes one or more heteroatoms selected from O, S or NR₈;

R⁷ selected from hydrogen, substituted or unsubstituted alkyl, substituted or
unsubstituted cycloalkyl, substituted or unsubstituted cycloalkylalkyl, substituted or
unsubstituted cycloalkenyl, substituted or unsubstituted aryl, substituted or unsubstituted
arylalkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heteroarylalkyl,
substituted or unsubstituted heterocyclyl or substituted or unsubstituted heterocyclylalkyl;

each occurrence of R₈ and R₉ may be same or different and are independently selected
from hydrogen, halogen, nitro, cyano, formyl, acetyl, -C(O)R₁₁, -C(O)OR₁₂, -C(O)NR₁₃R₁₄, -
S(O)ₙR₁₅, -S(O)ₙNR₁₆R₁₇, -NR₁₉R₁₀, -OR₁₉, -SR₁₉, substituted or unsubstituted alkyl, substituted or
unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted
cycloalkyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted
cycloalkenyl, substituted or unsubstituted cycloalkenylalkyl, substituted or unsubstituted
aryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heteroaryl, substituted or
unsubstituted heteroarylalkyl, substituted or unsubstituted heterocyclyl, or substituted or
unsubstituted heterocyclylalkyl;

each occurrence of R₁₀ and R₁₁ is independently selected from hydrogen, substituted or
unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl,
substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkylalkyl,
substituted or unsubstituted cycloalkenyl, substituted or unsubstituted cycloalkenylalkyl,
substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or
unsubstituted heteroaryl, substituted or unsubstituted heterocyclic group, substituted or
unsubstituted heterocyclylalkyl, or a substituted or unsubstituted heteroarylalkyl or a
protecting group; or when R₁₀ and R₁₁ are attached to a nitrogen atom, they may be joined to
form substituted or unsubstituted 3 to 7 membered saturated or unsaturated cyclic ring, which
may optionally include at one or more heteroatom(s) selected from O, S or NR₁₀;

R₁₂ is hydrogen, substituted or unsubstituted alkyl, or two R₁₂ attached to a common
carbon atom, form substituted or unsubstituted cycloalkyl;
P is (CH₂)ₙ, CH(Q)CH₂ or CH₂CH(Q)CH₂ wherein n’ is an integer of from 0, 1, 2 or 3; when n’ is 0, P represents a direct bond;

Q is substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkenyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted heterocyclylalkyl ring, substituted or unsubstituted heteroarylalkyl, or substituted or unsubstituted heterocyclyl;

Rᵣ is selected from hydrogen, formyl, acetyl, -C(O)R, -C(O)NRᵣRᵣ, -S(O)ₘRᵣ, -S(O)ₘNᵣRᵣRᵣ, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkenyl, substituted or unsubstituted alkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heterocyclylalkyl, substituted or unsubstituted heterocyclylalkyl, or a substituted or unsubstituted heterocyclylalkyl or a protecting group;

each occurrence of X is independently selected from C or N;

L is -NHR, or (CR₃R₆)ₙ;,

Y is O or S;

each occurrence of ‘m’ is an integer of from 0, 1, 2.

each occurrence of ‘n’ is an integer of from 0, 1, 2, 3, 4 or 5.

Accordingly, in another aspect, the present invention relates to VR₁ receptor ligands of general formula (II):

![Formula (II)](attachment)

a prodrug thereof, a pharmaceutically acceptable salt thereof, an N-oxide thereof, an ester thereof, a solvate thereof, a tautomer thereof, a stereoisomer thereof or a polymorph thereof,
wherein:

R\(^1\) and R\(^3\) are independently selected from hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted cycloalkenyl, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heteroarylalkyl, substituted or unsubstituted heterocyclyl or substituted or unsubstituted heterocyclylalkyl;

each occurrence of R\(^2\) and R\(^2\) are independently selected from hydrogen, nitro, cyano, formyl, acetyl, halogen, -OR\(^7\), -SR\(^7\), substituted or unsubstituted alkyl, fully or partially substituted haloalkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted cycloalkenyl, substituted or unsubstituted cycloalkenylalkyl, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heteroarylalkyl, substituted or unsubstituted heterocyclic group, substituted or unsubstituted heterocyclylalkyl, -C(O)R\(^5\), -C(O)OR\(^5\), -C(O)NR\(^5\)R\(^6\), -NR\(^5\)R\(^6\), -S(O)\(_m\)R\(^5\), or -S(O)\(_m\)NR\(^a\)R\(^b\);

each occurrence of R\(^5\) and R\(^6\) may be same or different and are independently selected from hydrogen, nitro, halo, cyano, -OR\(^a\), -SR\(^a\), substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted cycloalkenyl, substituted or unsubstituted cycloalkenylalkyl, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heteroarylalkyl, substituted or unsubstituted heterocyclic group, substituted or unsubstituted heterocyclylalkyl, substituted or unsubstituted heterocyclylalkyl, -C(O)R\(^3\), -C(O)OR\(^3\), -C(O)NR\(^3\)R\(^\_m\), -S(O)\(_m\)R\(^3\), -S(O)\(_m\)NR\(^a\)R\(^b\), or -NR\(^a\)R\(^b\); or

R\(^5\) and R\(^6\) are joined, together with the nitrogen to which they are attached, to form substituted or unsubstituted 3 to 7 membered saturated or unsaturated cyclic ring, which optionally includes one or more heteroatoms selected from O, S or NR\(^3\);

R\(^7\) selected from hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted cycloalkenyl, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heteroarylalkyl, substituted or unsubstituted heterocyclyl or substituted or unsubstituted heterocyclylalkyl;
each occurrence of R^a and R^b may be same or different and is independently hydrogen, halogen, nitro, cyano, formyl, acetyl, -C(O)R^a, -C(O)OR^a, -C(O)NR^aR^b, -S(O)^mR^a, -S(O)^nNR^aR^b, -NR^aR^b, -OR^a, -SR^b, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted cycloalkenyl, substituted or unsubstituted cycloalkenylalkyl, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heteroarylalkyl, or substituted or unsubstituted heteroarylalkyl;

each occurrence of R^c and R^d is independently hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted cycloalkenyl, substituted or unsubstituted cycloalkenylalkyl, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heterocyclic group, substituted or unsubstituted heterocyclylalkyl, substituted or unsubstituted heterocyclylalkyl or a protecting group; or

when R^c and R^d which they are attached to nitrogen atom, may be joined to form substituted or unsubstituted 3 to 7 membered saturated or unsaturated cyclic ring, which may optionally include at one or more heteroatom(s) selected from O, S or NR^c;

R^4 is hydrogen, substituted or unsubstituted alkyl, or two R^4 attached to a common carbon atom, form substituted or unsubstituted cycloalkyl;

P is (CH_2)V, CH(Q)CH_2 or CH_2CH(Q)CH_2, wherein n' is an integer of from 0, 1, 2 or 3; when n' is 0. P represents a direct bond;

Q is substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkenyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted heterocyclylalkyl ring, substituted or unsubstituted heteroarylalkyl, or substituted or unsubstituted heterocyclyl;

At each occurrence of X is independently selected from C or N;

Y is O or S;

each occurrence of 'n' is an integer of from 0, 1, 2, 3, 4 or 5.
Accordingly, in another aspect, the present invention relates to VRI receptor ligands of general formula (III):

![Formula (III)](image_url)

a prodrug thereof, a pharmaceutically acceptable salt thereof, an N-oxide thereof, an ester thereof, a solvate thereof, a tautomer thereof, a stereoisomer thereof or a polymorph thereof,

wherein:

R₁ and R₃ are independently selected from hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted cycloalkenyl, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heteroarylalkyl, substituted or unsubstituted heterocyclyl or substituted or unsubstituted heterocyclolalkyl;

each occurrence of R² and R⁵ are independently selected from hydrogen, nitro, cyano, formyl, acetyl, halogen, -OR₇, -SR₇, substituted or unsubstituted alkyl, fully or partially substituted haloalkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted cycloalkenyl, substituted or unsubstituted cycloalkylalkyl substituted or unsubstituted cycloalkenylalkyl, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heteroarylalkyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted heterocyclolalkyl, substituted or unsubstituted heterocyclic group, substituted or unsubstituted heterocyclylalkyl, -C(O)R⁵, -C(O)OR⁵, -C(O)NR⁵R⁶, -NR⁵R⁶, -S(O)ₙR⁵, or -S(O)ₙNR⁵R⁶;

each occurrence of R⁵ and R⁶ may be same or different and are independently selected from hydrogen, nitro, halo, cyano, -OR⁸, -SR⁸, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted cycloalkenyl, substituted or unsubstituted cycloalkenylalkyl, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heteroaryl, substituted or
unsubstituted heteroarylalkyl, substituted or unsubstituted heterocyclic group, substituted or unsubstituted heterocyclylalkyl, -C(O)R^a, -C(O)OR, -C(O)NR^aR^b, -S(O)\_nR, -S(O)\_mNR^aR^b, or -NR^aR^b; or

R^5 and R^6 are joined, together with the nitrogen to which they are attached, to form substituted or unsubstituted 3 to 7 membered saturated or unsaturated cyclic ring, which optionally includes one or more heteroatoms selected from O, S or NR^a;

R^7 selected from hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted cycloalkenyl, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heteroarylalkyl, substituted or unsubstituted heterocyclyl or substituted or unsubstituted heterocyclylalkyl;

each occurrence of R^a and R^b may be same or different and are independently selected from hydrogen, halogen, nitro, cyano, formyl, acetyl, -C(O)R, -C(O)OR, -C(O)NR^aR^b, -S(O)\_nR, -S(O)\_mNR^aR^b, -NR^aR^b, -OR, -SR, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted cycloalkenyl, substituted or unsubstituted cycloalkenylalkyl, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heterocyclyl, or substituted or unsubstituted heteroarylalkyl;

each occurrence of R^c and R^d is independently hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted cycloalkenyl, substituted or unsubstituted cycloalkenylalkyl, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted heterocyclylalkyl, substituted or unsubstituted heteroarylalkyl or a protecting group; or

when R^c and R^d which they are attached to nitrogen atom, may be joined to form substituted or unsubstituted 3 to 7 membered saturated or unsaturated cyclic ring, which may optionally include at one or more heteroatom(s) selected from O, S or NR^c;

R^4 is hydrogen, substituted or unsubstituted alkyl, or two R^4 attached to a common carbon atom, form substituted or unsubstituted cycloalkyl;

Y is O or S;

each occurrence of 'n' is an integer of from 0, 1, 2, 3, 4 or 5.
Representative examples of compounds of the present invention are provided below. These compounds are illustrative in nature only and do not limit the scope of the invention.

2-(3H-Benzimidazol-1-yl)-N-[3-(2,4-Difluorophenyl)-3-azabicyclo[3.1.0]hex-6-yl]-acetamide (Compound No. 1),

N-[3-(2,4-Difluorophenyl)-3-azabicyclo[3.1.0]hex-6-yl]-2-(2-methyl benzimidazol-1-yl)-acetamide (Compound No. 2),

N-[3-(2,4-Difluorophenyl)-3-azabicyclo[3.1.0]hex-6-yl]-2-(5-trifluoromethyl benzimidazol-1-yl)-acetamide (Compound No. 3),

2-(6,7-Difluoro benzimidazol-1-yl)-N-[3-(2,4-difluorophenyl)-3-azabicyclo[3.1.0]hex-6-yl]-acetamide (Compound No. 4),

N-[3-(2,4-Difluorophenyl)-3-azabicyclo[3.1.0]hex-6-yl]-2-imidazo[4,5]pyridine-3-yl-acetamide (Compound No. 5),

N-[3-(2,4-Difluorophenyl)-3-azabicyclo[3.1.0]hex-6-yl]-2-(5-fluoro benzimidazol-1-yl)-acetamide (Compound No. 6),

N-[3-(2,4-Difluorophenyl)-3-azabicyclo[3.1.0]hex-6-yl]-2-(6-methoxy benzimidazol-1-yl)-acetamide (Compound No. 7),

and a prodrug thereof, a pharmaceutically acceptable salt thereof, an N-oxide thereof, an ester thereof, a solvate thereof, a tautomer thereof, a stereoisomer thereof or a polymorph thereof.

The present invention also provides a pharmaceutical composition comprising at least one compound of the present invention and a pharmaceutically acceptable excipient (such as a pharmaceutically acceptable carrier or diluent). Preferably, the pharmaceutical composition comprises a therapeutically effective amount of at least one compound of the present invention. The compound of the present invention may be associated with a pharmaceutically acceptable excipient (such as a carrier or a diluent) or be diluted by a carrier, or enclosed within a carrier which can be in the form of a capsule, sachet, paper or other container.

Also provided herein is a method for preventing, ameliorating or treating a disease, disorder or syndrome mediated by vanilloid receptors (such as VR1) in a subject in need thereof by administering to the subject a therapeutically effective amount of one or more compounds of the present invention or a pharmaceutical composition of the present invention. Non-limiting examples of diseases, disorders and syndromes which can be mediated by vanilloid receptor 1 (VR1) include (1) migraine, (2) arthralgia, (3) diabetic
neuropathy, (4) neurodegeneration, (5) neurotic skin disorder, (6) stroke, (7) cardiac pain arising from an ischemic myocardium, (8) Huntington's disease, (9) memory deficits, (10) restricted brain function, (11) amyotrophic lateral sclerosis (ALS), (12) dementia, (13) urinary bladder hypersensitiveness, (14) urinary incontinence, (15) vulvodynia, (16) pruritic conditions such as uremic pruritus, (17) irritable bowel syndrome including gastro-esophageal reflux disease, (18) enteritis, (19) ileitis, (20) stomach-duodenal ulcer, (21) inflammatory bowel disease including Crohn's disease, (22) celiac disease, (23) inflammatory diseases (such as pancreatitis), (24) respiratory disorders such as allergic and non-allergic rhinitis, asthma or chronic obstructive pulmonary disease (COPD), (25) irritation of skin, eye or mucous membrane, (26) dermatitis, (27) fervescence, (28) retinopathy, (29) muscle spasms, (30) emesis, (31) dyskinesias, (32) depression, (33) pain such as acute, chronic, neuropathic pain or post-operative pain, (34) pain due to neuralgia or trigeminal neuralgia, (35) pain due to diabetic neuropathy, (36) dental pain, (37) cancer pain, (38) arthritis, (39) osteoarthritis, (40) diabetes, (41) obesity, (42) urticaria, (43) actinic keratosis, (44) keratoacanthoma, (45) alopecia, (46) Meniere's disease, (47) tinnitus, (48) hyperacusis, (49) anxiety disorders and (50) benign prostate hyperplasia. According to one preferred embodiment, the compounds of the present invention are administered to treat acute or chronic pain or neuropathic pain.

Also provided herein are processes for preparing compounds described herein.

**Detailed Description of the Invention**

The present invention provides 3-azabicyclo [3.1.0] hexane derivatives, which can be used as vanilloid receptor ligands, and processes for the synthesis of these compounds. Pharmaceutically acceptable salts, pharmaceutically acceptable solvates, enantiomers, diastereomers, polymorphs of these compounds having the same type of activity are also provided. Pharmaceutical compositions containing the described compounds together with pharmaceutically acceptable carriers, excipients or diluents, which can be used for the treatment of diseases, condition and/or disorders mediated by vanilloid receptors (such as VR1) are further provided.

**Definitions**

The term "alkyl" refers to a straight or branched hydrocarbon chain radical consisting solely of carbon and hydrogen atoms, containing no unsaturation, having from one to eight carbon atoms, and which is attached to the rest of the molecule by a single bond, e.g., methyl,
ethyl, n-propyl, 1-methylethyl (isopropyl), n-butyl, n-pentyl, and 1,1-dimethylethyl (t-butyl). The term "Ci₆ alkyl" refers to an alkyl chain having 1 to 6 carbon atoms.

The term "alkenyl" refers to an aliphatic hydrocarbon group containing a carbon-carbon double bond and which may be a straight or branched chain having 2 to about 10 carbon atoms, e.g., ethenyl, 1-propenyl, 2-propenyl (allyl), iso-propenyl, 2-methyl-1-propenyl, 1-butenyl, and 2-butenyl.

The term "alkynyl" refers to a straight or branched chain hydrocarbyl radical having at least one carbon-carbon triple bond, and having 2 to about 12 carbon atoms (with radicals having 2 to about 10 carbon atoms being preferred), e.g., ethynyl, propynyl, and butynyl.

The term "alkoxy" denotes an alkyl group attached via an oxygen linkage to the rest of the molecule. Representative examples of such groups are -OCH₃ and -OC₆H₅.

The term "cycloalkyl" denotes a non-aromatic mono or multicyclic ring system of 3 to about 12 carbon atoms, such as cyclopropyl, cyclobutyl, cyclopentyl, and cyclohexyl. Examples of multicyclic cycloalkyl groups include, but are not limited to, perhydronapththyl, adamantyl and norbornyl groups, bridged cyclic groups or spirroyclic groups, e.g., sprio (4,4) non-2-yl.

The term "cycloalkylalkyl" refers to a cyclic ring-containing radical having 3 to about 8 carbon atoms directly attached to an alkyl group. The cycloalkylalkyl group may be attached to the main structure at any carbon atom in the alkyl group that results in the creation of a stable structure. Non-limiting examples of such groups include cyclopropylmethyl, cyclobutylethyl, and cyclopentylethyl.

The term "cycloalkenyl" refers to a cyclic ring-containing radical having 3 to about 8 carbon atoms with at least one carbon-carbon double bond, such as cyclopropenyl, cyclobutenyl, and cyclopentenyl.

The term "aryl" refers to an aromatic radical having 6 to 14 carbon atoms such as phenyl, naphthyl, tetrahydronaphthyl, indanyl, and biphenyl.

The term "aryllalkyl" refers to an aryl group as defined above directly bonded to an alkyl group as defined above, e.g., -CH₂C₆H₅ and -C₆H₅C₆H₅.

The term "heterocyclic ring" refers to a stable 3- to 15-membered ring radical which consists of carbon atoms and from one to five heteroatoms selected from nitrogen, phosphorus, oxygen and sulfur. For purposes of this invention, the heterocyclic ring radical may be a monocyclic, bicyclic or tricyclic ring system, which may include fused, bridged or spiro ring systems, and the nitrogen, phosphorus, carbon, oxygen or sulfur atoms in the heterocyclic ring radical may be optionally oxidized to various oxidation states. In addition,
the nitrogen atom may be optionally quaternized; and the ring radical may be partially or fully saturated (i.e., heterocyclic or heteroaryl). Examples of such heterocyclic ring radicals include, but are not limited to, azetidinyl, acridinyl, benzodioxolyl, benzodioxanyl, benzofuranyl, carbazolyl, cinnolinyl, dioxolanyl, indoliziny, naphthyridinyl, perhydroazepinyl, phenazinyl, phenothiazinyl, phenoxazinyl, phthalazinyl, pyridyl, pteridinyl, purinyl, quinazolinyl, quinoxaliny, quinolinyl, isoquinolinyl, tetrazolyl, imidazolyl, tetrahydroisouinolyl, piperidinyl, piperazinyl, 2-oxopiperazinyl, 2-oxopiperidinyl, 2-oxopyrrolidinyl, 2-oxoazepinyl, azepinyl, pyrrolyl, 4-piperidonyl, pyrrolidinyl, pyrazinyl, pyrimidinyl, pyridazinyl, oxazolyl, oxazolinyl, oxasolidinyl, triazolyl, indany, isoxazolyl, isoxasolidinyl, moφ holinyl, thiazolyl, thiazoliny, thiazolidinyl, isothiazolidinyl, quinuclidinyl, isothiazolidinyl, indolyl, isoindolyl, indoliny, isoindoliny, octahydroindolyl, octahydroisoindolyl, quinolyl, isoquinolyl, decahydroisouinolyl, benzimidazolyl, thiadiazolyl, benzopyryl, benzothiazolyl, benzooxazolyl, furyl, tetrahydrofurtyl, tetrahydropranyl, thienyl, benzothenyl, thiamopholyn sulfoxide, thiophospholyn sulfone, dihydrophospholany, oxadiazolyl, chromany, and isochromany. The heterocyclic ring radical may be attached to the main structure at any heteroatom or carbon atom that results in the creation of a stable structure.

The term "heterocycl" refers to a heterocyclic ring radical as defined above. The heterocycl ring radical may be attached to the main structure at any heteroatom or carbon atom that results in the creation of a stable structure.

The term "heterocyclalkyl" refers to a heterocyclic ring radical directly bonded to an alkyl group. The heterocyclalkyl radical may be attached to the main structure at any carbon atom in the alkyl group that results in the creation of a stable structure.

The term "heteroaryl" refers to an aromatic heterocyclic ring radical. The heteroaryl ring radical may be attached to the main structure at any heteroatom or carbon atom that results in the creation of a stable structure.

The term "heteroarylalkyl" refers to a heteroaryl ring radical directly bonded to an alkyl group. The heteroarylalkyl radical may be attached to the main structure at any carbon atom in the alkyl group that results in the creation of a stable structure.

Unless otherwise specified, the term "substituted" as used herein refers to substitution with any one or any combination of the following substituents: hydroxy, halogen, carboxyl, cyano, nitro, oxo (=O), thio (=S), substituted or unsubstituted alkyl, substituted or unsubstituted alkoxy, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or
unsubstituted cycloalkyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted cycloalkenyl, substituted or unsubstituted amino, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heterocyclylalkyl ring, substituted or unsubstituted heteroarylalkyl, substituted or unsubstituted heterocyclic ring, substituted or unsubstituted guanidine, -COOR", -C(O)R_X, -C(S)R_X, -C(O)NR_yR_z, -C(O)ONR_yR_z, -NR_yCONR_yR_z, -N(R_y)SOR_y, -N(R_y)SO_2R_z, -N(=N-N(R_y)R_z), -NR_yC(O)OR_y, -NR_yC(O)NR_yR_z, -NR_yC(S)NR_yR_z, -SO_2NR_yR_z, -OR_y, -OR_yC(O)NR_yR_z, -OR_yC(O)OR_y, -OC(O)R", -OC(O)NR_yR_z, -R_yNR_yC(0)R_z, -R_yOR_y, -R_yC(0)OR_y, -R_yC(O)NR_yR_z, -R_yC(0)R_y, -R_yOC(O)R_y, -SR_y, -SOR_y, -SO_2R_y and -ONO_2, wherein R_x, R_y and R_z are independently selected from hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkoxy, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkenyl, substituted or unsubstituted amino, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted heterocyclylalkyl ring, substituted or unsubstituted heteroarylalkyl, or substituted or unsubstituted heterocyclic ring. The substituents in the aforementioned "substituted" groups cannot be further substituted. For example, when the substituent on "substituted alkyl" is "substituted aryl", the substituent on "substituted aryl" cannot be "substituted alkenyl".

The term "protecting group" or "PG" refers to a substituent that is employed to block or protect a particular functionality while other functional groups on the compound may remain reactive. For example, an "amino-protecting group" is a substituent attached to an amino group that blocks or protects the amino functionality in the compound. Suitable amino-protecting groups include, but are not limited to, acetyl, trifluoroacetyl, t-butoxycarbonyl (BOC), benzyloxycarbonyl (CBz) and 9-fluorenylmethyloxycarbonyl (Fmoc). Similarly, a "hydroxy-protecting group" refers to a substituent of a hydroxy group that blocks or protects the hydroxy functionality. Suitable hydroxy-protecting groups include, but are not limited to, acetyl, benzyl, tetrahydropyran and silyl. A "carboxy-protecting group" refers to a substituent of the carboxy group that blocks or protects the carboxy functionality. Suitable carboxy-protecting groups include, but are not limited to, -CH_2CH_2SO_2Ph, cyanoethyl, 2-(trimethylsilyl)ethyl, 2-(trimethylsilyl)ethoxymethyl, 2-(p-toluenesulfonyl)ethyl, 2-(p-nitrophenylsulfonyl)ethyl, 2-(diphenylphosphino)-ethyl, and nitroethyl. For a general description of protecting groups and their use, see, T. W. Greene, Protective Groups in Organic Synthesis, John Wiley & Sons, New York, 1991.
The term "prodrug" means a compound that is transformed in vivo to yield a compound of Formula (I) or a pharmaceutically acceptable salt, hydrate or solvate of the compound. The transformation may occur by various mechanisms, such as through hydrolysis in blood. A discussion of the use of prodrugs is provided by T. Higuchi and W. Stella, "Pro-drugs as Novel Delivery Systems," Vol. 14 of the A.C.S. Symposium Series, and in Bioreversible Carriers in Drug Design, ed. Edward B. Roche, American Pharmaceutical Association and Pergamon Press, 1987.

The term "treating" or "treatment" of a state, disorder or condition includes:

1. preventing or delaying the appearance of clinical symptoms of the state, disorder or condition developing in a subject that may be afflicted with or predisposed to the state, disorder or condition but does not yet experience or display clinical or subclinical symptoms of the state, disorder or condition;

2. inhibiting the state, disorder or condition, i.e., arresting or reducing the development of the disease or at least one clinical or subclinical symptom thereof; or

3. relieving the disease, i.e., causing regression of the state, disorder or condition or at least one of its clinical or subclinical symptoms.

The benefit to a subject to be treated is either statistically significant or at least perceptible to the subject or to the physician.

The term "subject" includes mammals (especially humans) and other animals, such as domestic animals (e.g., household pets including cats and dogs) and non-domestic animals (such as wildlife).

A "therapeutically effective amount" means the amount of a compound that, when administered to a subject for treating a state, disorder or condition, is sufficient to effect such treatment. The "therapeutically effective amount" will vary depending on the compound, the disease and its severity and the age, weight, physical condition and responsiveness of the subject to be treated.

Pharmaceutically acceptable salts forming part of this invention include salts derived from inorganic bases (such as Li, Na, K, Ca, Mg, Fe, Cu, Zn, and Mn), salts of organic bases (such as N,N'-diacetyldihylenediamine, glucamine, triethylamine, choline, hydroxide, dicyclohexylamine, metformin, benzylamine, trialkylamine, and thiamine), salts of chiral bases (such as alkylphenylamine, glycinol, and phenyl glycinol), salts of natural amino acids (such as glycine, alanine, valine, leucine, isoleucine, norleucine, tyrosine, cystine, cysteine, methionine, proline, hydroxy proline, histidine, ornithine, lysine, arginine, and serine), salts of non-natural amino acids (such as D-isomers or substituted amino acids), salts of guanidine,
salts of substituted guanidine (wherein the substituents are selected from nitro, amino, alkyl, alkenyl, or alkynyl), ammonium salts, substituted ammonium salts, and aluminum salts. Other pharmaceutically acceptable salts include acid addition salts (where appropriate) such as sulphates, nitrates, phosphates, perchlorates, borates, hydrohalides, acetates (such as trifluoroacetate), tartrates, maleates, citrates, fumarates, succinates, palmoates, methanesulphonates, benzoates, salicylates, benzenesulphonates, ascorbates, glycerophosphates, and ketoglutarates. Yet other pharmaceutically acceptable salts include, but are not limited to, quaternary ammonium salts of the compounds of invention with alkyl halides or alkyl sulphates (such as MeI or (Me)₂SO₄).

Pharmaceutically acceptable solvates includes hydrates and other solvents of crystallization (such as alcohols). The compounds of the present invention may form solvates with low molecular weight solvents by methods known in the art.

Certain compounds of present invention are capable of existing in stereoisomeric forms (e.g. diastereomers and enantiomers) and the invention extends to each of these stereoisomeric forms and to mixtures thereof including racemates. The different stereoisomeric forms may be separated one from the other by known methods, or any given isomer may be obtained by stereospecific or asymmetric synthesis. The invention also extends to any tautomeric forms and mixtures thereof. For example, both tautomeric forms of the following moiety are contemplated:

\[
\begin{align*}
\text{Pharmaceutical Compositions} \quad \text{R} & \quad \text{Y} \\
\text{N} & \quad \text{R} \\
\text{N} & \quad \text{R} \\
\text{N} & \quad \text{R}
\end{align*}
\]

The pharmaceutical composition of the present invention comprises at least one compound of the present invention and a pharmaceutically acceptable excipient (such as a pharmaceutically acceptable carrier or diluent). Preferably, the pharmaceutical composition comprises a therapeutically effective amount of the compound(s) of the present invention. The compound of the present invention may be associated with a pharmaceutically acceptable excipient (such as a carrier or a diluent) or be diluted by a carrier, or enclosed within a carrier which can be in the form of a capsule, sachet, paper or other container.

Examples of suitable carriers include, but are not limited to, water, salt solutions, alcohols, polyethylene glycols, polyhydroxyethoxylated castor oil, peanut oil, olive oil, gelatin, lactose, terra alba, sucrose, dextrin, magnesium carbonate, sugar, cyclodextrin, amylose, magnesium stearate, talc, gelatin, agar, pectin, acacia, stearic acid or lower alkyl
ethers of cellulose, silicic acid, fatty acids, fatty acid amines, fatty acid monoglycerides and diglycerides, pentaerythritol fatty acid esters, polyoxyethylene, hydroxymethylcellulose and polyvinylpyrrolidone.

The carrier or diluent may include a sustained release material, such as glyceryl monostearate or glyceryl distearate, alone or mixed with a wax.

The pharmaceutical composition may also include one or more pharmaceutically acceptable auxiliary agents, wetting agents, emulsifying agents, suspending agents, preserving agents, salts for influencing oxmetic pressure, buffers, sweetening agents, flavoring agents, colorants, or any combination of the foregoing. The pharmaceutical composition of the invention may be formulated so as to provide quick, sustained, or delayed release of the active ingredient after administration to the subject by employing procedures known in the art.

The pharmaceutical compositions of the present invention may be prepared by conventional techniques, e.g., as described in *Remington: The Science and Practice of Pharmacy*, 20th Ed., 2003 (Lippincott Williams & Wilkins). For example, the active compound can be mixed with a carrier, or diluted by a carrier, or enclosed within a carrier, which may be in the form of an ampoule, capsule, sachet, paper, or other container. When the carrier serves as a diluent, it may be a solid, semi-solid, or liquid material that acts as a vehicle, excipient, or medium for the active compound. The active compound can be adsorbed on a granular solid container, for example, in a sachet.

The pharmaceutical compositions may be in conventional forms, for example, capsules, tablets, aerosols, solutions, suspensions or products for topical application.

The route of administration may be any route which effectively transports the active compound of the invention to the appropriate or desired site of action. Suitable routes of administration include, but are not limited to, oral, nasal, pulmonary, buccal, subdermal, intradermal, transdermal, parenteral, rectal, depot, subcutaneous, intravenous, intraurethral, intramuscular, intranasal, ophthalmic (such as with an ophthalmic solution) or topical (such as with a topical ointment). The oral route is preferred.

Solid oral formulations include, but are not limited to, tablets, capsules (soft or hard gelatin), dragees (containing the active ingredient in powder or pellet form), troches and lozenges. Tablets, dragees, or capsules having talc and/or a carbohydrate carrier or binder or the like are particularly suitable for oral application. Preferable carriers for tablets, dragees, or capsules include lactose, cornstarch, and/or potato starch. A syrup or elixir can be used in cases where a sweetened vehicle can be employed.
A typical tablet that may be prepared by conventional tableting techniques may contain: (1) Core: Active compound (as free compound or salt thereof), 250 mg colloidal silicon dioxide (Aerosil®), 1.5 mg microcrystalline cellulose (Avicel®), 70 mg modified cellulose gum (Ac-Di-Sol®), and 7.5 mg magnesium stearate; (2) Coating: HPMC, approx. 9 mg Mywacett 9-40 T and approx. 0.9 mg acylated monoglyceride.

Liquid formulations include, but are not limited to, syrups, emulsions, soft gelatin and sterile injectable liquids, such as aqueous or non-aqueous liquid suspensions or solutions.

For parenteral application, particularly suitable are injectable solutions or suspensions, preferably aqueous solutions with the active compound dissolved in polyhydroxylated castor oil.

Methods of Treatment

The present invention provides compounds and pharmaceutical formulations thereof that are useful in the treatment of diseases, conditions and/or disorders modulated by vanilloid VR1 receptor antagonists.

The present invention further provides a method of treating a disease, condition and/or disorder modulated by vanilloid receptor antagonists in a subject in need thereof by administering to the subject a therapeutically effective amount of a compound or a pharmaceutical composition of the present invention. The method is particularly useful for treating diseases, conditions and/or disorders modulated by VR1 receptor antagonists.

Diseases, conditions, and/or disorders that are modulated by vanilloid receptor antagonists include, but are not limited to, migraine, arthralgia, diabetic neuropathy, neurodegeneration, neurotic skin disorder, stroke, cardiac pain arising from an ischemic myocardium, Huntington's disease, memory deficits, restricted brain function, amyotrophic lateral sclerosis (ALS), dementia, urinary bladder hypersensitiveness, urinary incontinence, vulvodynia, pruritic conditions such as uremic pruritus, irritable bowel syndrome including gastro-esophageal reflux disease, enteritis, ileitis, stomach-duodenal ulcer, inflammatory bowel disease including Crohn's disease, celiac disease and inflammatory diseases such as pancreatitis, and in respiratory disorders such as allergic and non-allergic rhinitis, asthma or chronic obstructive pulmonary disease, irritation of skin, eye or mucous membrane, dermatitis, and in non specific disorders such as fervescence, retinopathy, muscle spasms, emesis, dyskinesias or depression. Specifically in multiple sub-types of pain such as acute, chronic, neuropathic pain or post-operative pain, as well as in pain due to neuralgia (e.g. post herpetic neuralgia, trigeminal neuralgia; and in pain due to diabetic neuropathy or dental pain as well as in cancer pain. Additionally, VR1 antagonists hold potential benefit in the
treatment of inflammatory pain conditions e.g. arthritis, and osteoarthritis, diabetes, obesity, urticaria, actinic keratosis, keratoacanthoma, alopecia, Meniere's disease, tinnitus, hyperacusis and anxiety disorders.

The method is also particularly useful for treating pain, urinary incontinence, ulcerative colitis, asthma, and inflammation.

As indicated above, the compounds of the present invention and their pharmaceutically acceptable salts or pharmaceutically acceptable solvates have vanilloid receptor antagonist (VRI) activity and are useful for the treatment or prophylaxis of certain diseases or disorders mediated or associated with the activity of vanilloid receptor, including disorders such as pain, chronic pain, neuropathic pain, postoperative pain, rheumatoid arthritic pain, osteoarthritis pain, back pain, visceral pain, cancer pain, algesia, neuralgia, migraine, neuropathies, diabetic neuropathy, sciatica, HIV-related neuropathy, post-herpetic neuralgia, fibromyalgia, nerve injury, ischaemia, neurodegeneration, stroke, post stroke pain, multiple sclerosis, respiratory diseases, asthma, cough, COPD, inflammatory disorders, oesophagitis, gastrointestinal reflux disorder (GERD), irritable bowel syndrome, inflammatory bowel disease, pelvic hypersensitivity, urinary incontinence, cystitis, burns, psoriasis, emesis, stomach duodenal ulcer and pruritus.

Thus the invention also provides a compounds or a pharmaceutically acceptable salt thereof, for use as an active therapeutic substance, in particular in the treatment or prophylaxis of diseases or disorders mediated or associated with the activity of vanilloid receptor. In particular the invention provides a compound of formula (F) or a pharmaceutically acceptable salt thereof for use in the treatment or prophylaxis of pain.

The invention further provides a method of treatment or prophylaxis of diseases or disorders mediated or associated with the activity of vanilloid receptor, in mammals including humans, which comprises administering to the sufferer a therapeutically effective amount of a compound of the present invention.

The invention provides for the use of a compound of the present invention or a pharmaceutically acceptable salt thereof or a pharmaceutically acceptable solvate thereof in the manufacture of a medicament for the treatment or prophylaxis of diseases or disorders mediated or associated with the activity of vanilloid receptor.

The compound of the present invention has potent analgesic and antiinflammatory activity, and the pharmaceutical composition of the present invention thus may be employed to alleviate or relieve acute, chronic or inflammatory pains, suppress inflammation, or treat urinary incontinence (including urgent urinary incontinence).
In accordance with another aspect of the present invention, there is also provided a method for alleviating and/or treating migraine, arthralgia, diabetic neuropathy, neurodegeneration, neurotic skin disorder, stroke, cardiac pain arising from an ischemic myocardium, Huntington's disease, memory deficits, restricted brain function, amyotrophic lateral sclerosis (ALS), dementia, urinary bladder hypersensitivity, urinary incontinence, vulvodynia, pruritic conditions such as uremic pruritus, irritable bowel syndrome including gastro-oesophageal reflux disease, enteritis, ileitis, stomach-duodenal ulcer, inflammatory bowel disease including Crohn's disease, celiac disease and inflammatory diseases such as pancreatitis, and in respiratory disorders such as allergic and non-allergic rhinitis, asthma or chronic obstructive pulmonary disease, irritation of skin, eye or mucous membrane, dermatitis, and in non specific disorders such as fervescence, retinopathy, muscle spasms, emesis, dyskinesias or depression. Specifically in multiple sub-types of pain such as acute, chronic, neuropathic pain or post-operative pain, as well as in pain due to neuralgia (e.g. post herpetic neuralgia, trigeminal neuralgia; and in pain due to diabetic neuropathy or dental pain as well as in cancer pain. Additionally in the treatment of inflammatory pain conditions e.g. arthritis, and osteoarthritis, diabetes, obesity, urticaria, actinic keratosis, keratocanthoma, alopecia, Meniere's disease, tinnitus, hyperacusis and anxiety disorders.

According to a preferred embodiment there is provided a method of treating pain in a subject in need thereof comprising administering to the subject a therapeutically effective amount of a compound described herein. According to yet another preferred embodiment, pain is acute, chronic or post-operative pain. Yet another embodiment provides a method of treating neuropathic pain, urinary incontinence, ulcerative colitis, asthma or inflammation.

The compounds of the present invention in pharmaceutical dosage forms may be used in the form of their pharmaceutically acceptable salts, and also may be used alone or in appropriate association, as well as in combination with other pharmaceutically active compounds.

The compounds of the present invention (including the pharmaceutical compositions and processes used therein) may be used alone or in combination with other pharmaceutical agents in the manufacture of a medicament for the therapeutic applications described herein.

**Methods of Preparation**

The compounds described herein, including compounds of general formula (I), (II), (II) and specific examples, are prepared using techniques known to one skilled in the art through the reaction sequences depicted in Schemes I-VI. Furthermore, in the following
schemes, where specific acids, bases, reagents, coupling agents, solvents, etc. are mentioned, it is understood that other suitable acids, bases, reagents, coupling agents etc. may be used and are included within the scope of the present invention. Modifications to reaction conditions, for example, temperature, duration of the reaction or combinations thereof, are envisioned as part of the present invention. The compounds obtained by using the general reaction sequences may be of insufficient purity. These compounds can be purified by using any of the methods for purification of organic compounds known to persons skilled in the art, for example, crystallization or silica gel or alumina column chromatography using different solvents in suitable ratios. All possible stereoisomers are envisioned within the scope of this invention.

The starting materials for the synthetic schemes I-VI are commercially available or can be prepared according to methods known to one skilled in the art of organic synthesis. The synthetic schemes disclosed above are only specific approaches for the compounds of invention and anyone who is skilled in the art of synthesis may be able to prepare these intermediates and compounds of invention using alternative synthetic routes and approaches. More specific details of synthetic methods are given below to illustrate the scope of the present invention. The examples are provided by way of illustration only and therefore should not be construed to limit the scope of the invention, where in all symbols are as defined above.

Scheme I

A compound of general formula Ia (wherein all symbols are as defined herein above) can be prepared following the reaction sequence depicted in Scheme I. Thus, the compound
of the general formula (2) can be synthesized by reacting optionally substituted azabicycloamine of the general formula (1) with compound of formula Z-L-C(Y)-X' (wherein Z is a leaving group such as halide, alkoxy, aryloxy, hydroxyl, alkyl or aryl sulfonate; X' is a leaving group such as halide, alkoxy, alkoxycarbonyloxy or aryloxy; L is -NHR₃ or (CR₅R₆)ₙ; Y is O or S). The compound of general formula (2) can be further reacted with optionally substituted benzimidazole of formula (3) to form a compound of formula Ia.

The reaction of optionally substituted azabicycloamine of formula (1) with compound of formula Z-L-C(Y)-X' to form a compound of formula (2) can be carried out in absence or presence of a base such as triethylamine, pyridine, DMAP or HOBt, in a solvent such as toluene, tetrahydrofuran, dichloromethane or dimethylformamide. The reaction of a compound of formula (2) with optionally substituted benzimidazole of formula (3) to form a compound of formula Ia in presence of a base such as sodium hydride, potassium carbonate, potassium t-butoxide, sodium hydroxide or butyl lithium, in a solvent such as toluene, tetrahydrofuran, dichloromethane, dimethylformamide or water.

Alternatively, the compound of formula (Ia) can be prepared by the following reaction sequence depicted in Scheme II:

![Scheme II](image)

The reaction of a compound of general formula (1) compound of formula (4) to form a compound of formula Ia in presence of base such as triethylamine, pyridine, DMAP or HOBt, in a solvent such as toluene, tetrahydrofuran, dichloromethane, dimethylformamide or water.

The compound of general formula (4) [wherein R², R³, X and n are the same as defined earlier] can be prepared using Scheme III:
Thus, an optionally substituted benzimidazole of the general formula (3) is reacted with a carboxylic acid ester of formula Z-L-COOR (where R is H or alkyl) or with a nitrile of formula Z-L-CN (wherein Z is a leaving group such as halide, alkoxy, aryloxy, hydroxyl, alkyl or aryl sulfonate;) to give a compound of general formula (3a) or (3b), which upon hydrolysis under general acidic or basic conditions gives a compound of general formula (4). The reaction of an optionally substituted benzimidazole of general formula (3) with a carboxylic acid ester of formula Z-L-COOR or with a nitrile of formula Z-L-CN can preferably be carried out in presence of a base such as potassium carbonate or triethylamine, in a solvent such as toluene, tetrahydrofuran, dichloromethane, dimethylformamide or methanol.

Alternatively, the compound of general formula (4) can also be prepared as depicted in reaction Scheme IV using the procedures known to a person of ordinary skill in the art.

\[ P' = \text{COOR or CN or CHO or CH}_2\text{OH} \]
Compound of formula (5) can be reacted with formula L-P’ (where L is as defined above; and P’ = COOR or CN or CHO or CH$_2$OH where R is alkyl) to form compound of formula (6) in suitable reagent, compound of formula (6) further reacted to form compound of formula (7). P’ in compound of formula (7) get appropriate reaction such as oxidation or hydrolysis to form compound of formula (4) through the procedure known in the art.

Alternatively, the compound of general formula 7 can also be prepared as depicted in reaction Scheme V using the procedures known to a person of ordinary skill in the art.

Scheme V

$\text{(8)} \xrightarrow{\text{NH}_2 \cdot \text{L-P'}} \text{(6)}$

$P' = \text{COOR or CN or CHO or CH}_2\text{OH}$

$W = \text{halogen}$

Compound of formula (6) can be prepared by reacting compound of formula (8) with formula NH$_2$-L-P’.

Alternatively, the compound of formula I can be prepared by the following reaction sequence depicted in Scheme VI:

Scheme VI

$\text{(1)} \xrightarrow{\text{Q'-HN-L-COOR}} \text{(9)}$

$\text{(8)} \xrightarrow{\text{m(R)}} \text{(11)}$

Formula (Ia)

A compound of general formula Ia (all symbols as defined above.) can be prepared by following the reaction sequence depicted in Scheme VI above. Thus, the compound of the
The general formula (9) can be synthesized by reacting optionally substituted azabicycloamine of the general formula (1) with an optionally substituted protected amino acid of formula Q'-HN-L-COOR (wherein Q' is a protecting group such as Boc, Fmoc or Cbz; R is H or alkyl;). The compound of general formula (9) can be deprotected with a suitable deprotecting reagent to give a compound of general formula (10) which can be further reacted with a compound of general formula (8) (where in W is a halide such as F, Cl, Br or I;) to give a compound of general formula (11). The nitro group of the compound of general formula (11) can be reduced under reducing conditions such as iron in acetic acid or zinc in ammonium formate and catalytic hydrogenation in the presence of palladium or nickel to give a compound of general formula (12). The compound of general formula (12) can be reacted with an optionally substituted carboxylic acid, aldehyde or an orthoester to form a compound of general formula Ia.

The reaction of optionally substituted azabicycloamine of formula (1) with an optionally substituted, protected amino acid of formula Q'-HN-L-COOH to form a compound of formula (9) can be carried out in absence or presence of a base such as triethylamine, pyridine, DMAP or HOBt, using a suitable coupling agent such as dicyclohexyl carbodiimide or N-ethyl N'-dimethylamino propyl carbodiimide, in a solvent such as toluene, tetrahydrofuran, dichloromethane or dimethylformamide. The deprotection of a compound of formula (9) can be carried out in a solvent such as ethyl acetate or methanol using an acidic reagent such as HCl or PTSA or a basic reagent such as piperidine or morpholine or can also be deprotected under hydrogenation conditions to give a compound of general formula (10). The compound of general formula (10) can be coupled with a compound of general formula (8) in the presence of a base such as potassium carbonate, potassium tert-butoxide or sodium hydride in a solvent such as tetrahydrofuran, dimethyl formamide or dimethyl sulfoxide to give a compound of general formula (11) which can be reduced under reduction conditions such as iron in acetic acid, zinc in ammonium formate and catalytic hydrogenation in the presence of palladium or nickel, in the absence or presence of an acidic reagent such as hydrochloric acid in a solvent such as ethyl acetate, ethanol or methanol to give a compound of general formula (12). The compound of general formula (12) can be reacted with an optionally substituted carboxylic acid, aldehyde or an orthoester in the absence or presence of a solvent such as ethanol or tetrahydrofuran.

**Experimental**

26
Example 1: Preparation of 2-(3H-Benzimidazol-1-yl)-N-[3-(2,4-Difluorophenyl)-3-azabicyclo[3.1.0]hex-6-yl]-acetamide (Compound No. 1)

Step I: 2-Chloro-N-[3-(2,4-Difluorophenyl)-3-azabicyclo[3.1.0]hex-6-yl]-acetamide

To a solution of 3-(2,4-Difluorophenyl)-3-azabicyclo[3.1.0]hex-6-ylamine (150 mg, 0.714 mmole) in CH₂Cl₂ (15 mL), was added triethylamine (3.0 eq.) followed by chloroacetylchloride (0.78 mmole) and stirred the reaction mixture at rt for 2 h. The reaction mixture was then diluted with chloroform and washed water, dried over anhydrous sodium sulfate and concentrated to get 200 mg of the desired compound.

¹HNMR (DMSO-d₆, 300 MHz): δ 8.38 (s, 1H); 7.15-7.05 (m, 1H); 6.95-6.85 (m, 1H); 6.80-6.70 (m, 1H); 3.99 (s, 2H); 3.61 (d, J = 9.3 Hz, 2H); 3.18 (d, J = 7.8 Hz, 2H); 2.65 (s, 1H); 1.77 (s, 2H). MS: 287 (M+H)⁺

Step II: 2-(3H-Benzimidazol-1-yl)-N-[3-(2,4-Difluorophenyl)-3-azabicyclo[3.1.0]hex-6-yl]-acetamide

To a solution of benzimidazole (82 mg, 0.70 mmole) in dry DMF (6 mL), while stirring at 0°C, under N₂, was added sodium iodide (1.0 eq.) followed by potassium tert-butoxide (86 mg, 1.1 eq.) and the reaction mixture was stirred at rt for 30 min. To the above at 0°C, was added a solution of 2-Chloro-N-[3-(2,4-Difluorophenyl)-3-azabicyclo[3.1.0]hex-6-yl]-acetamide (from step I) (200 mg, 1.0 eq.) in dry DMF (3 mL) and stirred the reaction mixture at rt, overnight. The reaction mixture was then diluted with ethyl acetate (50 mL) and washed with water (3 x 30 mL). The organic layer was then dried over anhydrous sodium sulfate, concentrated and purified by column chromatography to get the title compound.

m.p: 235°C; IR (KBr): 3444, 3295, 1655, 1518, 1499, 1359, 1228, 1215, 1134, 950, 739. ¹HNMR (DMSO-d₆, 300 MHz): δ 8.53 (s, 1H); 8.12 (s, 1H); 7.62 (d, J = 6.9 Hz, 1H); 7.41 (d, J = 7.8 Hz, 1H); 7.22-7.17 (m, 2H); 7.12-7.07 (m, 1H); 6.95-6.80 (m, 1H); 6.75-6.65
Example 2: Preparation of N-r3-(2.4-Difluorophenyl)-3-azabicyclo[3.1.0]hex-6-yll-2-(2-methyl benzimidazol-l-yl)-acetamide (Compound No. 2)


To a solution of 2-methyl benzimidazole (68 mg, 0.46 mmole) in dry DMF (5 mL), while stirring at 0°C, under N₂, was added potassium t-butoxide (114 mg, 2.2 eq.) and the reaction mixture was stirred at it for 30 min. To the above at 0°C, was added a solution of 2-Chloro-N-[3-(2,4-Difluorophenyl)-3-azabicyclo[3.1.0]hex-6-yl]-acetamide (from step 1, compound No. 1) (133 mg, 1.0 eq.) in dry DMF (3 mL) and stirred the reaction mixture at rt, overnight. The reaction mixture was then diluted with ethyl acetate (50 mL) and washed with water (3 x 30 mL). The organic layer was then dried over anhydrous sodium sulfate, concentrated and purified by column chromatography to get the title compound, m.p: 213°C; 1HNMR (DMSOd₆, 300 MHz): δ 8.53 (s, IH); 7.48 (br d, IH); 7.34 (br d, IH); 7.05-7.20 (m, 3H); 6.90-6.85 (m, IH); 6.70-6.80 (m, IH); 4.79 (s, 2H); 3.59 (d, J = 9.9 Hz, 2H); 3.17 (d, J = 6.9 Hz, 2H); 2.66 (s, IH); 1.78 (s, 2H).

Example 3: Preparation of N-[3-(2,4-Difluorophenyl)-3-azabicyclo[3.1.0]hex-6-yll-2-(5-trifluoromethyl benzimidazol-l-yl)-acetamide (Compound No. 3)

Step 1: {(3-(2,4-Difluorophenyl)-3-azabicyclo[3.1.0]hex-6-ylcarbamoyl)methU-carbamic acid tert-butyl ester
To a solution of 3-(2,4-Difluorophenyl)-3-azabicyclo[3.1.0]hex-6-ylamine (1.76 g, 8.5 mmole) in CH₂Cl₂ (15 mL), was added N-Boc glycine (2.96 g, 2.0 eq) followed by EDCI (2.42 g, 1.5 eq.), DMAP (103 mg, 0.1 eq) and triethylamine (2.56 g, 3.0 eq.) and stirred the reaction mixture at rt for 48 h. The reaction mixture was then diluted with chloroform, washed with IN HCl followed by water, dried over anhydrous sodium sulfate and concentrated. The crude material was then purified by column chromatography to get 1.23 g of the desired compound.

¹HNMR (DMSO-d₆, 300 MHz): δ 7.94 (d, J = 3.9 Hz, IH); 7.13-7.04 (m, IH); 6.88-6.85 (m, 2H); 6.78-6.73 (m, IH); 3.62-3.58 (dd, J = 9.0 Hz and 2.4 Hz, 2H); 3.46 (d, J = 5.7 Hz, 2H); 3.18 (d, J = 8.7 Hz, 2H); 2.60 (s, IH); 1.72 (s, 2H); 1.37 (s, 9H). MS: 368 (M+H)⁺

Step II: 2-Amino-N-[3-(2,4-difluorophenyl)3-azabicyclo[3.1.0]hex-6-yl]acetamide Hydrochloride

To [(3-(2,4-Difluorophenyl)-3-azabicyclo[3.1.0]hex-6-yl)carbamoyl]methyl]-carbamic acid tert-butyl ester (1.23 g) was added ethyl acetate saturated with HCl (25 mL) and stirred the reaction mixture at rt for 1 h. Solvent was then evaporated from the reaction mixture on rotavapor and dried under vacum to get the desired compound in quantitative yield.

Step III: 2-(2-Nitro-4-trifluoromethyl-phenylamino)-N-r3-(2,4-difluorophenyl3-azabicyclo[3.1.0]hex-6-yl)acetamide

To a solution of 2-Amino-N-[3-(2,4-Difluorophenyl)-3-azabicyclo[3.1.0]hex-6-yl]acetamide Hydrochloride (230 mg, 0.68 mmole) in DMF (5 mL), was added K₂CO₃ (2 eq) and stirred the reaction mixture at rt for 30 min. To the above was then added 4-Fluoro-3-
nitro benzotrifluoride (142 mg, 1 eq) and stirred the reaction mixture at rt for 16 h. The reaction mixture was then diluted with ethyl acetate, washed with water, dried over anhydrous sodium sulfate and concentrated. The crude material was then purified by column chromatography to get 190 mg of the desired compound.

1HNMR (DMSO-d$_6$, 300 MHz): $\delta$ 8.75 (br t, IH); 8.32 (s, 2H); 7.82 (d, J = 9.3 Hz, IH); 7.13-7.06 (m, IH); 6.95-6.87 (m, 2H); 6.79-6.74 (m, IH); 4.05 (d, J = 5.4 Hz, 2H); 3.61 (d, J = 7.5 Hz, 2H); 3.19 (d, J = 9.3 Hz, 2H); 2.65 (s, IH); 1.75 (s, 2H). MS: 457 (M+H)$^+$

Step IV: 2-(2-Amino-4-trifluoromethyl-phenylamino)-N-[3-(2,4-difluorophenyl)-3-azabicyclo[3.1.0]hex-6-yl]acetamide

To a solution of 2-(2-Nitro-4-trifluoromethyl-phenylamino)-N-[3-(2,4-difluorophenyl)-3-azabicyclo[3.1.0]hex-6-yl]acetamide (180 mg) in Methanol (15 mL) was added 10% Pd/C (100 mg, 50% wet) and subjected to hydrogenation in parr apparatus at 50 psi for 2 hr at rt. The reaction mixture was then filtered over celite, washed the celite bed with methanol, combined the filtrate and washings and concentrated to get 50 mg of the desired compound.

Step V: N-r3-(2,4-Difluorophenyl)-3-azabicyclo[3.1.0]hex-6-yl-2-(5-trifluoromethyl benzimidazol-1-yl)-acetamide

A solution of 2-(2-Amino-4-trifluoromethyl-phenylamino)-N-[3-(2,4-difluorophenyl)-3-azabicyclo[3.1.0]hex-6-yl]acetamide (50 mg) in triethyl orthoformate (10 mL) was heated at 80°C while stirring for 4 h. The solvent was then evaporated from the reaction mixture on rotavapor and the residue was purified by column chromatography to get 20 mg of the title compound as pale yellow solid.

1HNMR (DMSO-d$_6$, 300 MHz): $\delta$ 8.56 (d, J = 3.3 Hz, IH); 8.36 (s, IH); 8.01 (s, IH); 7.67 (d, J = 8.1 Hz, IH); 7.57 (d, J = 8.1 Hz, IH); 7.13-7.04 (m, IH); 6.91-6.87 (m, IH); 6.78-6.73 (m, IH); 4.98 (s, 2H); 3.61-3.58 (dd, J = 9.0 Hz and 2.7 Hz, 2H); 3.18 (d, J = 8.1 Hz, 2H); 2.66 (s, IH); 1.78 (s, 2H). MS: 437 (M+H)$^+$

Example 4: Preparation of 2-(6J-Difluoro benzimidazol-1-yl)-N-[3-(2,4-difluorophenyl)-3-azabicyclo[3.1.0]hex-6-vH-acetamide (Compound No. 4)
Step III: 2-(2,3-Difluoro-6-nitro phenylamino)-N-r3-(2,4-difluorophenyl)-3-azabicycloD. 1.Olhex-6-yllacetamide

To a solution of 2-Amino-N-[3-(2,4-Difluorophenyl)-3-azabicyclo[3.1.0]hex-6-yl]acetamide Hydrochloride (100 mg, 0.3 mmole) (from step II of example 3) in DMF (5 mL), was added K$_2$CO$_3$ (2 eq) and stirred the reaction mixture at rt for 30 min. To the above was then added 2,3,4-trifluoro-nitrobenzene (52 mg, 1 eq) and stirred the reaction mixture at rt for 16 h. The reaction mixture was then diluted with ethyl acetate, washed with water, dried over anhydrous sodium sulfate and concentrated. The crude material was then purified by column chromatography to get 50 mg of the desired compound.

$^1$HNMR (DMSOd$_6$, 300 MHz): $\delta$ 8.43 ( br s, IH); 8.34 ( br d, IH); 8.00 ( m, IH); 7.14-7.10 (m, IH); 6.90-6.80 (m, IH); 6.80-6.70 (m, IH); 4.19 ( s, 2H); 3.61 ( d, J = 6.9 Hz, 2H); 3.18 (d, J = 7.8 Hz, 2H); 2.64 (s, IH); 1.73 (s, 2H).

Step IV: 2-(6-Amino-2,3-difluoro-phenylamino)-N-[3-(2,4-difluorophenyl)-3-azabicyclo[3.1.0]hex-6-yl]acetamide

To a solution of 2-(2,3-Difluoro-6-nitro phenylamino)-N-[3-(2,4-difluorophenyl)-3-azabicyclo[3.1.0]hex-6-yl]acetamide (50 mg) in Methanol (15 mL) was added 10 % Pd/C (50 mg, 50 % wet) and subjected to hydrogenation in parr apparatus at 50 psi for 2 hr at rt. The reaction mixture was then filtered over celite, washed the celite bed with methanol, combined the filtrate and washings and concentrated to get 40 mg of the desired compound.
Step V: 2-(6,7-Difluoro benzimidazol-1-yl)-N-r3-(2,4-difluorophenyl)-3-azabicvclo[3.1.0]hex-6-yl]acetamide

A solution of 2-(6-Amino-2,3-difluoro-phenylamino)-N-[3-(2,4-difluorophenyl)-3-azabicyclo[3.1.0]hex-6-yl]acetamide (40 mg) in triethyl orthoformate (10 mL) was heated at 80°C while stirring for 4 h. The solvent was then evaporated from the reaction mixture on rotavapor and the residue was purified by column chromatography to get 15 mg of the title compound as pale yellow solid.

$^1$HNMR (DMSO-d$_6$, 300 MHz): δ 8.52 (d, J = 1.5 Hz, 1H); 8.18 (s, 1H); 7.45-7.40 (m, 1H); 7.30-7.20 (m, 1H); 7.10-7.00 (m, 1H); 6.85-6.95 (m, 1H); 6.80-6.70 (m, 1H); 4.99 (s, 2H); 3.60 (d, J = 6.9 Hz, 2H); 3.18 (d, J = 7.8 Hz, 2H); 2.65 (s, 1H); 1.76 (s, 2H).

MS: 403 (M-H)$^+$

Example 5: Preparation of N-[3-(2,4-Difluorophenyl)-3-azabicyclo[3.1.0]hex-6-yl]-2-imidazo[4,5|pyridine-3-yl-acetamide] (Compound No. 5)

Step III: 2-(3-nitro pyridin-2-ylamino)-N-[3-(2,4-Difluorophenyl)-3-azabicyclo[3.1.0]hex-6-yl]acetamide

To a solution of 2-Amino-N-[3-(2,4-difluorophenyl)-3-azabicyclo[3.1.0]hex-6-yl]acetamide Hydrochloride (120 mg, 0.36 mmole) (from step II of example 3) in DMF (5 mL), was added K$_2$CO$_3$ (3 eq) and stirred the reaction mixture at rt for 30 min. To the above was then added 2-Chloro-3-nitropyridine (67 mg, 1.2 eq) and stirred the reaction mixture at rt for 16 h. The reaction mixture was then diluted with ethyl acetate, washed with water, dried over anhydrous sodium sulfate and concentrated. The crude material was then purified by column chromatography to get 55 mg of the desired compound.

$^1$HNMR (DMSO-d$_6$, 300 MHz): δ 8.65 (br t, 1H); 8.50-8.40 (m, 2H); 8.14 (br s, 1H); 7.15-7.05 (m, 1H); 6.95-6.85 (m, 1H); 6.80-6.70 (m, 1H); 4.10 (d, J = 5.4 Hz, 2H); 3.60 (d, J = 7.8 Hz, 2H); 3.18 (d, J = 9.0 Hz, 2H); 2.61 (s, 1H); 1.72 (s, 2H).

Step IV: 2-(3-Amino pyridin-2-ylamino)-N-[3-(2,4-Difluorophenyl)-3-azabicyclo[3.1.0]hex-6-yl]acetamide
To a solution of 2-(3-nitro pyridin-2-ylamino)-N-[3-(2,4-difluorophenyl)-3-azabicyclo[3.1.0]hex-6-yl]acetamide (55 mg) in Methanol (15 mL) was added 10 % Pd/C (25 mg, 50 % wet) and subjected to hydrogenation in parr apparatus at 50 psi for 2 hr at rt. The reaction mixture was then filtered over celite, washed the celite bed with methanol, combined the filtrate and washings and concentrated to get 40 mg of the desired compound.

Step V: N-[3-(2,4-Difluorophenyl)-3-azabicyclo[3.1.0]hex-6-yl]-2-imidazo[4,5-1]pyridine-3-yl-acetamide

A solution of 2-(3-Amino pyridin-2-ylamino)-N-[3-(2,4-difluorophenyl)-3-azabicyclo[3.1.0]hex-6-yl]acetamide (40 mg) in triethyl orthoformate (10 mL) was heated at 80°C while stirring for 4 h. The solvent was then evaporated from the reaction mixture on rotavapor and the residue was purified by column chromatography to get 11 mg of the title compound as pale yellow solid.

\(^1\)HNMR (DMSO\(_d_6\), 300 MHz): \(\delta\) 8.54 (br d, 1H); 8.37 (s, 1H); 8.31 (d, \(J = 5.4\) Hz, 1H); 8.07 (d, \(J = 7.8\) Hz, 1H); 7.29-7.24 (m, 1H); 7.10-7.00 (m, 1H); 6.90-6.80 (m, 1H); 6.80-6.70 (m, 1H); 4.92 (s, 2H); 3.59 (d, \(J = 6.6\) Hz, 2H); 3.18 (d, \(J = 8.4\) Hz, 2H); 2.65 (s, 1H); 1.77 (s, 2H). MS: 370 (M+H)+

Example 6: Preparation of N-[3-(2,4-Difluorophenyl)-3-azabicyclo[3.1.0]hex-6-yl]-2-(5-fluoro benzimidazol-1-yl)-acetamide (Compound No. 6)

Step III: 2-(4-Fluoro-2-nitro phenylamino)-N-[3-(2,4-difluorophenyl)-3-azabicyclo[3.1.0]hex-6-yl]acetamide
To a solution of 2-Amino-N-[3-(2,4-Difluorophenyl)-3-azabicyclo[3.1.0]hex-6-yl]acetamide hydrochloride (100 mg, 0.3 mmole) (from step II of example 3) in DMF (5 mL), was added K₂CO₃ (2 eq) and stirred the reaction mixture at rt for 30 min. To the above was then added 2,5-difluoro-nitrobenzene (1 eq) and stirred the reaction mixture at rt for 16 h. The reaction mixture was then diluted with ethyl acetate, washed with water, dried over anhydrous sodium sulfate and concentrated. The crude material was then purified by column chromatography to get 50 mg of the desired compound.

\(^1\)HNMR (DMSOd \(_6\), 300 MHz): \(\delta\) 8.38 (br t, IH); 8.31 (d, J = 3.6 Hz, IH); 7.89-7.85 (dd, J = 9.6 Hz and 3.0 Hz, IH); 7.56-7.51 (m, IH); 7.14-7.07 (m, IH); 6.91-6.83 (m, IH); 6.82-6.74 (m, IH); 3.97 (d, J = 5.4 Hz, 2H); 3.63-3.59 (dd, J = 9.3 Hz and 2.4 Hz, 2H); 3.18 (d, J = 8.1 Hz, 2H); 2.64 (s, IH); 1.74 (s, 2H).

Step IV: 2-(2-Amino-4-fluoro-phenylamino)-N-[3-(2,4-difluorophenyl)-3-azabicyclo[3.1.0]hex-6-yl]acetamide

To a solution of 2-(4-Fluoro-2-nitro phenylamino)-N-[3-(2,4-difluorophenyl)-3-azabicyclo [3.1.0] hex-6-yl]acetamide (50 mg) in Methanol (15 mL) was added 10 % Pd/C (50 mg, 50 % wet) and subjected to hydrogenation in Parr apparatus at 50 psi for 2 hr at rt. The reaction mixture was then filtered over celite, washed the celite bed with methanol, combined the filtrate and washings and concentrated to get 40 mg of the desired compound.

Step V: N-r3-(2,4-Difluorophenyl)-3-azabicyclo [3.1.01hex-6-yl]-2-(5-fluoro benzimidazol-1-yl)-acetamide

A solution of 2-(2-Amino-4-fluoro-phenylamino)-N-[3-(2,4-difluorophenyl)-3-azabicyclo [3.1.0]hex-6-yl]acetamide (40 mg) in triethyl orthoformate (10 mL) was heated at 80°C while stirring for 4 h. The solvent was then evaporated from the reaction mixture on rotavapor and the residue was purified by column chromatography to get 15 mg of the title compound as pale yellow solid.

\(^1\)HNMR (DMSO-d\(_6\), 300 MHz): \(\delta\) 8.55 (d, J = 3.0 Hz, IH); 8.20 (s, IH); 7.45-7.40 (m, 2H); 7.20-7.00 (m, 2H); 6.95-6.85 (m, IH); 6.80-6.70 (m, IH); 4.90 (s, 2H); 3.61-3.58 (dd, J = 9.3Hz, and 2.4 Hz, 2H); 3.18 (d, J = 8.4 Hz, 2H); 2.66 (s, IH); 1.78 (s, 2H). MS: 387 (M+H)+
Example 7: Preparation of N-[3-(2,4-Difluorophenyl)-3-azabicyclo[3.1.0]hex-6-yl-2-(6-methoxy benzimidazol-1-yl)-acetamide (Compound No. 7)

Step III: 2-(5-Methoxy-2-nitrophenylamino)-N-[3-(2,4-difluorophenyl)-3-azabicyclo[3.1.0]hex-6-yl]acetamide

To a solution of 2-Amino-N-[3-(2,4-Difluorophenyl)-3-azabicyclo[3.1.0]hex-6-yl]acetamide hydrochloride (100 mg, 0.3 mmole) from step II of example 3) in DMF (5 mL), was added K2CO3 (2 eq) and stirred the reaction mixture at rt for 30 min. To the above was then added 3-fluoro-4-nitroanisole (1 eq, obtained by methylation of 3-Fluoro-4-nitrophenol) and stirred the reaction mixture at rt for 16 h. The reaction mixture was then diluted with ethyl acetate, washed with water, dried over anhydrous sodium sulfate and concentrated. The crude material was then purified by column chromatography to get 50 mg of the desired compound.

1H NMR (DMSO-d6, 300 MHz): δ 8.66 (br s, IH); 8.37 (br s, IH); 8.04 (d, J = 9.3 Hz, 2H); 7.20-7.10 (m, IH); 6.95-6.85 (m, IH); 6.80-6.70 (m, IH); 6.33 (d, J = 7.5 Hz, IH); 6.08 (s, IH); 3.98 (d, J = 5.4 Hz, 2H); 3.61 (d, J = 6.6 Hz, 2H); 3.19 (d, J = 7.8 Hz, 2H); 2.66 (s, IH); 1.75 (s, 2H).

Step IV: 2-(2-Amino-5-methoxy-phenylamino)-N-[3-(2,4-difluorophenyl)-3-azabicyclo[3.1.0]hex-6-yl]acetamide

To a solution of 2-(5-Methoxy-2-nitro phenylamino)-N-[3-(2,4-difluorophenyl)-3-azabicyclo[3.1.0]hex-6-yl]acetamide (50 mg) in Methanol (15 mL) was added 10 % Pd/C (50 mg, 50 % wet) and subjected to hydrogenation in parr apparatus at 50 psi for 2 hr at rt.
The reaction mixture was then filtered over celite, washed the celite bed with methanol, combined the filtrate and washings and concentrated to get 40 mg of the desired compound.

Step V: N-r3-(2,4-Difluorophenyl)-3-azabicyclo[3.1.0]hex-6-ylacetamide

A solution of 2-(2-Amino-5-methoxy-phenylamino)-N-[3-(2,4-difluorophenyl)-3-azabicyclo[3.1.0]hex-6-yl]acetamide (40 mg) in triethyl orthoformate (10 mL) was heated at 80°C while stirring for 4 h. The solvent was then evaporated from the reaction mixture on rotavapor and the residue was purified by column chromatography to get 15 mg of the title compound as pale yellow solid.

$^1$HNMR (DMSO-d$_6$, 300 MHz): δ 8.52 (br s, IH); 8.00 (s, IH); 7.50 (d, J = 8.4 Hz, IH); 7.10-7.00 (m, IH); 6.99 (s, IH); 6.95-6.85 (m, IH); 6.80-6.70 (m, 2H); 4.83 (s, 2H); 3.78 (s, 3H); 3.60 (d, J = 7.8 Hz, 2H); 3.18 (d, J = 8.1 Hz, 2H); 2.67 (s, IH); 1.78 (s, 2H). MS: 399 (M+H)$^+$

Example 8: Screening for TRPV1 antagonist using $^{45}$Ca (ICN) uptake assay:

The inhibition of TRPV1 receptor activation was followed as inhibition of capsaicin induced cellular uptake of radioactive calcium which represents calcium influx exclusively through the plasma membrane associated TRPV1 receptor.

Materials:
A stock solution of capsaicin was made in ethanol and test compounds were prepared in 100% DMSO. Stock solutions were diluted to appropriate final concentrations in assay buffer keeping the final DMSO concentration between 0.1% and 0.55%.

$^{45}$Ca was used at a final concentration of 2.5 µCi/ml ($^{45}$Ca, ICN). Assay buffer was composed of F-12 DMEM medium supplemented with 1.8 mM CaCl$_2$ (final cone.) and 0.1% Bovine serum albumin (BSA from SIGMA) The wash buffer was Tyrodes solution supplemented with 0.1% BSA and 1.8 mM calcium. Lysis buffer contained 50 mM Tris-HCl, pH7.5, 150 mM NaCl, 1% Triton X-100, 0.5% deoxycholate and 0.1% Sodium dodecyl sulphate (SDS,SIGMA).

Method:
The assay was carried out with some modifications of the procedure as described by Toth et.al. (See Toth A et. al, Life Sciences 73 p 487-498, 2003). Human TRPV1 expressing CHO cells were grown in F-12 DMEM (Dulbecco's modified Eagle's medium -GIBCO) medium with 10% FBS (fetal bovine serum Hyclone), 1% penicillin-streptomycin solution, and 400 µg / ml of G-418. Cells were seeded 48 h prior to the assay in 96 well plates to obtain ~ 50,000 cells per well on the day of experiment. Plates were incubated at 37°C in the
presence of 5 % CO₂. Cells were then washed twice with 200 µl of assay buffer and re-
suspended in 144 µl of the same. Assay was carried out at 30°C in total volume of 200 µl. Test compounds were added to the cells fifteen minutes before addition of capsaicin. The final concentration of capsaicin in the assay was 250 nM. After 5 minutes of agonist treatment, the drug was washed out and the wells were rinsed with 300 µl of ice cold wash buffer 3X. The cells were lysed in 50 µl lysis buffer for 20 min. 40 µl of cell lysate was mixed with 150 µl of Microscint PS, left overnight for equilibration. Radioactivity in samples was measured as counts per minute (cpm) using Packard Biosciences Top Count. The drug / vehicle / capsaicin treated ⁴⁵Ca uptake values were normalized over basal ⁴⁵Ca value. Data was expressed as % inhibition of ⁴⁵Ca uptake by test compound with respect to maximum ⁴⁵Ca uptake induced by capsaicin alone. IC₅₀ value was calculated from dose response curve by nonlinear regression analysis using GraphPadPRISM software.

The activity results are given in the following table

<table>
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<th>Compound No.</th>
<th>% inhibition at 1 uM</th>
<th>IC₅₀</th>
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<tr>
<td>1</td>
<td>82.87</td>
<td>320.8 nM</td>
</tr>
<tr>
<td>2</td>
<td>1.20</td>
<td>--</td>
</tr>
<tr>
<td>3</td>
<td>14.22</td>
<td>--</td>
</tr>
<tr>
<td>4</td>
<td>95.06</td>
<td>235.8 nM</td>
</tr>
<tr>
<td>5</td>
<td>8.02</td>
<td>--</td>
</tr>
<tr>
<td>6</td>
<td>3.47</td>
<td>--</td>
</tr>
<tr>
<td>7</td>
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</table>

Although the invention herein has been described with reference to particular embodiments, it is to be understood that these embodiments are merely illustrative of the principles and applications of the present invention. It is therefore to be understood that numerous modifications may be made to the illustrative embodiments and that other arrangements may be devised without departing from the spirit and scope of the present invention as described above.

All publications, patents, and patent applications cited in this application are herein incorporated by reference to the same extent as if each individual publication, patent, or patent application was specifically and individually indicated to be incorporated herein by reference.
We Claim

1. A compound of Formula (I)

![Formula (I)]

a prodrug thereof, a pharmaceutically acceptable salt thereof, an N-oxide thereof, an ester thereof, a solvate thereof, a tautomer thereof, a stereoisomer thereof or a polymorph thereof,

wherein:

R<sub>1</sub> and R<sub>3</sub> are independently selected from hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted cycloalkenyl, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heteroarylalkyl, substituted or unsubstituted heterocyclyl or substituted or unsubstituted heterocyclylalkyl;

each occurrence of R<sub>2</sub> and R<sub>2</sub>' are independently selected from hydrogen, nitro, cyano, formyl, acetyl, halogen, -OR<sup>7</sup>, -SR<sup>7</sup>, substituted or unsubstituted alkyl, fully or partially substituted haloalkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkenyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted cycloalkenyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted cycloalkenylalkyl, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heteroarylalkyl, substituted or unsubstituted heterocyclic group, substituted or unsubstituted heterocyclylalkyl, -C(O)R<sup>5</sup>, -C(O)OR<sup>5</sup>, -C(O)NR<sup>5</sup>R<sup>6</sup>, -NR<sup>5</sup>R<sup>6</sup>, -S(O)<sub>m</sub>R<sup>5</sup>, or -S(O)<sub>m</sub>NR<sup>5</sup>R<sup>6</sup>;

each occurrence of R<sup>5</sup> and R<sup>6</sup> may be same or different and are independently selected from hydrogen, nitro, halo, cyano, -OR<sup>8</sup>, -SR<sup>8</sup>, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkenyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted cycloalkenylalkyl, substituted or unsubstituted cycloalkenylalkyl, substituted or unsubstituted aryl,
substituted or unsubstituted arylalkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heteroarylalkyl, substituted or unsubstituted heterocyclic group, substituted or unsubstituted heterocyclylalkyl, -C(O)R³, -C(O)OR⁴, -C(O)NR⁵R⁶, -S(O)mR⁴, -S(O)mNR⁵R⁶, or -NR⁵R⁶; or

R⁵ and R⁶ are joined, together with the nitrogen to which they are attached, to form substituted or unsubstituted 3 to 7 membered saturated or unsaturated cyclic ring, which optionally includes one or more heteroatoms selected from O, S or NR²;

R⁷ selected from hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted cycloalkenyl, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heteroarylalkyl, substituted or unsubstituted heterocyclylalkyl; or

each occurrence of R² and R³ may be same or different and is independently hydrogen, halogen, nitro, cyano, formyl, acetyl, -C(O)R⁸, -C(O)OR⁹, -C(O)NR⁷R⁹, -S(O)mR⁸, -S(O)mNR⁷R⁹, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted cycloalkenyl, substituted or unsubstituted cycloalkenylalkyl, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heterocyclylalkyl, or a substituted or unsubstituted heteroarylalkyl;

each occurrence of R⁸ and R⁹ is independently hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted cycloalkenyl, substituted or unsubstituted cycloalkenylalkyl, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heterocyclylalkyl, or a substituted or unsubstituted heteroarylalkyl; or

when R⁸ and R⁹ are attached to a nitrogen atom, they may be joined to form substituted or unsubstituted 3 to 7 membered saturated or unsaturated cyclic ring, which may optionally include at one or more heteroatom(s) selected from O, S or NR³;

R⁴ is hydrogen, substituted or unsubstituted alkyl, or two R⁴ attached to a common carbon atom, form substituted or unsubstituted cycloalkyl;
P is (CH₂)ₙ, CH(Q)CH₂, or CH₂CH(Q)CH₂; wherein n' is an integer of from 0, 1, 2 or 3; when n' is 0, P represents a direct bond;

Q is substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkenyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroary1, substituted or unsubstituted heterocyclylalkyl ring, substituted or unsubstituted heteroarylalkyl, or substituted or unsubstituted heterocycyl;

Rᵣ is selected from hydrogen, formyl, acetyl, -C(O)R, -C(O)NRᵣd, -S(O)ₘRᵣc, -S(O)ₘNᵣRᵣcRᵣd, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted arylalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkenyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heterocyclylalkyl, substituted or unsubstituted heterocyclylalkyl, or a substituted or unsubstituted heterocyclic group, substituted or unsubstituted heterocyclylalkyl, or a protecting group;

each occurrence of X is independently selected from C or N;

L is -NHR₃ or (CR₃R₀)n;

Y is O or S;

each occurrence of 'm' is an integer of from 0, 1, 2;

each occurrence of 'n' is an integer of from 0, 1, 2, 3, 4 or 5.

2. A compound of claim 1, wherein L is CH₂, X is C, Y is O, R¹ is hydrogen, R² is fluorine or trifluoromethyl, R² is fluorine, R³ is methyl and R⁴ is hydrogen.

3. A compound of Formula (II)

a prodrug thereof, a pharmaceutically acceptable salt thereof, an N-oxide thereof, an ester thereof, a solvate thereof, a tautomer thereof, a stereoisomer thereof or a polymorph thereof,
wherein:

R\(^1\) and R\(^3\) are independently selected from hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted cycloalkenyl, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heteroarylalkyl, substituted or unsubstituted heterocyclyl or substituted or unsubstituted heterocyclylalkyl;

each occurrence of R\(^2\) and R\(^2\) are independently selected from hydrogen, nitro, cyano, formyl, acetyl, halogen, -OR\(^7\), -SR\(^7\), substituted or unsubstituted alkyl, fully or partially substituted haloalkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted cycloalkenyl, substituted or unsubstituted cycloalkenylalkyl, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heteroarylalkyl, substituted or unsubstituted heteroaromatic group, substituted or unsubstituted heterocyclic group, substituted or unsubstituted heterocyclylalkyl, -C(O)R\(^5\), -C(O)OR\(^5\), -C(O)NR\(^5\)R\(^6\), -NR\(^5\)R\(^6\), -S(O)\(_m\)R\(^5\), or -S(O)\(_m\)NR\(^5\)R\(^6\);

each occurrence of R\(^5\) and R\(^6\) may be same or different and are independently selected from hydrogen, nitro, halo, cyano, -OR\(^a\), -SR\(^a\), substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted cycloalkenyl, substituted or unsubstituted cycloalkenylalkyl, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heteroarylalkyl, substituted or unsubstituted heterocyclic group, substituted or unsubstituted heterocyclic group, substituted or unsubstituted heterocyclylalkyl, -C(O)R\(^a\), -C(O)OR\(^a\), -C(O)NR\(^a\)R\(^b\), -S(O)\(_m\)R\(^a\), -S(O)\(_m\)NR\(^a\)R\(^b\), or -NR\(^a\)R\(^b\); or

R\(^5\) and R\(^6\) are joined, together with the nitrogen to which they are attached, to form substituted or unsubstituted 3 to 7 membered saturated or unsaturated cyclic ring, which optionally includes one or more heteroatoms selected from O, S or NR\(^3\);

R\(^7\) selected from hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted cycloalkenyl, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heteroarylalkyl, substituted or unsubstituted heterocyclyl or substituted or unsubstituted heterocyclylalkyl;
each occurrence of $R^a$ and $R^b$ may be same or different and is independently hydrogen, halogen, nitro, cyano, formyl, acetyl, -C(O)R, -C(O)OR, -C(O)NR, -S(O)$_m$R, -S(O)$_m$NR, -NR, -OR, -SR, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heterocyclylalkyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted cyano, substituted or unsubstituted cycloalkenyl, substituted or unsubstituted cycloalkenylalkyl, substituted or unsubstituted aryalkyl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heteroarylalkyl, substituted or unsubstituted heterocyclic group, substituted or unsubstituted heterocyclic group, or a substituted or unsubstituted heterocyclylalkyl;

each occurrence of $R^c$ and $R^d$ is independently hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkene, substituted or unsubstituted cycloalkenylalkyl, substituted or unsubstituted cycloalkenyl, substituted or unsubstituted cycloalkenylalkyl, substituted or unsubstituted aryl, substituted or unsubstituted aryalkyl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heterocyclylalkyl, or a substituted or unsubstituted heterocyclic group, substituted or unsubstituted heterocyclic group, or a substituted or unsubstituted heterocyclylalkyl, or a substituted or unsubstituted heterocyclic group, or a substituted or unsubstituted heteroarylalkyl or a protecting group, or when $R^c$ and $R^d$ are attached to a nitrogen atom, they may be joined to form substituted or unsubstituted 3 to 7 membered saturated or unsaturated cyclic ring, which may optionally include at one or more heteroatom(s) selected from O, S or NR;

$R^4$ is hydrogen, substituted or unsubstituted alkyl, or two $R^4$ attached to a common carbon atom, form substituted or unsubstituted cycloalkyl;

$R^e$ is selected from hydrogen, formyl, acetyl, -C(O)R, -C(O)NR, -S(O)$_m$R, -S(O)$_m$NR, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkene, substituted or unsubstituted cycloalkenyl, substituted or unsubstituted cycloalkenylalkyl, substituted or unsubstituted cycloalkenyl, substituted or unsubstituted aryalkyl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heterocyclylalkyl, or a substituted or unsubstituted heterocyclic group, or a substituted or unsubstituted heterocyclylalkyl or a protecting group;

P is (CH$_2$CH)$_n$, CH(Q)CH$_2$, or CH$_2$CH(Q); where n' is an integer of from 0, 1, 2 or 3; when n' is 0, P represents a direct bond;

Q is substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted aryl, substituted or
unsubstituted arylalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkenyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted heterocyclylalkyl ring, substituted or unsubstituted heteroarylalkyl, or substituted or unsubstituted heterocycyl;  

X is C or N; Y is O or S;  
each occurrence of 'm' is an integer of from 0, 1, 2;  
each occurrence of 'n' is an integer of from 0, 1, 2, 3, 4 or 5.  

4. A compound of claim 3, wherein X is C, Y is O, R^1 is hydrogen, R^2 is fluorine or trifluoromethyl, R^2 is fluorine, R^3 is methyl and R^4 is hydrogen.  

5. A compound of Formula (III)  

![Formula III](image)

a prodrug thereof, a pharmaceutically acceptable salt thereof, an N-oxide thereof, an ester thereof, a solvate thereof, a tautomer thereof, a stereoisomer thereof or a polymorph thereof,  

wherein:  
R^1 and R^3 are independently selected from hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted cycloalkenyl, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heteroarylalkyl, substituted or unsubstituted heterocyclyl or substituted or unsubstituted heterocyclyl alkyl;  
each occurrence of R^2 and R^2 are independently selected from hydrogen, nitro, cyano, formyl, acetyl, halogen, -OR^7, -SR^7, substituted or unsubstituted alkyl, fully or partially substituted haloalkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted cycloalkenyl, substituted or unsubstituted cycloalkenylalkyl, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heteroarylalkyl, substituted or unsubstituted heteroarylalkyl, substituted or
unsubstituted heterocyclic group, substituted or unsubstituted heterocyclylalkyl, -C(O)R^5, -C(O)OR^5, -C(O)NR^5R^6, -NR^5R^6, -S(O)_mR^5, or -S(O)_mNR^5R^6;

each occurrence of R^5 and R^6 may be same or different and are independently selected from hydrogen, nitro, halo, cyano, -OR^a, -SR^a, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted cycloalkenyl, substituted or unsubstituted cycloalkenylalkyl, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heteroarylalkyl, substituted or unsubstituted heteroaryalkyl, substituted or unsubstituted heterocyclic group, substituted or unsubstituted heterocyclylalkyl, -C(O)R^3, -C(O)OR^a, -C(O)NR^aR^b, -S(O)_mR^a, -S(O)_mNR^aR^b, or -NR^aR^b; or

R^5 and R^6 are joined, together with the nitrogen to which they are attached, to form substituted or unsubstituted 3 to 7 membered saturated or unsaturated cyclic ring, which optionally includes one or more heteroatoms selected from O, S or NR^a;

R^7 selected from hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted cycloalkenyl, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heteroarylalkyl, substituted or unsubstituted heterocyclyl or substituted or unsubstituted heterocyclylalkyl;

each occurrence of R^a and R^b may be same or different and is independently hydrogen, halogen, nitro, cyano, formyl, acetyl, -C(O)R^c, -C(O)OR^c, -C(O)NR^cR^d, -S(O)_mR^c, -S(O)_mNR^cR^d, -NR^cR^d, -OR^c, -SR^d, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted cycloalkenyl, substituted or unsubstituted cycloalkenylalkyl, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heteroarylalkyl, substituted or unsubstituted heterocyclic group, substituted or unsubstituted heterocyclylalkyl, or a substituted or unsubstituted heteroaryalkyl;

each occurrence of R^c and R^d is independently hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted cycloalkenyl, substituted or unsubstituted cycloalkenylalkyl, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heterocyclic group, substituted or unsubstituted
heterocyclylalkyl, or a substituted or unsubstituted heteroarylalkyl or a protecting group; or when \( R^c \) and \( R^d \) are attached to a nitrogen atom, they may be joined to form substituted or unsubstituted 3 to 7 membered saturated or unsaturated cyclic ring, which may optionally include at one or more heteroatom(s) selected from O, S or NR\(^e\):

\[ R^4 \] is hydrogen, substituted or unsubstituted alkyl, or two \( R^4 \) attached to a common carbon atom, form substituted or unsubstituted cycloalkyl;

\( R^e \) is selected from hydrogen, formyl, acetyl, -C(O)R\(^e\), -C(O)NR\(^e\)R\(^d\), -S(O)\(m\)R\(^e\), -S(O)\(m\)NR\(^e\)R\(^d\), substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted cycloalkenyl, substituted or unsubstituted cycloalkenylalkyl, substituted or unsubstituted aryalkyl, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heterocyclic group, substituted or unsubstituted heterocyclylalkyl, or a substituted or unsubstituted heteroarylalkyl or a protecting group;

Y is O or S;

each occurrence of 'm' is an integer of from 0, 1, 2;

each occurrence of 'n' is an integer of from 0, 1, 2, 3, 4 or 5.

6. A compound of claim 5, wherein, Y is O, \( R^1 \) is hydrogen, \( R^2 \) is fluorine or trifluoromethyl, \( R^2 \) is fluorine, \( R^3 \) is methyl and \( R^4 \) is hydrogen.

7. A compound according to claim 1, wherein the compound is selected from:

\( 2-(3H-Benimidazol-1-yl)-N-[3-(2,4-Difluorophenyl)-3-azabicyclo[3.1.0]hex-6-yl]-acetamide \) (Compound No. 1),

\( N-[3-(2,4-Difluorophenyl)-3-azabicyclo[3.1.0]hex-6-yl]-2-(2-methyl benzimidazol-1-yl)-acetamide \) (Compound No. 2),

\( N-[3-(2,4-Difluorophenyl)-3-azabicyclo[3.1.0]hex-6-yl]-2-(5-trifluoromethyl benzimidazol-1-yl)-acetamide \) (Compound No. 3),

\( 2-(6,7-Difluoro benzimidazol-1-yl)-N-[3-(2,4-difluorophenyl)-3-azabicyclo[3.1.0]hex-6-yl]-acetamide \) (Compound No. 4),

\( N-[3-(2,4-Difluorophenyl)-3-azabicyclo[3.1.0]hex-6-yl]-2-imidazo[4,5]pyridine-3-yl-acetamide \) (Compound No. 5),

\( N-[3-(2,4-Difluorophenyl)-3-azabicyclo[3.1.0]hex-6-yl]-2-(5-fluoro benzimidazol-1-yl)-acetamide \) (Compound No. 6),

\( N-[3-(2,4-Difluorophenyl)-3-azabicyclo[3.1.0]hex-6-yl]-2-(6-methoxy benzimidazol-1-yl)-acetamide \) (Compound No. 7) and
pharmaceutically acceptable salts thereof.
8. A pharmaceutical composition comprising a compound according to any one of claims 1-7 and a pharmaceutically acceptable excipient.
9. The pharmaceutical composition according to claim 8, wherein the pharmaceutically acceptable excipient is a carrier or diluent.
10. A method for preventing, ameliorating or treating a vanilloid receptor mediated disease, disorder or syndrome in a subject in need thereof comprising administering to the subject a therapeutically effective amount of a compound according to any of claims 1-7.
11. The method according to claim 10, wherein the vanilloid receptor mediated disease, disorder or syndrome is a pain or inflammatory disease, disorder or syndrome mediated by vanilloid receptor 1 (VRI).
12. The method according to claim 10, wherein the disease, disorder or syndrome is selected from the group consisting of pain, acute pain, chronic pain, nociceptive pain, neuropathic pain, post-operative pain, dental pain, cancer pain, cardiac pain arising from an ischemic myocardium, pain due to migraine, arthralgia, neuropathies, neuralgia, trigeminal neuralgia nerve injury, diabetic neuropathy, neurodegeneration, retinopathy, neurotic skin disorder, stroke, urinary bladder hypersensitiveness, urinary incontinence, vulvodynia, gastrointestinal disorders such as irritable bowel syndrome, gastro-esophageal reflux disease, enteritis, ileitis, stomach-duodenal ulcer, inflammatory bowel disease, Crohn's disease, celiac disease, an inflammatory disease such as pancreatitis, a respiratory disorder such as allergic and non-allergic rhinitis, asthma or chronic obstructive pulmonary disease, irritation of skin, eye or mucous membrane, dermatitis, pruritic conditions such as uremic pruritus, fervescence, muscle spasms, emesis, dyskinesias, depression, Huntington's disease, memory deficits, restricted brain function, amyotrophic lateral sclerosis (ALS), dementia, arthritis, osteoarthritis, diabetes, obesity, urticaria, actinic keratosis, keratocanthoma, alopecia, Meniere's disease, tinnitus, hyperacusis, anxiety disorders and benign prostate hyperplasia.
13. A method of treating pain in a subject in need thereof comprising administering to the subject a therapeutically effective amount of a compound according to any of claims 1-7.
14. The method of claim 10, wherein the pain is acute pain.
15. The method of claim 10, wherein the pain is chronic pain.
16. The method of claim 10, wherein the pain is post-operative pain.
17. A method of treating neuropathic pain in a subject in need thereof comprising administering to the subject a therapeutically effective amount of a compound according to any of claims 1-7.
18. A method of treating urinary incontinence in a subject in need thereof comprising administering to the subject a therapeutically effective amount of a compound according to any of claims 1-7.
19. A method of treating ulcerative colitis in a subject in need thereof comprising administering to the subject a therapeutically effective amount of a compound according to any of claims 1-7.
20. A method of treating asthma in a subject in need thereof comprising administering to the subject a therapeutically effective amount of a compound according to any of claims 1-7.
21. A method of treating inflammation in a subject in need thereof comprising administering to the subject a therapeutically effective amount of a compound according to any of claims 1-7.
22. The process for the preparation of compound of formula (Ia)

\[
\text{Formula (Ia)}
\]

wherein:

\( R^1 \) and \( R^3 \) are independently selected from hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted cycloalkenyl, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heteroarylalkyl, substituted or unsubstituted heterocyclyl or substituted or unsubstituted heterocyclylalkyl;

each occurrence of \( R^2 \) and \( R^{2'} \) are independently selected from hydrogen, nitro, cyano, formyl, acetyl, halogen, -OR\(^7\), -SR\(^7\), substituted or unsubstituted alkyl, fully or partially substituted haloalkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted cycloalkenyl, substituted or unsubstituted cycloalkenylalkyl, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heteroarylalkyl, substituted or unsubstituted heterocyclic group, substituted or unsubstituted heterocyclylalkyl, -C(O)R\(^5\), -C(O)OR\(^5\), -C(O)NR\(^3\)R\(^6\), -NR\(^3\)R\(^6\), -S(O)\(_m\)R\(^5\), or -S(O)\(_m\)NR\(^3\)R\(^6\);
each occurrence of $R^5$ and $R^6$ may be same or different and are independently selected from hydrogen, nitro, halo, cyano, -OR$^a$, -SR$^a$, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted cycloalkenyl, substituted or unsubstituted cycloalkenylalkyl, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heteroarylalkyl, substituted or unsubstituted heteroarylalkyl, substituted or unsubstituted heterocyclic group, substituted or unsubstituted heterocycliclalkyl, substituted or unsubstituted heterocycliclalkyl, substituted or unsubstituted heterocycliclalkyl, substituted or unsubstituted heterocycliclalkyl, or a substituted or unsubstituted heteroarylalkyl; or

$R^5$ and $R^6$ are joined, together with the nitrogen to which they are attached, to form substituted or unsubstituted 3 to 7 membered saturated or unsaturated cyclic ring, which optionally includes one or more heteroatoms selected from O, S or NR$^a$;

$R^7$ selected from hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted cycloalkenyl, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heteroarylalkyl, substituted or unsubstituted heterocycliclalkyl or substituted or unsubstituted heterocycliclalkyl;

each occurrence of $R^a$ and $R^b$ may be same or different and is independently hydrogen, halogen, nitro, cyano, formyl, acetyl,-C(O)R$^c$, -C(O)OR$^c$, -C(O)NR$^d$, -S(O)$_m$R$^c$, -S(O)$_m$NR$^d$, -NR$^d$, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted cycloalkenyl, substituted or unsubstituted cycloalkenylalkyl, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heteroarylalkyl, or a substituted or unsubstituted heteroarylalkyl;

each occurrence of $R^c$ and $R^d$ is independently hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted cycloalkenyl, substituted or unsubstituted cycloalkenylalkyl, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heteroarylalkyl, or a substituted or unsubstituted heteroarylalkyl or a protecting group; or

when $R^c$ and $R^d$ are attached to a nitrogen atom, they may be joined to form
substituted or unsubstituted 3 to 7 membered saturated or unsaturated cyclic ring, which may optionally include at one or more heteroatom(s) selected from O, S or NR

R^4 is hydrogen, substituted or unsubstituted alkyl, or two R^4 attached to a common carbon atom, form substituted or unsubstituted cycloalkyl;

R^e is selected from hydrogen, formyl, acetyl, -C(O)R, -C(O)NR^dR, -S(O)_mNR, -S(O)_mNRR^d, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkenyl, substituted or unsubstituted cycloalkenylalkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted arenyl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heterocyclic group, substituted or unsubstituted heterocyclylalkyl, or a substituted or unsubstituted heteroarylalkyl or a protecting group;

L is -NHR_3 or (CR_5Re)_n;

Y is O or S;

each occurrence of 'm' is an integer of from 0, 1, 2;

each occurrence of 'n' is an integer of from 0, 1, 2, 3, 4 or 5.

The method comprising the steps of:

(i) the compound of formula (1) coupled with formula Z-L-C(Y)-X' (wherein Z is a leaving group such as halide, alkoxy, aryloxy, hydroxyl, alkyl or aryl sulfonate; X' is a leaving group such as halide, alkoxy, alkoxycarbonyloxy or aryloxy). To form compound of formula (2) in presence of base for example triethylamine.

(ii) compound of formula (2) coupled with compound of formula (3) to form compound of formula (1a) in presence of alkali halide for example sodium iodide; and base for example alkalimetal salt of t-butoxide preferably potassium t-butoxide.

23. The process for the preparation of compound of formula (1a)
wherein:

R¹ and R³ are independently selected from hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted cycloalkenyl, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heteroarylalkyl, substituted or unsubstituted heterocyclyl or substituted or unsubstituted heterocyclylalkyl;

each occurrence of R² and R² are independently selected from hydrogen, nitro, cyano, formyl, acetyl, halogen, -OR₇, -SR₇, substituted or unsubstituted alkyl, fully or partially substituted haloalkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkenyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted cycloalkenyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted heterocyclylalkyl, substituted or unsubstituted heterocyclic group, substituted or unsubstituted heterocyclylalkyl, -C(O)R⁵, -C(O)OR⁵, -C(O)NR³R⁶, -NR³R⁶, -S(O)ₘR⁵, or -S(O)ₘNR³R⁶;

each occurrence of R⁵ and R⁶ may be same or different and are independently selected from hydrogen, nitro, halo, cyano, -ORᵃ, -SRᵃ, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted cycloalkenyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted cycloalkenylalkyl, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heteroarylalkyl, substituted or unsubstituted heterocyclylalkyl, substituted or unsubstituted heterocyclic group, substituted or unsubstituted heterocyclylalkyl, -C(O)R³, -C(O)ORᵃ, -C(0)NRᵃRᵇ, -S(O)ₘR³, -S(O)ₘNRᵃRᵇ, or -NRᵃRᵇ; or

R⁵ and R⁶ are joined, together with the nitrogen to which they are attached, to form substituted or unsubstituted 3 to 7 membered saturated or unsaturated cyclic ring, which optionally includes one or more heteroatoms selected from O, S or NRᵃ;
R^7 selected from hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted cycloalkenyl, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heteroarylalkyl, substituted or unsubstituted heterocyclyl or substituted or unsubstituted heterocyclylalkyl;

each occurrence of R^a and R^b may be same or different and is independently hydrogen, halogen, nitro, cyano, formyl, acetyl,-C(O)R^c, -C(O)OR^c, -C(O)NR^dR^e, -S(O)\_mR^c, -S(O)\_mNR^cR^d, -NR^d, -OR^c, -SR^d, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted cycloalkenyl, substituted or unsubstituted arylalkyl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heteroarylalkyl, or a substituted or unsubstituted heterocyclylalkyl;

each occurrence of R^c and R^d is independently hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted cycloalkenyl, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heteroarylalkyl, substituted or unsubstituted heterocyclic group, substituted or unsubstituted heterocyclylalkyl, or a substituted or unsubstituted heteroarylalkyl;

when R^c and R^d are attached to a nitrogen atom, they may be joined to form substituted or unsubstituted 3 to 7 membered saturated or unsaturated cyclic ring, which may optionally include at one or more heteroatom(s) selected from O, S or NR^e;

R^4 is hydrogen, substituted or unsubstituted alkyl, or two R^4 attached to a common carbon atom, form substituted or unsubstituted cycloalkyl;

R^e is selected from hydrogen, formyl, acetyl, -C(O)R^c, -C(O)NR^dR^e, -S(O)\_mR^c, -S(O)\_mNR^cR^d, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted cycloalkenyl, substituted or unsubstituted cycloalkenylalkyl, substituted or unsubstituted arylalkyl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heterocyclylalkyl, or a substituted or unsubstituted heteroarylalkyl or a protecting group;
Y is O or S;

each occurrence of 'm' is an integer of from 0, 1, 2;

each occurrence of 'n' is an integer of from 0, 1, 2, 3, 4 or 5.

The method comprising the steps of:

(i) compound of formula (1) can be protected by using suitable protecting group for example N-Boc-glycine and EDCI in presence of base for example DMAP (dimethyl amino pyridine) and/or triethyl amine

(ii) deprotection of compound of formula (9) to form compound of formula (10) in presence of acetic reagent, for example ethyl acetate which is saturated with HCl

(iii) compound of formula (10) (either in free or salt form) coupled with compound of formula (8) in presence of base for example alkali metal carbonate preferably potassium carbonate to form compound of formula (11)

(iv) compound of formula (11) reduced to give compound of formula (11) in presence of reducing agent for example alcohol (for example methanol) and 10% Pd/C and subjected to hydrogenation

(11)
compound of formula (Ia) prepared by reacting compound of formula (12) with trialkyl ortho formate for example triethyl orthoformate