Abstract:
The present invention relates to indazole derivatives of the following formula I, which can be used as vanilloid receptor ligands, processes for their preparation, and their use in treating diseases, conditions and/or disorders modulated by vanilloid receptor ligands. (I)
INDAZOLE DERIVATIVES AND THEIR USE AS VANILLOID RECEPTOR LIGANDS


Field of the Invention

The present invention relates to indazole derivatives, which can be used as vanilloid receptor ligands, processes for their preparation, and their use in treating diseases, conditions and/or disorders modulated by vanilloid receptors.

Background of the Invention

Pain is the most common symptom for which patients seek medical advice and treatment. Pain can be either 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 further 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 (such as vanilloid receptor 1 or VR1) (V. Di Marzo et ai, Current Opinion in Neurobiology 12: 372-379, 2002) to pain processing.

The lipophillic vanilloid, Capsaicin (8-methyl-N-vanillyl-6-nonanamides; 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 transient receptor potential cation channel, subfamily V, member 1 or 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 (Wriggleworth and Walpore, 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 (GERD), 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 and trigeminal neuralgia), and in pain due to diabetic neuropathy, dental pain, and
cancer pain. Additionally, VR1 antagonists will also prove useful in the treatment of inflammatory pain conditions such as arthritis 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 1 (VR1) has been characterized by the presence of a vanillyl (4-hydroxy 3-methoxybenzyl) group or a functionally equivalent group and has 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.

European Patent Publication No. EP 462761 discloses (benzopyranyl) phenylureas and related compounds as potassium channel activators and a method of using these and other compounds having potassium channel activating activity as antiischemic and/or anti-arrhythmic agents.

PCT Publication No. WO 2003/080578 discloses heteroaromatic ureas as vanilloid receptor (VR1) modulators, in particular antagonists, for treating pain and/or inflammation. PCT Publication No. WO 05/007652 describes substituted quinolin-4-yl-amine analogues useful in the treatment of conditions related to capsaicin receptor activation.


There is a need for better analgesics for the treatment of both acute and chronic pain, and the treatment of various neuropathic pain states.

Summary of the Invention

The present invention provides vanilloid receptor ligands of the formula I
and pharmaceutically acceptable salts thereof, N-oxides thereof, and prodrugs thereof, wherein:

each occurrence of $R^1$, $R^3$ and $R^4$ is independently hydrogen, hydroxy, halogen, cyano, nitro, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted alkoxy, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted cycloalkenyl, substituted or unsubstituted cycloalkenylalkyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted heterocyclylalkyl, substituted or unsubstituted arenyl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heteroarylalkyl, substituted or unsubstituted amino, COOR$^2$, C(O)$R^2$, C(S)$R^2$, C(O)NR$^2$$R^2$, C(O)ONR$^2$$R^2$, NR$^2$CONR$^2$$R^2$, N(R$^2$)SOR$^2$, N(R$^2$)SO$_2$R$^2$, (=N-N(R$^2$)R$^2$), NR$^2$C(O)OR$^2$, NR$^2$R$^2$, NR$^2$C(O)R$^2$, NR$^2$C(S)R$^2$, NR$^2$C(S)NR$^2$$R^2$, SONR$^2$$R^2$, SO$_2$NR$^2$$R^2$, OR$^2$, OR$^2$C(O)NR$^2$$R^2$, OR$^2$C(O)OR$^2$, OC(O)R$^2$.  

OC(O)NR$^2$$R^2$, R$^2$NR$^2$C(O)R$^2$, R$^2$OR$^2$, R$^2$C(0)OR$^2$, R$^2$C(O)NR$^2$$R^2$, R$^2$C(O)R$^2$, R$^2$OC(O)R$^2$, SR$^2$, SOR$^2$ or SO$_2$R$^2$;

$R^2$ is hydrogen, alkoxy carbonyl, nitro, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted amino, substituted or unsubstituted heteroaryl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted heteroarylalkyl, substituted or unsubstituted amino, COOR$^2$, C(O)$R^2$, C(S)$R^2$, C(O)NR$^2$$R^2$, C(O)ONR$^2$$R^2$, NR$^2$CONR$^2$$R^2$, N(R$^2$)SOR$^2$, N(R$^2$)SO$_2$R$^2$, (=N-N(R$^2$)R$^2$), NR$^2$C(O)OR$^2$, NR$^2$R$^2$, NR$^2$C(O)R$^2$, NR$^2$C(S)R$^2$, NR$^2$C(S)NR$^2$$R^2$, SONR$^2$$R^2$, SO$_2$NR$^2$$R^2$, OR$^2$, OR$^2$C(O)NR$^2$$R^2$, OR$^2$C(O)OR$^2$, OC(O)R$^2$.  

OC(O)NR$^2$$R^2$, R$^2$NR$^2$C(O)R$^2$, R$^2$OR$^2$, R$^2$C(0)OR$^2$, R$^2$C(O)NR$^2$$R^2$, R$^2$C(O)R$^2$, R$^2$OC(O)R$^2$, SR$^2$, SOR$^2$ or SO$_2$R$^2$;

$R^2$ is hydrogen, alkoxy carbonyl, nitro, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted amino, substituted or unsubstituted heteroaryl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted heteroarylalkyl, substituted or unsubstituted amino, COOR$^2$, C(O)$R^2$, C(S)$R^2$, C(O)NR$^2$$R^2$, C(O)ONR$^2$$R^2$, NR$^2$CONR$^2$$R^2$, N(R$^2$)SOR$^2$, N(R$^2$)SO$_2$R$^2$, (=N-N(R$^2$)R$^2$), NR$^2$C(O)OR$^2$, NR$^2$R$^2$, NR$^2$C(O)R$^2$, NR$^2$C(S)R$^2$, NR$^2$C(S)NR$^2$$R^2$, SONR$^2$$R^2$, SO$_2$NR$^2$$R^2$, OR$^2$, OR$^2$C(O)NR$^2$$R^2$, OR$^2$C(O)OR$^2$, OC(O)R$^2$.  

OC(O)NR$^2$$R^2$, R$^2$NR$^2$C(O)R$^2$, R$^2$OR$^2$, R$^2$C(0)OR$^2$, R$^2$C(O)NR$^2$$R^2$, R$^2$C(O)R$^2$, R$^2$OC(O)R$^2$, SR$^2$, SOR$^2$ or SO$_2$R$^2$;

$R^2$ is hydrogen, alkoxy carbonyl, nitro, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted amino, substituted or unsubstituted heteroaryl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted heteroarylalkyl, substituted or unsubstituted amino, COOR$^2$, C(O)$R^2$, C(S)$R^2$, C(O)NR$^2$$R^2$, C(O)ONR$^2$$R^2$, NR$^2$CONR$^2$$R^2$, N(R$^2$)SOR$^2$, N(R$^2$)SO$_2$R$^2$, (=N-N(R$^2$)R$^2$), NR$^2$C(O)OR$^2$, NR$^2$R$^2$, NR$^2$C(O)R$^2$, NR$^2$C(S)R$^2$, NR$^2$C(S)NR$^2$$R^2$, SONR$^2$$R^2$, SO$_2$NR$^2$$R^2$, OR$^2$, OR$^2$C(O)NR$^2$$R^2$, OR$^2$C(O)OR$^2$, OC(O)R$^2$.  

OC(O)NR$^2$$R^2$, R$^2$NR$^2$C(O)R$^2$, R$^2$OR$^2$, R$^2$C(0)OR$^2$, R$^2$C(O)NR$^2$$R^2$, R$^2$C(O)R$^2$, R$^2$OC(O)R$^2$, SR$^2$, SOR$^2$ or SO$_2$R$^2$;
heteroaryl, substituted or unsubstituted heterocyclylalkyl, substituted or unsubstituted heteroarylalkyl, or substituted or unsubstituted heterocyclyl.

In one embodiment, R² is hydrogen.

In another embodiment, R² is benzyl or ethoxycarbonyl.

In yet another embodiment, R³ is bromo, fluoro or pyrrolidine-2-one.

In yet another embodiment, R⁴ is hydrogen or fluorine.

In yet another embodiment, R¹ is hydrogen.

According to one preferred embodiment, the vanilloid receptor ligands are those having the formula II

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and pharmaceutically acceptable salts thereof, N-oxides thereof, and prodrugs thereof, wherein:

each occurrence of R¹, R³ and R⁴ is independently hydrogen, hydroxy, halogen, cyano, nitro, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted alkoxy, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted cycloalkenyl, substituted or unsubstituted cycloalkenylalkyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted heterocyclylalkyl, substituted or unsubstituted amino, COOR X, C(O)R X, C(S)R X, C(O)NR X R Y, C(O)ONR X R Y, NR X CONR Y R Z, N(R X)SOR Y, N(R X)SO₂R Y, (=N-N(R X)R Y), NR X C(O)OR Y, NR X R Y, NR X C(O)R Y, NR X C(S)R Y, NR X C(S)NR X R Y, NR X SO₂R Y, OR X, OR X C(O)NR X R Z, OR X C(O)OR Y, OC(O)R X, OC(O)NR X R Y, R X NR X C(O)R Z, R X OR Y, R X C(O)OR Y, R X C(O)NR X R Z, R X C(O)R Y, R X OC(O)R Y, SR X, SOR X or SO₂R X;

R² is hydrogen, arylalkyl or alkoxy carbonyl;

m is 0, 1, 2, 3 or 4;
n is 0, 1, 2 or 3; and

R^x, R^y and R^z are independently 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 cycloalkylalkyl, substituted or unsubstituted cycloalkenyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heterocyclylalkyl, substituted or unsubstituted heteroaryalkyl, or substituted or unsubstituted heterocyclyl.

Representative compounds of the present invention include those specified below and pharmaceutically acceptable salts thereof, N-oxides thereof, and prodrugs thereof. The present invention should not be construed to be limited to them.

(±) -1-(3,4-dihydrospiro[chromene-2, 1'-cyclobutan]-4-yl)-3-(1H-indazol-4-yl)urea (Compound No. 1),

(±) -1-(3,4-dihydrospiro[chromene-2, r-cyclobutan]-4-yl)-3-(l H-indazol-4-yl)urea (Compound No. 2),

(-) -1-(3,4-dihydrospiro[chromene-2, 1'-cyclobutan]-4-yl)-3-((1-ethoxycarbonyl-1H-indazol-4-yl)urea (Compound No. 3)

(+) -1-(3,4-dihydrospiro[chromene-2, 1'-cyclobutan]-4-yl)-3-((1-ethoxycarbonyl-1H-indazol-4-yl)urea (Compound No. 4)

(+)-1-(3,4-dihydrospiro[chromene-2, 1'-cyclobutan]-4-yl)-3-((1H-indazol-4-yl)urea (Compound No. 5)

(+) -1-(3,4-dihydrospiro[chromene-2, 1'-cyclobutan]-4-yl)-3-((1H-indazol-4-yl)urea (Compound No. 6)

(±) -1-(6-fluoro-3,4-dihydrospiro[chromene-2, r-cyclobutan]-4-yl)-3-((1-ethoxycarbonyl-1H-indazol-4-yl)urea (Compound No. 7)

(±) -1-(6-fluoro-3,4-dihydrospiro[chromene-2, 1'-cyclobutan]-4-yl)-3-(lH-indazol-4-yl)urea (Compound No. 8)

(±) -1-(7-fluoro-3,4-dihydrospiro[chromene-2, 1'-cyclobutan]-4-yl)-3-(1-ethoxycarbonyl-1H-indazol-4-yl)urea (Compound No. 9)

(±) -1-(7-fluoro-3,4-dihydrospiro[chromene-2, l'-cyclobutan]-4-yl)-3-(lH-indazol-4-yl)urea (Compound No. 10)

(±) -1-(6,8-difluoro-3,4-dihydrospiro[chromene-2, r-cyclobutan]-4-yl)-3-((1-ethoxycarbonyl-1H-indazol-4-yl)urea (Compound No. 11)
(±)-1-(6,8-difluoro-3,4-dihydrospiro[chromene-2, r-cyclobutan]-4-yl)-3-(1 H-indazol-4-yl)urea (Compound No. 12),

(+)-1-(6,8-difluoro-3,4-dihydrospiro[chromene-2, r-cyclobutan]-4-yl)-3-(1-ethoxy carbonyl -lH-indazol-4-yl)urea (Compound No. 13),

(+)-1-(6,8-difluoro-3,4-dihydrospiro[chromene-2, 1'-cyclobutan]-4-yl)-3-(1 H-indazol -4-yl)urea (Compound No. 14),

(±)-1-(1-ethoxycarbonyl-l H-indazol-4-yl)-3-(7-methyl-3,4-dihydrospiro[chromene-2, r-cyclobutan]-4-yl)urea. (Compound No. 15),

(±)-1-(l H-indazol-4-yl)-3-(7-methyl-3,4-dihydrospiro[chromene-2, 1'-cyclobutan]-4-yl)urea. (Compound No. 16),

(±)-1-(1-ethoxycarbonyl-1H-indazol-4-yl)-3-(7-methoxy-3,4-dihydrospiro[chromene-2, 1'-cyclobutan]-4-yl)urea. (Compound No. 17),

(±)-1-(l H-indazol-4-yl)-3-(7-methoxy-3,4-dihydrospiro[chromene-2, r-cyclobutan]-4-yl)urea. (Compound No. 18),

(±)-1-(1-ethoxycarbonyl-1H-indazol-4-yl)-3-(7-chloro-3,4-dihydrospiro[chromene-2, 1'-cyclobutan]-4-yl)urea. (Compound No. 19),

(±)-1-(1 H-indazol-4-yl)-3-(7-chloro-3,4-dihydrospiro[chromene-2, r-cyclobutan]-4-yl)urea. (Compound No. 20),

(±)-1-(1-ethoxycarbonyl-6-bromo-l H-indazol-4-yl)-3-(3,4-dihydrospiro[chromene-2, 1'-cyclobutan]-4-yl)urea. (Compound No. 21),

(±)-1-(3,4-dihydrospiro[chromene-2, 1'-cyclobutan]-4-yl)-3-(6-bromo-1 H-indazol-4-yl)urea (Compound No. 22),

(±)-1-(1-ethoxycarbonyl-6-fluoro-1H-indazol-4-yl)-3-(3,4-dihydrospiro[chromene-2, 1'-cyclobutan]-4-yl)urea. (Compound No. 23),

(±)-1-(3,4-dihydrospiro[chromene-2, l'-cyclobutan]-4-yl)-3-(6-fluoro-1 H-indazol-4-yl)urea (Compound No. 24),

(±)-1-(l-benzyl-6-pyrrolidin-2-one-lH-indazol-4-yl)-3-(3,4-dihydrospiro[chromene-2, 1'-cyclobutan]-4-yl)urea. (Compound No. 25),

(+)-l-(1-ethoxycarbonyl-6-fluoro-lH-indazol-4-yl)-3-(3,4-dihydrospiro[chromene-2, 1'-cyclobutan]-4-yl)urea. (Compound No. 26),

(+)-l-(3,4-dihydrospiro[chromene-2, r-cyclobutan]-4-yl)-3-(6-fluoro-1 H-indazol-4-yl)urea (Compound No. 27),

(±)-1-(1-ethoxycarbonyl-6-methoxy-1H-indazol-4-yl)-3-(3,4-dihydrospiro [chromene -2,1'-cyclobutan]-4-yl)urea. (Compound No. 28),

(±)-1-(6,8-difluoro-3,4-dihydrospiro[chromene-2, r-cyclobutan]-4-yl)-3-(1 H-indazol-4-yl)urea (Compound No. 28),
(±) 1-(3,4-dihydrospiro[chromene-2,1'-cyclobutan]-4-yl)-3-(6-methoxy-1H-indazol-4-yl)urea (Compound No. 29),

(+) 1-(6,8-difluoro-3,4-dihydrospiro[chromene-2,1'-cyclobutan]-4-yl)-3-(1-ethoxycarbonyl-1H-indazol-4-yl)urea (Compound No. 30),

(-) 1-(6,8-difluoro-3,4-dihydrospiro[chromene-2,1'-cyclobutan]-4-yl)-3-(1H-indazol-4-yl)urea (Compound No. 31),

(-) 1-(6,8-difluoro-3,4-dihydrospiro[chromene-2,1'-cyclobutan]-4-yl)-3-(1H-indazol-4-yl)urea (Compound No. 32),

(-) 1-(6,8-difluoro-3,4-dihydrospiro[chromene-2,1'-cyclobutan]-4-yl)-3-(lH-indazol-4-yl)urea (Compound No. 33),

(±) 1-(6-pyrrolidin-2-one-1-ethoxycarbonyl-1H-indazol-4-yl)-3-(3,4-dihydrospirochormene-2,1'-cyclobutan]-4-yl)urea. (Compound No. 34), and

(±) 1-(6-pyrrolidin-2-one-1H-indazol-4-yl)-3-(3,4-dihydrospiro[chromene-2,1'-cyclobutan]-4-yl)urea. (Compound No. 35).

The compound of the present invention can also be any compound disclosed as a VRl antagonist in International Publication No. WO 2007/121299 and U.S. Patent Publication No. 2007-0249614, which are hereby incorporated by reference in their entireties.

Also provided herein is a pharmaceutical composition comprising one or more of the aforementioned compounds together with one or more pharmaceutically acceptable excipients (such as a pharmaceutically acceptable carrier or diluent). Preferably, the pharmaceutical composition comprises a therapeutically effective amount of one or more compounds of the present invention. One or more compounds of the present invention may be diluted with 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 a vanilloid receptor (such as VRl) 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 (VRl) 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) keratocanthoma, (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 indazole derivatives, which can be used as vanilloid receptor ligands, and processes for the synthesis of these compounds. 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.

The following definitions apply to the terms as used herein:

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 "alkenyl" refers to an aliphatic hydrocarbon group containing a carbon-carbon double bond and which may be a straight or branched chain having from 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 from 2 to about 12 carbon atoms (with
radicals having from 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 -OC₂H₅.  

The term "alkoxycarbonyl" denotes an alkyl group attached via a carbonyl linkage to the rest of the molecule. Representative examples of such groups are -COOCH₃ and -COOC₂H₅.  

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

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

The term "cycloalkenylalkyl" refers to a cyclic ring-containing radical having from 3 to about 8 carbon atoms and at least one carbon-carbon double bond, which is directly attached to an alkyl group. The cycloalkenylalkyl 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.  

The term "aryl" refers to an aromatic radical having from 6 to 14 carbon atoms such as phenyl, naphthyl, tetrahydronaphthyl, indany1, and biphenyl.  

The term "arylalkyl" refers to an aryl group as defined above directly bonded to an alkyl group as defined above, e.g., -CH₂C₆H₅ and -C₂H₅C₆H₅.  

The terms "heterocyclyl" and "heterocyclic ring" refer 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

- 10 -
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, indolizinyl, naphthyridinyl,
perhydroazepinyl, phenazinyl, phenothiazinyl, phenoazinyl, phthalazinyl, pyridyl,
ppteridinyl, purinyl, quinazoliny, quinoxalinyl, quinolinyl, isoquinolinyl, tetrazoyl,
imidazolyl, tetrahydroisouinolyl, piperidinyl, piperezinyl, 2-oxopiperazinyl, 2-oxopiperidinyl,
2-oxopyrrolidinyl, 2-oxazepinyl, azepinyl, pyrrolyl, 4-piperidonyl, pyrrolidinyl, pyrazinyl,
pyrimidinyl, pyridazinyl, oxazolyl, oxazoliny, oxazolidinyl, triazolyl, indany, isoxazolyl,
isoxazolidinyl, morpholinyl, thiazolyl, thiazoliny, thiazolidinyl, isothiazolino, quinclidinyl,
isothiazolidinyl, indolyl, isoindolyl, indoliny, isoindoliny, octahydropyridolyl,
ocydrosoindolyl, quinolyl, isoquinolyl, decahydroisoquinolyl, benzimidazolyl,
thiadiazolyl, benzopyryny, benothiazolyl, benzoxazolyl, furyl, tetrahydrofurtyl,
tetrahydropranyln, thienyl, benzothienyl, thiamorpholinyl, thiamopholiny, sulfoxide,
thiamorpholinyl sulfone, dioxaphospholany, oxadiazolyl, chromanyl, and isochromanyl.
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 "heterocyclylalkyl" refers to a heterocyclic ring radical directly bonded to
an alkyl group. The heterocyclylalkyl 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 "heteroaryllalkyl" refers to a heteroaryl ring radical directly bonded to an
alkyl group. The heteroaryllalkyl 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 cycloalkenylalkyl, substituted or
unsubstituted cycloalkenyl, substituted or unsubstituted amino, substituted or unsubstituted
aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heterocyclylalkyl ring, substituted or unsubstituted heteroaryalkyl, substituted or unsubstituted heterocyclic ring, substituted or unsubstituted guanidine, -COOR, -C(O)R, -C(S)R, -C(O)NR, -C(O)0NR, -NR, -NR CONR, -N(R)S02R, -N(R)SO2R, -(=N-N(R)R)0, -NR-C(O)OR, -NR-SR, -NR-SO2R, -OR, -OR-C(O)NR, -OR-C(O)0R, -OC(O)R, -OC(O)0R, -R-NR-C(O)R, -R-OR, -R-C(O)OR, -R-C(O)0R, -SR, -SOR, -SO2R, and -ONO2, wherein R, R' and R'' 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 aryl or substituted alkyl, substituted or unsubstituted heteroaryl, substituted heterocyclylalkyl ring, substituted or unsubstituted heteroaryalkyl, 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 functional group from reacting with another chemical molecule or reagent, while other functional groups on the compound 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), benzylxycarbonyl (CBz) and 9-fluorenylmethylenoxycarbonyl (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, tetrahydroprpyranyl (THP), and silyl protecting groups such as trimethyl silyl (TMS) or t-butyldimethylsilyl (TBS). 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, -CH2CH2SO2Ph, 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 (II) 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, disease, disorder or condition includes:

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

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

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

The benefit to a subject receiving treatment 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, disease, disorder or condition, is sufficient to effect such treatment. The "therapeutically effective amount" will vary depending on the compound, the state, disease, disorder or condition and its severity and the age, weight, physical condition and responsiveness of the subject receiving treatment.

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'-diacetylenediamine, 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 the invention with alkyl halides or alkyl sulphates (such as MeI or (Me)₂SO₄).

Pharmaceutically acceptable solvates include 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 the 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:

\[
\begin{align*}
\text{Pharmaceutical Compositions}
\end{align*}
\]

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, cycloextrin,
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 glycercyl monostearate or glycercyl distearate, alone or mixed with a wax.

The pharmaceutical composition may also include one or more pharmacetically acceptable auxiliary agents, wetting agents, emulsifying agents, suspending agents, preserving agents, salts for influencing osmotic 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 pharmacutical 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 tabletting 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 VRL 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 VRL 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 hypersensitivity, urinary incontinence, vulvodynia, pruritic conditions such as uremic pruritus, irritable bowel syndrome including gastro-esophageal reflux disease (GERD), enteritis, ileitis, stomach-duodenal ulcer, inflammatory bowel disease including Crohn's disease, celiac disease and inflammatory diseases such as pancreatitis. They also include respiratory disorders such as allergic and non-allergic rhinitis, asthma or chronic obstructive pulmonary disease, irritation of skin, eye or mucous membrane, dermatitis, and non-specific disorders such as fervescence, retinopathy, muscle spasms, emesis, dyskinesias and depression. They further include multiple sub-types
of pain such as acute, chronic, neuropathic and post-operative pain, as well as pain due to neuralgia (e.g., post herpetic neuralgia trigeminal neuralgia), pain due to diabetic neuropathy, dental pain, and cancer pain. Additionally, VR1 antagonists are useful 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 (VR1) antagonist 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, osteoarthritic 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, gastroesophageal 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 compound 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 the vanilloid receptor. In particular the invention provides a compound of formula (I) or (II) 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 subject in need thereof a therapeutically effective amount of a compound or composition 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 the 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 pain, 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 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, respiratory disorders such as allergic and non-allergic rhinitis, asthma or chronic
obstructive pulmonary disease, irritation of skin, eye or mucous membrane, dermatitis, and
non specific disorders such as fervescence, retinopathy, muscle spasms, emesis, dyskinesias
or depression. The method also includes alleviating and/or treating any of multiple sub-types
of pain such as acute, chronic, neuropathic and post-operative pain, pain due to neuralgia
(e.g., post herpetic neuralgia and trigeminal neuralgia), pain due to diabetic neuropathy,
dental pain, and cancer pain. Additionally, the method can be used 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.

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 of formula I can be prepared by Schemes I, II, III and IV shown
below.
A compound of formula I can be prepared as shown in Scheme I above. The compound of formula (1) is allowed to react with cyclobutanone of formula (2) to form a bicyclic compound of formula (3). The oxo group of formula (3) is converted to an oxime group, such as by reaction with hydroxylamine hydrochloride, forming a compound of formula (4). The oxime group of the compound of formula (4) is reduced to an amine group, forming the compound of formula (5). The compound of formula (5) is acylated, such as with a formate of the formula (6) X'C(O)OR where X' is a leaving group (e.g., halogen) and R is hydrogen, alkyl or aryl (e.g., phenyl) (such as phenylchloroformate), to form the compound of formula (7). The compound of formula (7) is reacted with an amine of formula (8) to provide a compound of formula I.

The compound of formula (1) can be reacted with cyclobutanone of formula (2) in one or more suitable organic bases including, but not limited to, pyrrolidine, morpholine, pyridine or a mixture thereof. The compound of formula (1) can also be reacted in one or more solvents including, but not limited to, polar protic solvents (e.g., methanol, ethanol, isopropylalcohol and mixtures thereof), aprotic polar solvents (e.g., dichloromethane, acetonitrile, dichloroethane, tetrahydrofuran, dibromomethane and mixtures thereof), or a mixture thereof. The compound of formula (3) can be reacted with hydroxylamine.
hydrochloride in one or more suitable solvents including, but not limited to, polar protic solvents (e.g., methanol, ethanol, isopropylalcohol or a mixture thereof), aprotic polar solvents (e.g., dichloromethane, dichloroethane, tetrahydrofuran, dibromomethane or a mixture thereof), or a mixture thereof. The compound of formula (4) can be reduced to form an amine of formula (5) in the presence of one or more reducing agents including, but not limited to, catalytic reducing agents (e.g., Nickel-Aluminum/hydrogen, palladium-carbon/hydrogen, platinum-carbon/hydrogen, Raney-Nickel/hydrogen or mixtures thereof) and boron reagents (e.g., sodium borohydride, sodium cyanoborohydride, BH₃, THF, BH₃-dimethylsulfide and mixtures thereof).

The compound of formula (5) can be reacted with the compound of formula (6) in one or more suitable solvents including, but not limited to, polar protic solvents (e.g., methanol, ethanol, isopropylalcohol or a mixture thereof), aprotic polar solvents (e.g., dichloromethane, dichloroethane, tetrahydrofuran, dibromomethane or a mixture thereof), or a mixture thereof.

The compound of formula (7) can be reacted with a compound of formula (8) in a solvent and/or in the presence of a base. Suitable bases include, but are not limited to, potassium bicarbonate, potassium carbonate, sodium carbonate, sodium bicarbonate, triethylamine, ammonium hydroxide, pyridine, alkylamines and mixtures thereof. Suitable solvents include, but are not limited to, polar protic solvents (e.g., methanol, ethanol, isopropylalcohol and mixtures thereof), aprotic polar solvents (e.g., dichloromethane, dichloroethane, tetrahydrofuran, dibromomethane dimethylsulfoxide, dimethylformamide and mixtures thereof), and mixtures thereof.

Scheme II

Step 1

Step 2
The compound of formula I can also be prepared by the above Scheme II. In this scheme, a compound of formula (8) is reacted with a compound of formula (6), where \( X' \) and \( R_P \) are as defined in Scheme I (e.g., the compound of formula (6) can be phenylchloroformate) to form a compound of formula (9). The compound of formula (9) can also be prepared following the procedures described in U.S. Patent Publication Nos. 2004/0254188 and 2006/0128689. The compound of formula (9) is reacted with a compound of formula (5) to yield a compound of formula I. Alternatively, a compound of formula (9') can be reacted with a compound of formula (5) to yield a compound of formula I. The compound of formula (9') (e.g., 4-isocyanato-1,3-substituted-1H-indazole compounds) may be formed by reaction of the corresponding 4-amino-1H-indazole of formula (8) and an appropriate reagent, for example, phosgene, triphosgene, or a similar condensing agent.

The compound of formula (8) can be reacted with the compound of formula (6) in one or more suitable organic bases including, but not limited to, pyrrolidine, morpholine, pyridine or a mixture thereof. The compound of formula (8) can also be reacted in one or more solvents including, but not limited to, polar protic solvents (e.g., methanol, ethanol, isopropylalcohol and mixtures thereof), aprotic polar solvents (e.g., dichloromethane, acetonitrile, dichloroethane, tetrahydrofuran, dibromomethane, ether and mixtures thereof), or a mixture thereof.

The compound of formula (9) or formula (9') can be reacted with the compound of formula (5) in one or more suitable solvents including, but not limited to, polar protic solvents (e.g., methanol, ethanol, isopropylalcohol or a mixture thereof), aprotic polar solvents (e.g., dichloromethane, dichloroethane, tetrahydrofuran, dibromomethane, dimethylsulfoxide or a mixture thereof), or a mixture thereof. Optionally, the reaction can be
performed in the presence of one or more suitable organic bases, including, but not limited to, triethylamine, pyridine, pyrrolidine, morpholine or a mixture thereof.

Scheme III

The compound of formula I can also be prepared as shown above Scheme III. In this manner, a compound of formula (10) is allowed to react with an amine of formula (8) to form a compound of formula I. The reaction can be performed in one or more suitable solvents including, but not limited to, polar protic solvents (e.g., methanol, ethanol, isopropylalcohol or a mixture thereof), aprotic polar solvents (e.g., dichloromethane, dichloroethane, tetrahydrofuran, dibromomethane or a mixture thereof), or a mixture thereof.

Scheme IV

The compound of formula (5), where \( R^4 \) and \( m \) are as defined for formula I above, can be prepared by the method shown above in Scheme IV. The oxo group in the compound of formula (3) is reduced to form an alcohol compound of formula (11), which is converted to a compound of formula (12) (for example, by reaction with acetamide). In an alternate embodiment, the alcohol of formula (11) is converted to a better leaving group, such as a halogen, or the like, prior to conversion to a compound of formula (12). The compound of formula (12) is hydrolyzed to form a compound of formula (5).

The compound of formula (3) can be reduced to form the compound of formula (11) in the presence of one or more reducing agents. Suitable reducing agents include, but are not limited to, catalytic reducing agents (e.g., Nickel-Aluminum/hydrogen, palladium-carbon/hydrogen, platinum-carbon/hydrogen, Raney-Nickel/hydrogen or a mixture thereof) and boron reagents (e.g., sodium borohydride, sodium cyanoborohydride, \( BH_3^- \).
tetrahydrofuran, BH$_3$-dimethylsulfoxide or a mixture thereof). The reduction can be performed, for example, in one or more aprotic polar solvents, e.g., dichloromethane, dichloroethane, tetrahydrofuran, dibromomethane or a mixture thereof.

The compound of formula (11) can be converted to the compound of formula (12), for example, in the presence of acetonitrile and sulfuric acid. The compound of formula (12) can be hydrolyzed in the presence of a base (such as potassium bicarbonate, potassium carbonate, sodium carbonate, sodium bicarbonate, triethylamine, ammonium hydroxide, pyridine, alkylamines or a mixture thereof) or an acid (such as hydrochloric acid, trifluoroacetic acid or a mixture thereof).

Alternatively, the compound of formula (3) can be directly converted to the compound of formula (5), for example, by subjecting the compound of formula (3) to reductive amination. The reductive animation may be performed in the presence of one or more reducing agents including, but not limited to, sodium borohydride, sodium cyanoborohydride, sodium triacetoxyborohydride, boranes or a mixture thereof. The reductive animation may be performed in the presence of ammonia, ammonium acetate, ammonium chloride, liquor ammonia or any mixture thereof.

Acid addition salts of the compounds described herein can be prepared following procedures known to a person of ordinary skill in the art.

**Examples**

**Example 1: Preparation of (±)-l-(3,4-dihydrospiro[chromene-2',cyclobutan-1'-4-yl]-3-(1-ethoxycarbonyl-1 H-indazol-4-yl)urea (Compound No. 1)

```
    H
   / \NC
  /   /
 C   N
   \  /
    \/
     O
      OCH$_2$CH$_3$
```

A solution of phenyl (1-ethoxycarbonyl-1 H-indazol-4-yl) carbamate (1 mmol) and (±)-3,4-dihydrospiro[chromene-2',cyclobutan-1'-4-amine (1 mmol) in dimethylsulfoxide was stirred at room temperature in the presence of triethylamine (2 mmol). A few drops of water were added in the reaction mixture. The product was precipitated out of solution, filtered and washed with water. The resulting compound was purified by column chromatography to afford the desired urea as a white solid.

$^1$H NMR (DMSO- $d_6$): δ 1.40 (t,3H, J = 6.9 Hz); 1.72-1.98 (m, 3H); 2.10-2.44 (m, 5H); 4.49 (q, 2H, J = 7.2 Hz and 6.9 Hz); 5.00 (m IH); 6.80 (IH, t, J = 7.5 Hz); 6.91 (IH, t, J
The following compounds were prepared by following the procedure as described for Example 1:

(-)-3,4-dihydrospiro[chromene-2,1'-cyclobutan]-4-yl)-3-(l-ethoxycarbonyl-l H-indazol-4-yl)urea (Compound No. 3)

This compound was prepared using phenyl (l-ethoxycarbonyl-l H-indazol-4-yl) carbamate (1 mmol) and (±)-3,4-dihydrospiro[chromene-2,1'-cyclobutan]-4-amine (1 mmol).

1H NMR (DMSO- D$_2$): $\delta$ 1.40 (t, 3H, J = 6.9 Hz); 1.72-1.98 (m, 3H); 2.10-2.44 (m, 5H); 4.47 (q, 2H, J = 7.2 Hz and 6.9 Hz); 5.00 (m IH); 6.77 (IH, t, J = 7.5 Hz); 6.89 (IH, t, J = 7.5 Hz); 7.14 (IH, t, J = 7.8 Hz); 7.26 (IH, d, J = 7.5 Hz); 7.51 (IH, t, J = 8.1 Hz); 7.68 (IH, d, J = 8.1 Hz); 7.89 (IH, d, J = 7.8 Hz); 8.39 (IH, s); 8.98 (IH, s). IR (KBr) (cm$^{-1}$): 3327, 2934, 1732, 1634, 1563, 1423, 1307, 1271, 1185, 1085, 982, 762. MS [M-I$^+$]: 419.66.

(+)-1-(3,4-dihydrospirofchromene-2, l'-cyclobutan]-4-yl)-3-[l-ethoxycarbonyl-l H-indazol-4-yl]urea (Compound No. 5)

This compound was prepared using phenyl (l-ethoxycarbonyl-l H-indazol-4-yl) carbamate (1 mmol) and (±)-3,4-dihydrospiro[chromene-2,1'-cyclobutan]-4-amine (1 mmol).

1H NMR (DMSO- D$_2$): $\delta$ 1.40 (t, 3H, J = 6.9 Hz); 1.72-1.98 (m, 3H); 2.10-2.44 (m, 5H); 4.47 (q, 2H, J = 7.2 Hz and 6.9 Hz); 5.00 (m IH); 6.77 (IH, t, J = 7.5 Hz); 6.89 (IH, t, J = 7.5 Hz); 7.14 (IH, x J = 7.8 Hz); 7.26 (IH, d, J = 7.5 Hz); 7.49 (IH, t, J = 8.1 Hz); 7.68 (IH, d, J = 8.1 Hz); 7.88 (IH, d, J = 7.8 Hz); 8.39 (IH, s); 8.98 (IH, s). IR (KBr) (cm$^{-1}$): 3327, 2934, 1732, 1634, 1563, 1423, 1307, 1271, 1185, 1085, 982, 762. MS [M$^+$]: 419.6

(+)-1-(6-fluoro-3,4-dihydrospirofchromene-2, 1'-cyclobutan]-4-ylV3- [l-ethoxycarbonyl-l H-indazol-4-yl]urea (Compound No. 7)

This compound was prepared using phenyl (l-ethoxycarbonyl-l H-indazol-4-yl) carbamate (1 mmol) and (±)-6-fluoro-3,4-dihydrospiro[chromene-2,1'-cyclobutan]-4-amine (1 mmol).

1H NMR (DMSO- D$_2$): $\delta$ 1.40 (t, 3H, J = 7.5 Hz); 1.72-2.44 (m, 8H); 4.48 (q, 2H, J = 7.5 Hz); 4.98 (m, IH); 6.79 - 6.84 (m, 2H); 6.98 - 7.06 (m, 2H); 7.49 (t, IH, J = 8.1 Hz); 7.69 (d, IH, J = 8.1 Hz); 7.87 (d, IH, J = 7.8 Hz); 8.41 (s, IH); 9.02 (s, IH).

IR (KBr) (cm$^{-1}$): 3303, 2984, 1744, 1634, 1568, 1423, 1309, 1271, 1189, 1028, 984, 760.

(+)-1-(7-fluoro-3,4-dihydrospiro [chromene-2, 1'-cyclobutan] -4-y1)-3-[l-ethoxycarbonyl-l H-indazol-4-y]urea (Compound No. 9)
This compound was prepared by using the same procedure described in example 1 using phenyl (1-ethoxycarbonyl-1H-indazol-4-yl) carbamate (1 mmol) and (±)-7-fluoro-3,4-dihydrospiro[chromene-2,1'-cyclobutan]-4-amine (1 mmol).

\(^1^H\) NMR (DMSO- d6): \(\delta\) 1.40 (t, 3H, \(J = 6.9\) Hz); 1.75-2.37 (m, 8H); 4.48 (q, 2H, \(J = 6.9\) Hz); 4.96 (m, IH); 6.65 (d, IH, \(J = 9.6\) Hz); 6.74 (s, IH); 6.77 (s, IH); 7.28 (t, IH, \(J = 8.7\) Hz); 7.49 (t, IH, \(J = 7.8\) Hz); 7.69 (d, IH, \(J = 8.4\) Hz); 7.87 (d, IH, \(J = 7.8\) Hz); 8.4 (s, IH); 8.99 (s, IH)

(±)-1-(6,8-difluoro-3,4-dihydrospirochromene-2, 1'-cyclobutan]-4-vD-3-(1-ethoxycarbonyl-
1H-indazol-4-yl)urea (Compound No. 11)

This compound was prepared by using the same procedure described in example 1 using phenyl (1-ethoxycarbonyl-1H-indazol-4-yl) carbamate (1 mmol) and (±)-6,8-fluoro-3,4-dihydrospiro[chromene-2,1'-cyclobutan]-4-amine (1 mmol).

\(^1^H\) NMR (DMSO- d6): \(\delta\) 1.4 (t, 3H, \(J = 6.9\) Hz); 1.65-2.44 (m, 8H); 4.48 (q, 2H, \(J = 6.6\) Hz); 4.99 (m, IH); 6.87-6.94 (m, 2H); 7.19 (t, IH, \(J = 8.4\) Hz); 7.49 (t, IH, \(J = 8.7\) Hz); 7.70 (d, IH, \(J = 8.4\) Hz); 7.85 (d, IH, \(J = 7.8\) Hz); 8.42 (s, IH); 9.08 (s, IH).

IR (KBr) (cm⁻¹): 3348, 2939, 1744, 1620, 1555, 1421, 1270, 1187, 1053, 999, 761.

(±)-1-(1-ethoxycarbonyl-1H-indazol-4-yl) -3-(7-methyl-3,4-dihydrospirochromene-2J'-
cyclobutan]-4-yl)urea (Compound No. 15)

This compound was prepared by using the same procedure described in example 1 using phenyl (1-ethoxycarbonyl-1H-indazol-4-yl) carbamate and (±)-7-methyl-3,4-dihydrospiro[chromene-2, 1'-cyclobutan]-4-amine.

\(^1^H\) NMR (DMSO- d6): \(\delta\) 1.4 (t, 3H, \(J = 6.9\) Hz); 1.71-2.41 (m, 8H); 4.48 (q, 2H, \(J = 6.6\) Hz); 2.22 (s, 3H); 4.94 (m, IH); 6.61 (s, IH); 6.70 (m, 2H); 7.06 (d, IH, \(J = 8.1\) Hz); 7.13 (d, IH, \(J = 7.8\) Hz); 7.20 (t, IH, \(J = 7.8\) Hz); 7.68 (d, IH, \(J = 7.2\) Hz); 8.03 (s, IH); 8.68 (s, IH).

(-)-1-(1-ethoxycarbonyl-1H-indazol-4-yl) -3-(7-methoxy-3,4-dihydrospiro[chromene-2J'-
cyclobutan]-4-yl)urea (Compound No. 17)

This compound was prepared by using the same procedure described in example 1 using phenyl (1-ethoxycarbonyl-1H-indazol-4-yl) carbamate and (±)-7-methoxy-3,4-dihydrospiro[chromene-2, 1'-cyclobutan]-4-amine.
\( ^1\)H NMR (DMSO-\( \text{d}_6 \)): \( \delta \) 1.40 (t, 3H, \( J = 6.9 \) Hz); 1.74-2.35 (m, 8H); 3.69 (s, 3H); 4.48 (q, 2H, \( J = 6.9 \) Hz); 4.91 (m, IH); 4.36 (s, IH); 6.51 (d, IH, \( J = 9.3 \) Hz); 6.67 (d, IH, \( J = 8.1 \) Hz); 7.15 (d, IH, \( J = 8.4 \) Hz); 7.48 (t, IH, \( J = 7.8 \) Hz); 7.68 (d, IH, \( J = 8.4 \) Hz); 7.88 (d, IH, \( J = 7.8 \) Hz); 8.38 (s, IH); 8.94 (s, IH)

This compound was prepared by using the same procedure described in example 1 using phenyl (1-ethoxycarbonyl-1H-indazol-4-yl) carbamate and (±)-3-chloro-3,4-dihydrospiro[chromene-2,1'-cyclobutan]-4-amine.

\( ^1\)H NMR (DMSO-\( \text{d}_6 \)): \( \delta \) 1.40 (t, 3H, \( J = 6.9 \) Hz); 1.72-2.42 (m, 8H); 4.47 (q, 2H, \( J = 6.9 \) Hz); 4.98 (m, IH); 6.80 (d, IH, \( J = 9 \) Hz); 6.86 (d, IH, \( J = 2.1 \) Hz); 6.95 (d, IH, \( J = 8.4 \) Hz); 7.27 (t, IH, \( J = 8.4 \) Hz); 7.49 (t, IH, \( J = 8.4 \) Hz); 7.69 (d, IH, \( J = 8.7 \) Hz); 7.86 (d, IH, \( J = 7.8 \) Hz); 8.41 (s, IH); 9.03 (s, IH)

IR (KBr) (cm\(^{-1}\)): 3339, 2936, 1744, 1600, 1554, 1482, 1420, 1353, 1295, 1184, 1087, 968, 781, 759; M S [M-I]: 453.64

(±)-1-(1-ethoxycarbonyl-6-bromo-1H-indazol-4-yl) -3-(3,4-dihydrospiro[chromene-2, 1'-cyclobutan]-4-vDurea (Compound No. 21)

This compound was prepared by using the same procedure described in example 1 using phenyl (1-ethoxycarbonyl-6-bromo-1H-indazol-4-yl) carbamate and (±)3,4-dihydrospiro[chromene-2, 1'-cyclobutan]-4-amine.

\( ^1\)H NMR (DMSO-\( \text{d}_6 \)): \( \delta \) 1.40 (t, 3H); 1.83 (m, 4H); 2.14 (m, 4H); 4.47 (q, 2H); 4.98 (m, IH); 6.78 (d, IH); 6.89 (t, IH); 7.15 (t, IH); 7.25 (s, IH); 7.49 (d, IH); 7.66 (d, IH); 7.87 (d, IH); 8.39 (s, IH); 8.97 (s, IH)

(+)-1-(6,8-difluoro-3,4-dihydrospiro[chromene-2,l'-cyclobutan]-4-v π-3-(l-ethoxy carbonyl 1H-indazol-4-yl)urea (Compound No. 13)

This compound was prepared by using the same procedure described in example 1 using phenyl (1-ethoxycarbonyl-1H-indazol-4-yl) carbamate (1 mmol) and (+) - 6,8-fluoro-3,4-dihydrospiro [chromene-2,1'-cyclobutan] -4-amine (1 mmol).

\( ^1\)H NMR (DMSO-\( \text{d}_6 \)): \( \delta \) 1.4 (t, 3H, \( J = 6.9 \) Hz); 1.65-2.44 (m, 8H); 4.48 (q, 2H, \( J = 6.6 \) Hz); 4.99 (m, IH); 6.87-6.94 (m, 2H); 7.19 (t, IH, \( J = 8.4 \) Hz); 7.49 (t, IH, \( J = 8.7 \) Hz); 7.70 (d, IH, \( J = 8.4 \) Hz); 7.85 (d, IH, \( J = 7.8 \) Hz); 8.42 (s, IH); 9.08 (s, IH).
IR (KBr) (cm⁻¹): 3348, 2939, 1744, 1620, 1555, 1421, 1270, 1187, 1053, 999, 761.

(±)-1-(1-ethoxycarbonyl-6-fluoro-1H-indazol-4-yl)-3-(3,4-dihydropirrolochromene-2,1'-cyclobutan)-4-yl)urea (Compound No. 23)

STEP 1: 5-fluoro-2-methyl-1,3-dinitrobenzene

Fuming sulphuric acid (7.2 mL) was added dropwise to 4-fluoro-2-nitrotoluene (13.4 mmol) at 0-5°C. A mixture of fuming nitric acid (1.2 mL) and fuming sulphuric acid (3.6 mL) was added dropwise to the above mixture over 1 h. The reaction was then allowed to warm to room temperature. After stirring for 3 h, the mixture was poured on ice slowly and the product was extracted in methylene chloride, dried over sodium sulphate, and filtered, and the solvent was evaporated. The crude product was purified by column chromatography.

1H NMR (DMSO-d6): δ 1.42 (t, 3H, J = 7.5 Hz); 4.52 (q, 2H, J = 7.5 Hz); 8.28-8.35 (m, 1H).

STEP 2: 5-fluoro-2-methyl-3-nitroaniline

To the stirred solution of 5-fluoro-2-methyl-1,3-dinitrobenzene (2 mmol) in ethanol (20 mL), pyridine (10 mmol) was added and refluxed. A 20% solution of ammonium sulhide (30 mmol) was further diluted with 4 mL of water added to refluxing mixture over 1 h. After addition, the reflux was continued for 2 h and then cooled to room temperature. The reaction mixture was poured into a 1:1 mixture of water and ice. The solid product was filtered and dried under vacuum.

1H NMR (CDCl3): δ 2.19 (s, 3H); 4.02 (bs, 2H); 6.55 (d, IH, J = 9.6 Hz); 6.87 (d, IH, J = 8.4 Hz).

STEP 3: 6-fluoro-4-nitro-1H-indazole

To the stirred solution of 5-fluoro-2-methyl-3-nitroaniline (1.4 mmol) in acetic acid was added sodium nitrate (3.2 mmol) at 4°C. The mixture was allowed to warm to room temperature and stirred overnight. The solvent was removed under reduced pressure. The residue was treated with water and filtered.

1H NMR (DMSO-d6): δ 7.96 (d, 1H, J = 7.8 Hz); 8.06 (d, IH, J = 9.3 Hz); 8.52 (s, IH); 13.94 (s, IH).

STEP 4: Ethyl 6-fluoro-4-nitro-1H-indazole-1-carboxylate

6-fluoro-4-nitro-1H-indazole (0.89 mmol) was treated with sodium hydride (1.1 mmol) in DMF at 0°C. The mixture was allowed to warm to room temperature and stirred for 1 h. The mixture was treated with ethyl chloroformate (1.1 mmol) and stirred at room temperature for 3 h. Water was added, and the solution was filtered to obtain a solid product.

1H NMR (DMSO-d6): δ 1.42 (t, 3H, J = 7.5 Hz); 4.52 (q, 2H, J = 7.5 Hz); 8.28-8.35
STEP 5: Ethyl 4-amino-6-fluoro-1H-indazole-1-carboxylate

To a stirred solution of ethyl 6-fluoro-4-nitro-1H-indazole-1-carboxylate (2.76 mmol) in ethanol, was added (50% w/w) of Pd/C, and the reaction mixture was subjected to hydrogenation at 10 psi for 4 hrs. The reaction mixture was filtered to remove the catalyst, and the filtrate was concentrated to obtain the desired product.

STEP 6: Ethyl 6-fluoro-1H-indazol-4-yl)urea

To a stirred solution of Ethyl 4-amino-6-fluoro-1H-indazole-1-carboxylate (2 mmol) in DCM, was added phenyl chloroformate (4 mmol) and pyridine (2 mmol). The reaction mixture was stirred for 3 hrs at room temperature. Water was added to the reaction mixture and extracted with dichloromethane. The organic layer was then dried over Na$_2$SO$_4$ and concentrated to obtain a crude product, which was purified by column chromatography.

$^1$H NMR (DMSO-$d_6$): $\delta$ 1.24 (t, 3H, $J$ = 6.3 Hz); 4.11 (q, 2H, $J$ = 7.2 Hz); 7.08- 7.21 (m, 5H); 7.37- 7.40 (m, 2H); 9.04 (s, IH); 9.63 (bs, IH).

STEP 7: 1-(1-ethoxycarbonyl-6-fluoro-1H-indazol-4-yl) -3-(3,4-dihydrospiro [chromene-2,1'-cyclobutan]-4-yl)urea

This compound was prepared by using the same procedure described in example 1 using ethyl 6-fluoro-4-[(phenoxycarbonyl)amino]-1H-indene-1-carboxylate and 3,4-dihydrospiro[chromene-2,1'-cyclobutan]-4-yl)urea.

$^1$H NMR (DMSO-$d_6$): $\delta$ 1.39 (t, 3H, $J$ = 6.9 Hz); 1.82- 2.45 (m, 8H); 4.48 (q, 2H, $J$ = 7.2 Hz); 4.9 (m, IH); 6.75- 6.91 (m, 3H); 7.05- 7.23 (m, 3H): 7.68 (d, IH, $J$ = 12 Hz); 7.87 (s, IH); 8.98 (s, IH).

(±)-1-(1-benzyl-6-pyrrolidin-2-one-1H-indazol-4-yl) -3-(3,4-dihydrospiro [chromene-2,1'-cyclobutan]-4-yl)urea (Compound No. 25)

STEP 1: 5-iodo-2-methyl-1,3-dinitrobenzene

To a well-stirred solution of 2,6-dinitro toluene (2.7 mmol) in 1,1,1-trifluoroacetic anhydride (1.2 mL) was added slowly N-iodo succinimide (2.7 mmol). The reaction mixture was then stirred for 15-17 hrs at room temperature. The reaction mixture was then diluted with a 1% solution of sodium metabisulfite in water and extracted with ethyl acetate. The organic layer was washed with water, dried over anhydrous sodium sulfate and concentrated under vacuum to obtain a crude product. The crude product was then purified through a silica gel column using ethyl acetate in petroleum ether as the eluent to yield 400 mg of the desired product.

$^1$H NMR (CDCl$_3$): 2.34 (s, 3H); 8.55 (m, 2H).
STEP 2: 5-iodo-2-methyl-3-nitroaniline
To a solution of 5-iodo-2-methyl-1,3-dinitrobenzene (3.8 mmol) and pyridine (19.1 mmol) in ethanol (10.0 mL) was added ammonium sulfide (40-45%) (57.0 mmol). The mixture was refluxed at reflux temperature. Reflux was continued for 2-3 hours. The reaction mixture was then cooled to room temperature and diluted with water. A yellow solid separated and was filtered off and dried to obtain 300 mg of the desired product.

$^1$H NMR (DMSO-$d_6$): δ 52.00 (s, 3H); 5.75 (s, 2H); 7.20 (m, 2H).

STEP 3: 6-iodo-4-nitro-1H-indazole
To the stirred solution of 5-iodo-2-methyl-3-nitroaniline (1.2 mmol) in acetic acid was added sodium nitrate (1.2 mmol) at 4°C. The mixture was allowed to warm to room temperature and stirred overnight. The solvent was removed under reduced pressure. The residue was treated with water and filtered to obtain the desired product in crude form.

$^1$H NMR (DMSO-$d_6$): δ 8.27 (s, 1H); 8.47 (m, 2H); 13.91 (s, 1H).

STEP 4: 1-benzyl-6-iodo-4-nitro-1H-indazole
To a well-stirred suspension of 6-iodo-4-nitro-1H-indazole (1.0 mmol) and anhydrous potassium carbonate (2.0 mmol) in DMF was added benzyl bromide (1.1 mmol), which was heated to 70-80°C for 2-3 hours. The usual work up was carried out, and the crude product was column purified to obtain 200 mg of the desired product.

$^1$H NMR (DMSO-$d_6$): δ 5.55 (s, 2H); 7.24-7.43 (m, 5H); 8.65 (s, 1H); 8.77 (s, 1H); 9.21 (s, 1H).

STEP 5: 1-(T-benzyl-4-nitro-1H-indazol-6-yl)pyrrolidin-2-one
A well-stirred suspension of 1-benzyl-6-iodo-4-nitro-1H-indazole (0.5 mmol), anhydrous potassium carbonate (0.75 mmol) and copper powder (0.75 mmol) in DMF was added 2-pyrrolidinone (0.75 mmol), which was heated to 130-150°C for 10-12 hours. The reaction mixture was then cooled to room temperature and diluted with water. It was then extracted with ethyl acetate. The combined organic layers were washed with water and dried over anhydrous sodium sulfate. The crude product obtained after removal of the solvent was purified through a silica gel column to afford 150 mg of the pure desired product.

$^1$H NMR (DMSO-$d_6$): δ 2.12 (m, 2H); 2.61 (m, 2H); 3.97 (m, 2H); 5.77 (s, 2H); 7.25 (m, 5H); 8.21 (s, 1H); 8.48 (s, 1H); 8.89 (s, 1H).

STEP 6: 1-(4-amino-1-benzyl-1H-indazol-6-yl)pyrrolidin-2-one
To a stirred solution of 1-(1-benzyl-4-nitro-1H-indazol-6-yl)pyrrolidin-2-one (0.44 mmol) in methanol, was added a catalytic amount of Raney Ni catalyst, and the reaction mixture was
subjected to hydrogenation at 60 psi for 2-3 hrs. The reaction mixture was filtered to remove
the catalyst, and the filtrate was concentrated to yield 100 mg of the desired product.

\[^1\text{H NMR (DMSO-} d_6\text{):} \delta 2.30 \text{ (m, 2H); 2.88 (m, 2H); 3.79 (m, 2H); 5.46 (m, 2H); 6.68 (s, IH); 6.88 (s, IH); 7.13 (s, IH); 7.24 (m, 5H); 8.20 (s, 2H).}\]

STEP 7: (±)-1-(1-benzyl-1H-indazol-6-yl)pyrrolidin-2-one -4-ylcarbamate

This compound was prepared by reacting (4-amino-1-benzyl-1H-indazol-6-yl) pyrrolidin-2-one (0.35 mmol) with phenyl chloroformate (0.5 mmol) in the presence of pyridine in THF. The crude compound obtained after the usual work up was used for the next step without further purification.

STEP 8: (±)-1-(1-benzyl-1H-indazol-6-yl)pyrrolidin-2-one -1H-indazoM-νD -3-(3,4-dihydrospirochromene-2, l'-cyclobutan] -4-yl)urea.

This compound was prepared by using the same procedure described in example 1 using phenyl [1-(1-benzyl-1H-indazol-6-yl)pyrrolidin-2-one]-4-ylcarbamate (0.3 mmol) and 3,4-dihydro spiro[chromene-2,l'-cyclobutan]-4-amine (0.3 mmol).

\[^1\text{H NMR (DMSO-} d_6\text{):} \delta 1.08 \text{ (t, 3H, J = 6.9 Hz); 1.75 \text{ (m, 2H); 3.38 (m, 2H); 3.86 (m, 2H); 4.99 (m, IH); 5.55 (m, 2H); 6.79 (m, 2H); 6.90 (t, IH); 7.14 \text{ - 7.26 (m, 7H); 7.51 (s, IH); 8.05 (m, 2H); 8.78 (s, IH).}\]

MS [M+] 522.03

(+)-1-d-ethoxycarbonyl-6-fluoro-1H-indazoM-vD -3-(3,4-dihydrospirochromene-2,r-cyclobutan1-4-y0urea (Compound No. 26)

This compound was prepared by using the same procedure described in example 1 using ethyl 6-fluoro-4-[(phenoxy carbonyl)amino]-1H-indene-1-carboxylate and (+) 3,4-dihydro spiro[chromene-2,l'-cyclobutan]-4-amine.

\[^1\text{H NMR (DMSO-} d_6\text{):} \delta 1.40 \text{ (t, 3H, J = 6.9 Hz); 1.72 \text{ - 2.41 (m, 8H); 4.48 (q, 2H, J = 7.2 Hz); 5.00 (m, IH); 6.77 \text{ - 6.91 (m, 3H); 7.15 (t, IH, J = 7.2 Hz); 7.20 (d, IH, J = 7.2 Hz); 7.38 (d, IH, J = 9.3 Hz); 7.86 (dd, IH, J = 13.8 Hz); 8.37 (s, IH); 9.23 (s, IH).}\]

(±)-1-π -ethoxycarbonyl-6-methoxy-1H-indazoM-y1 ) -3-(3,4-dihydrospiro [chromene -2.1'-cyclobutan1-4-y]urea (Compound No. 28)

STEP 1: 5-methoxy-2-methyl-1,3-dinitrobenzene

To the stirred solution of 5-fluoro-2-methyl-1,3-dinitrobenzene (3 mmol) was added dropwise a solution of freshly prepared sodium methoxide (Na metal 90 mg + MeOH 10 mL ) at room temperature. After 2 h of reflux, the solution was concentrated to a small volume and filtered.
**U NMR** (CDCl₃): δ 2.47 (s, 3H); 3.90 (s, 3H); 7.49 (s, 2H).

**STEP 2:** 5-methoxy-2-methyl-3-nitroaniline

This compound was prepared by same procedure described in example 21, step 2.

**U NMR** (DMSO-ck): δ 2.49 (s, 3H); 3.68 (s, 3H); 5.53 (s, 2H); 6.45 (s, IH), 6.52 (d, IH).

**STEP 3:** 6-methoxy-4-nitro-1H-indazole

This compound was prepared by same procedure described in example 21, step 3.

**H NMR** (DMSO- d₆): δ 3.92 (s, 3H); 7.46 (s, IH); 7.69 (s, IH), 8.38 (s, IH); 13.63 (s, IH).

**STEP 4:** Ethyl 6-methoxy-4-nitro-1H-indazole-1-carboxylate

This compound was prepared by same procedure described in example 21, step 4.

**U NMR** (DMSO- d₆): δ \( \Lambda \) 2 (t, 3H, \( J = 6.9 \) Hz); 3.98 (s, 3H); 4.52 (q, 2H, \( J = 6.9 \) Hz); 7.86 (s, IH); 7.99 (s, IH), 8.69 (s, IH).

**STEP 5:** Ethyl 4-amino-6-methoxy-1H-indazole-1-carboxylate

This compound was prepared by same procedure described in example 21, step 5.

**H NMR** (DMSO- d₆): \( \chi \) 1.37 (t, 3H, \( J = 6.6 \) Hz); 3.73 (s, 3H); 4.41 (q, 2H, \( J = 6.6 \) Hz); 6.01 (s, IH); 6.11 (s, 2H), 6.77 (s, IH), 7.29 (s, IH).

**STEP 6:** Ethyl 6-methoxy-4-[(phenoxy carbonyl)amino]-1H-indazole-1-carboxylate

This compound was prepared by same procedure described in example 21, step 6.

**H NMR** (DMSO- d₆): \( \delta \) 1.39 (t, 3H, \( J = 5.7 \) Hz); 3.83 (s, 3H); 4.47 (q, 2H, \( J = 7.2 \) Hz); 7.26-7.46 (m, 7H); 8.64 (s, IH), 10.69 (bs, IH).

**STEP 7:** \( \pm \) 1-d-ethoxy carbonyl-6-methoxy-1H-indazol-4-yl-3-G.4-dihydrospiro[chromene-2, 1'-cyclobutan]-4-yl]urea

This compound was prepared by using the same procedure described in example 1 using ethyl 6-methoxy-4-[(phenoxy carbonyl)amino]-1H-indazole-1-carboxylate and 3,4-dihydro spiro[chromene-2,1'-cyclobutan]-4-amine.

**H NMR** (DMSO- d₆): \( \delta \) 1.39 (t, 3H, \( J = 6.9 \) Hz); 1.82-2.45 (m, 8H); 4.48 (q, 2H, \( J = 7.2 \) Hz); 4.9 (m, IH); 6.75-6.91 (m, 3H); 7.05-7.23 (m, 3H); 7.68 (d, IH, \( J = 12 \) Hz); 7.87 (s, IH); 8.98 (s, IH).

**STEP 8:** \( \pm \) 1-(6,8-difluoro-3,4-dihydrospiro[chromene-2, 1'-cyclobutan]-4-yl)-3-(1-ethoxycarbonyl-1H-indazol-4-yl]urea (Compound No. 30)

This compound was prepared by using the same procedure described in example 1 using phenyl (1-ethoxycarbonyl-1H-indazol-4-yl) carbamate (1 mmol) and \( \pm \) 6,8-difluoro-S'-dihydrospirotchromene-S'-cyclobutan-S'-amine (lmmol)
\[ ^1H \text{NMR (DMSO-}d_6): \delta \ 1.4 \ (t, \ 3H, J = 6.9 \text{ Hz}); \ 1.77-2.44 \ (m, \ 8H) \]; 4.48 \ (q, \ 2H, J = 6.3 \text{ Hz}); \ 5.00 \ (m, \ 1H) \; 6.84- \ 7.2 \ (m, \ 2H) \]; 7.19 \ (t, \ 1H) \; 7.49 \ (t, \ 1H, J = 7.8 \text{ Hz}); \ 7.70 \ (d, \ 1H, J = 7.8 \text{ Hz}); \ 7.85 \ (d, \ 1H, J = 8.4 \text{ Hz}); \ 8.42 \ (s, \ 1H); \ 9.05 \ (s, \ 1H). \]

MS [M+1]^+ \ 457.24

(-) 1-(6,8-difluoro-3,4-dihydropyrrolo[chromene-2, \ 1'-cyclobutan]-4-yl)-3-(1-ethoxycarbonyl-1H-indazol-4-yl)-urea (Compound No. 32)

This compound was prepared by using the same procedure described in example 1 using phenyl (1-ethoxycarbonyl-1H-indazol-4-yl) carbamate (1 mmol) and (-) 6,8-difluoro-S^-dihydropyrrolo[chromene]-J'-cyclobutanJ^-amine (1mmol)

\[ ^1H \text{NMR (DMSO-}d_6): \delta \ 1.4 \ (t, \ 3H, J = 7.2 \text{ Hz}); \ 1.74-2.49 \ (m, \ 8H) \]; 4.48 \ (q, \ 2H, J = 7.2 \text{ Hz}); \ 5.02 \ (m, \ 1H) \; 6.84- \ 6.94 \ (m, \ 2H) \]; 7.19 \ (t, \ 1H) \; 7.49 \ (t, \ 1H, J = 8.1 \text{ Hz}); \ 7.70 \ (d, \ 1H, J = 8.1 \text{ Hz}); \ 7.85 \ (d, \ 1H, J = 7.8 \text{ Hz}); \ 8.42 \ (s, \ 1H); \ 9.05 \ (s, \ 1H).

(±) 1-(6-pyrroloidin-2-one-1-ethoxycarbonyl-1H-indazol-4-yl)-3-(3,4-dihydropyrrolo[chromene-2, \ 1'-cyclobutan]-4-yl)urea (Compound No. 34)

STEP 1: 1-(4-nitro-1H-indazol-6-yl)pyrroloidin-2-one
To the stirred solution of 6-iodo-4-nitro-1H-indazole (1 mmol) and pyrroloidin-2-one (1.5 mmol) and potassium phosphate (2 mmol) in toluene was added CuI (0.5 mmol) and dimethyl ethylene diamine (2 mmol), which was then heated at 80°C for 1-2 h. Water was added and extracted with ethyl acetate. The product was purified by column chromatography.

\[ ^1H \text{NMR (DMSO-}d_6): \delta \ 2.09- \ 2.26 \ (m, \ 2H); \ 2.56 - \ 2.72 \ (m, \ 2H); \ 3.97 - \ 4.07 \ (m, \ 2H); \ 8.15 \ (s, \ 1H); \ 8.45 \ (s, \ 1H); \ 8.82 \ (s, \ 1H); \ 13.76 \ (bs, \ 1H) \]

STEP 2: Ethyl 4-nitro-6-(2-oxypyrroloidin-1-yl)-1H-indazole-1-carboxylate
This compound was prepared by the procedure described in example 21, step 4 using 1-(4-nitro-1H-indazol-6-yl)pyrroloidin-2-one.

\[ ^1H \text{NMR (DMSO-}d_6): \delta \ 1.43 \ (t, \ 1H, J = 6.9 \text{ Hz}); \ 3.20 - \ 3.23 \ (m, \ 2H); \ 3.40 \ (m, \ 2H); \ 3.85 \ (m, \ 2H); \ 4.52 \ (q, \ 1H, J = 7.2 \text{ Hz}); \ 8.22 \ (s, \ 1H); \ 8.43 \ (s, \ 1H); \ 8.73 \ (s, \ 1H). \]

STEP 3: Ethyl 4-amino-6-(2-oxypyrroloidin-1-yl)1H-indazole-1-carboxylate
This compound was prepared by the procedure described in example 21, step 5 using ethyl 4-nitro-6-(2-oxypyrroloidin-1-yl)-1H-indazole-1-carboxylate.

\[ ^1H \text{NMR (DMSO-}d_6): \delta \ 1.37 \ (t, \ 1H, J = 7.2 \text{ Hz}); \ 2.05 \ (m, \ 2H); \ 3.40 \ (m, \ 4H); \ 3.82 \ (m, \ 2H); \ 4.42 \ (q, \ 1H, J = 7.5 \text{ Hz}); \ 6.87 \ (s, \ 1H); \ 7.51 \ (s, \ 1H); \ 8.36 \ (s, \ 1H). \]
STEP 4: Ethyl 6-(2-oxopyrrolidin-1-yl)-4-[(phenoxycarbonyl)amino]-1H-indazole-1-carboxylate

This compound was prepared by the procedure described in example 21, step 6 using ethyl 4-amino-6-(2-oxopyrrolidin-1-yl)-1H-indazole-1-carboxylate.

STEP 5: (±)-l-(6-pyrrolidin-1-ethoxycarbonyl-1H-indazol-4-yl)-3-G.4-dihydrospiro[chromene-2,1'-cyclobutane]-4-yl)urea.

This compound was prepared by the procedure described in example 21, step 7 using ethyl 6-(2-oxopyrrolidin-1-yl)-4-[(phenoxycarbonyl)amino]-1H-indazole-1-carboxylate.

$^1$H NMR (DMSO-$d_6$): δ 1.40 (t, 3H, $J = 7.2$ Hz); 1.72-2.57 (m, 10H); 3.38 (m, 2H); 3.89 (t, 2H); 4.48 (q, 2H, $J = 7.2$ Hz); 4.98 (m, 1H); 6.74-6.80 (m, 2H); 6.89 (t, $J = 7.5$ Hz); 7.15 (t, $J = 7.5$ Hz); 7.26 (d, $J = 7.2$ Hz); 8.18 (m, 2H); 8.32 (s, 1H); 9.01 (s, 1H).

Example 2: Preparation of (±)-1-(3,4-dihydrospiro[chromene-2,1'-cyclobutane]-4-yl)-3-(1H-indazol-4-yl)urea (Compound No. 2)

A mixture of 1-(3,4-dihydrospiro[chromene-2,1'-cyclobutane]-4-yl)-3-(1-ethoxycarbonyl-1H-indazol-4-yl)urea (1 mmol) and sodium hydroxide (2.8 mmol) in a mixture of methanol and tetrahydrofuran was stirred at room temperature for approximately 4-5 hours. The crude product was obtained after work up and extraction with ethyl acetate. The resulting compound was purified using silica gel column chromatography to provide the desired product as a buff colored solid.

$^1$H NMR (DMSO-$d_6$): δ 1.76-2.44 (m, 8H); 5.01 (m, 1H); 6.80 (IH, t, $J = 7.5$ Hz); 6.79 (2H, m); 6.91 (IH, t, $J = 7.8$ Hz); 7.07-7.29 (4H, m); 7.71 (IH, d, $J = 7.8$ Hz); 8.06 (IH, s); 8.71 (IH, s); 13.04 (IH, s). IR (KBr) (cm$^{-1}$): 3316, 2925, 1627, 1566, 1455, 1371, 1232, 1158, 951, 768. MS (M$^{+}$+): 349.5

The following compounds were prepared by following the procedure described for Example 2:

(-)-l-(3,4-dihydrospiro[chromene-2,1'-cyclobutane]-4-yl)-3-(1H-indazol-4-yl)urea (Compound No. 4)
This was prepared using (S)-l-(3,4-dihydrospiro[chromene-2,r-cyclobutan]-4-yl)-3-(l-ethoxycarbonyl- lH-indazol-4-yl)urea.

\[ \text{1H NMR (DMSO-} \text{d}_6\text{)}: \delta 1.75-2.42 \ (8H, m); \ 4.97 \ (IH, m); \ 6.77 \ (IH, t, J = 10.2 \ Hz); \ 6.89 \ (IH, t, J = 7.5 \ Hz); \ 7.05 \ (IH, d, J = 8.7 \ Hz); \ 7.12-7.27 \ (3H, m); \ 7.68 \ (IH, d, J = 7.2 \ Hz); \ 8.04 \ (IH, s); \ 8.69 \ (IH, s); \ 13.00 \ (IH, s). \]

M S [(M-\text{I})+ : 349.5. \ M.P.: > 250^\circ \text{C.}]

(+) 1-(3,4-dihydrospiro [chromene-2, 1'-cyclobutan] -4-V-3-( lH-indazol-4-yl)urea

(Compound No. 6)

This was prepared using (+)-l-(3,4-dihydrospiro[chromene-2,1'-cyclobutan]-4-yl)-3-(l-ethoxycarbonyl- lH-indazol-4-yl)urea.

\[ \text{1H NMR (DMSO-} \text{d}_6\text{)}: \delta 1.71-2.43 \ (8H, m); \ 4.99 \ (IH, m); \ 6.77 \ (IH, t, J = 10.2 \ Hz); \ 6.89 \ (IH, t, J = 7.5 \ Hz); \ 7.05 \ (IH, d, J = 8.7 \ Hz); \ 7.12-7.27 \ (3H, m); \ 7.68 \ (IH, d, J = 7.2 \ Hz); \ 8.03 \ (IH, s); \ 8.69 \ (IH, s); \ 13.00 \ (IH, s). \]

IR (KBr) (cm\(^{-1}\)): 3315, 2930, 2927, 1627, 1565, 1451, 1378, 1236, 1162, 959, 768. M S [(M+\text{I})^+ : 349.5. \ M.P.: 187-189^\circ \text{C.}]

(±)-1-(6-fluoro-3,4-dihydrospiro [chromene-2, 1-cyclobutan] -4-V-3-( lH-indazol-4-yl)urea

(Compound No. 8)

This was prepared using (±)-1-(6-fluoro-3,4-dihydrospiro[chromene-2, 1'-cyclobutan]-4-yl)-3-(1-ethoxycarbonyl-lH-indazol-4-yl)urea.

\[ \text{1H NMR (DMSO-} \text{d}_6\text{)}: \delta 1.72- 2.40 \ (m, 8H); \ 4.96 \ (m, IH); \ 6.82 \ (m, 2H); \ 7.00 - 7.08 \ (m, 3H); \ 7.21 \ (t, IH, J = 7.8 \ Hz); \ 7.66 \ (d, IH, J = 7.5 \ Hz); \ 8.05 \ (s, IH); \ 8.74 \ (s, IH); \ 13.01 \ (s, IH). \]

IR (KBr) (cm\(^{-1}\)): 3309, 2936, 1636, 1565, 1487, 1373, 1241, 1170, 944, 779.

Cf-4V- (7-fluoro-3,4-dihydrospiro[chromene-2, r-cyclobutan1-4-yl]-3-( lH-indazol-4-yl)urea

(Compound No. 10)

This compound was prepared by using the same procedure described in example 2 using (±)-1-(7-fluoro-3,4-dihydrospiro[chromene-2, r-cyclobutan]-4-yl)-3-(1-ethoxycarbonyl-lH-indazol-4-yl)urea (1 mmol).

\[ \text{1H NMR (DMSO-} \text{d}_6\text{)}: \delta 1.72 - 2.43 \ (m, 8H); \ 4.94 \ (m, IH); \ 6.65 \ (d, IH, J = 10.2 \ Hz); \ 6.74 \ (s, IH); \ 6.77 \ (s, IH); \ 7.06 \ (t, IH, J = 8.1 \ Hz); \ 7.18 - 7.31 \ (m, 2H); \ 7.67 \ (d, IH, J = 7.2 \ Hz); \ 8.04 \ (s, IH); \ 8.72 \ (s, IH); \ 13.00 \ (s, IH). \]

IR (KBr) (cm\(^{-1}\)): 3312, 2935, 1732, 1629, 1595, 1567, 1498, 1428, 1371, 1308, 1272, 1242, 1138, 1117, 990, 951, 850, 774.

M S [(M-I)+ : 365.6. \ M.P. - > 250^\circ \text{C.}]

- 34 -
(±VI-ô^-difluoro-S^-dihydrospirorchromene^-y1VS-d^-H-indazol^-)

vPurea (Compound No. 12)

This compound was prepared by using the same procedure described in example 2 using 1-(6,8-difluoro-3,4-dihydrospiro[chromene-2,r-cyclobutan]-4-yl)-3-(1-ethoxycarbonyl-1^-H^-indazol-4-yl)urea.

1H NMR (CDCl₃): δ 1.72 - 2.33 (m, 8H); 5.00 (m, IH); 6.91 (m, 2H); 7.08 (d, IH, J = 9 Hz); 7.20 (m, 2H); 7.65 (d, IH, J = 7.5 Hz); 8.07 (s, IH); 8.82 (s, IH); 13.00 (s, IH).

IR (KBr) (cm⁻¹): 3309, 2938, 1632, 1603, 1562, 1483, 1373, 1269, 1228, 1169, 1114, 949, 853, 777.

MS [M+I] + 385.53 M.P. - 200 - 203°C

(±)-l-d H-indazol-4-yl)-3-(7-methoxy-3,4-dihydrospiro[chromene-2,r-cyclobutan]-4-yl)urea

(Compound No. 18)

This compound was prepared by using the same procedure described in example 2 using (±)-1-(1-ethoxycarbonyl- ^H^-indazol-4-yl)-3-(7-methoxy-3,4-dihydrospiro[chromene-2, l^-cyclobutan]^-4-yl)urea.

1H NMR (DMSO- d₆): δ 1.82-2.35 (m, 8H); 3.69 (s, 3H); 4.89 (m, IH); 6.35 (s, IH); 6.50 (d, IH, J = 8.4 Hz); 6.73 (d, IH, J = 8.1Hz); 7.05 (d, IH, J = 7.8 Hz); 7.13- 7.20 (m, 2H); 7.68 (d, IH, J = 8.4 Hz); 8.04 (s, IH); 8.71 (s, IH); 12.98 (s, IH).

IR (KBr) (cm⁻¹): 3311, 2941, 1628, 1560, 1504, 1422, 1312, 1271, 1201, 1163, 1036, 949, 839, 775.

MS [M-I] + 377.81 M.P. 249 - 251°C
This compound was prepared by using the same procedure described in example 2 using (±)-l-(1-ethoxycarbonyl-1H-indazol-4-yl)-3-(7-chloro-3,4-dihydrospiro[chromene-2,1'-cyclobutan]-4-yl)urea.

\[ \delta \text{ H NMR (CDCl}_3\text{):} \begin{align*} &1.72-2.44 \text{ (m, 8H)}; \\ &4.95 \text{ (m, IH)}; \\ &6.77 \text{ (d, IH, } J = 8.4 \text{ Hz)}; \\ &6.87 \text{ (s, IH)}; \\ &6.95 \text{ (d, IH, } J = 8.4 \text{ Hz)}; \\ &7.07 \text{ (d, IH, } J = 7.8 \text{ Hz)}; \\ &7.15-7.28 \text{ (m, 2H)}; \\ &7.67 \text{ (d, IH, } J = 7.8 \text{ Hz)}; \\ &8.05 \text{ (s, IH)}; \\ &8.73 \text{ (s, IH)}; \\ &13.00 \text{ (s, IH).} \end{align*} \]

IR (KBr) (cm\(^{-1}\)): 3312, 2941, 1629, 1566, 1484, 1412, 1308, 1229, 1087, 951, 774.

MS [M+1]: 383

M.P. 261 - 262 °C

This compound was prepared by using the same procedure described in example 2 using (±)-l-(1-ethoxycarbonyl-1H-indazol-4-yl)-3-(3,4-dihydrospiro[chromene-2,1'-cyclobutan]-4-yl)urea.

\[ \delta \text{ H NMR (DMSO-} d_6\text{):} \begin{align*} &1.86 \text{ (m, 4H)}; \\ &2.14 \text{ (m, 4H)}; \\ &4.99 \text{ (m, IH)}; \\ &6.77 - 6.89 \text{ (m, 2H)}; \\ &7.26 \text{ (m, 4H)}; \\ &7.62 \text{ (d, IH)}; \\ &8.04 \text{ (s, IH)}; \\ &8.72 \text{ (s, IH)}; \\ &13.06 \text{ (s, IH).} \end{align*} \]

IR (KBr) (cm\(^{-1}\)): 3323, 2925, 1633, 1564, 1483, 1427, 1304, 1238, 1074, 948, 751.

MS [M+1]: 427

M.P. 261 - 262 °C

This compound was prepared by using the same procedure described in example 2 using (±)-l-(1-ethoxycarbonyl-6-fluoro-1H-indazol-4-yl)-3-(3,4-dihydrospiro[chromene-2,1'-cyclobutan]-4-yl)urea.

\[ \delta \text{ H NMR (DMSO-} d_6\text{):} \begin{align*} &1.71-2.43 \text{ (m, 8H)}; \\ &4.97 \text{ (m, IH)}; \\ &6.84 \text{ (m, 4H)}; \\ &7.16-7.25 \text{ (m, 2H)}; \\ &7.62 \text{ (d, IH)}; \\ &8.04 \text{ (s, IH)}; \\ &8.96 \text{ (s, IH)}; \\ &13.06 \text{ (s, IH).} \end{align*} \]

MS [M-IV]: 365.47.
(+)-1-(6,8-difluoro-3,4-dihydrospiro[chromene-2,1'-cyclobutan]-4-yl)-3-(1H-indazol-4-yl)urea (Compound No. 14)

This compound was prepared by using the same procedure described in example 2 using (+)-1-(6,8-difluoro-3,4-dihydrospiro[chromene-2,1'-cyclobutan]-4-yl)-3-(1-ethoxycarbonyl-1H-indazol-4-yl)urea.

\[ ^1H \text{NMR (CDCl}_3): \delta \ 1.73-2.49 (m, 8H); 4.99 (m, 1H); 6.83-6.93 (2x d, 2H); 7.07 (d, 1H, J = 9 Hz); 7.09-7.24 (m, 2H); 7.66 (d, 1H, J = 7.5 Hz); 8.06 (s, 1H); 8.77 (s, 1H). \]

IR (KBr) (cm\(^{-1}\)): 3304, 2933, 1630, 1607, 1564, 1479, 1377, 1270, 1224, 1167, 1112, 951, 860, 778.

MS [M+H] \(^{+}\) : 385.53 M.P. -219 -221°C

(+)-1-(3,4-dihydrospiro[chromene-2J'-cyclobutan]-4-yl)-3-(6-fluoro-1H-indazol-4-yl)urea (Compound No. 27)

This compound was prepared by using the same procedure described in example 2 using (+)-1-(1-ethoxycarbonyl-6-fluoro-1H-indazol-4-yl)-3-(3,4-dihydrospiro[chromene-2,1'-cyclobutan]-4-yl)urea and sodium hydroxide.

\[ ^1H \text{NMR (DMSO-} d_6): \delta \ 1.75-2.41 (m, 8H); 4.97 (m, 1H); 6.77-6.92 (m, 4H); 7.15 (t, 1H, J = 6.9 Hz); 7.25 (d, 1H, J = 7.8 Hz); 7.61 - 7.66 (dd, 1H); 8.03 (s, 1H); 8.93 (s, 1H); 13.06 (s, 1H). \]

IR (KBr) (cm\(^{-1}\)): 3337, 3249, 2936, 1642, 1559, 1484, 1313, 1276, 1232, 1197, 1135, 1081, 1038, 949, 834, 749.

MS [M-H]- : 365.17 M.P. -199 -201°C

(+)-1-(3,4-dihydrospiro[chromene-2J'-cyclobutan]-4-yl)-3-(6-methoxy-1H-indazol-4-yl)urea (Compound No. 29)

This compound was prepared by using the same procedure described in example 2 using (+)-1-(1-ethoxycarbonyl-6-methoxy-1H-indazol-4-yl)-3-(3,4-dihydrospiro[chromene-2,1'-cyclobutan]-4-yl)urea and sodium hydroxide.

\[ ^1H \text{NMR (CDCl}_3): \delta \ 1.6 - 2.4 (m, 8H); 3.77 (s, 3H); 5.00 (m, 1H); 6.48 (s, 1H); 6.77 (t, 1H, J = Hz); 6.89 (t, IH); 7.14 (t, IH); 7.25 (d, IH, J = Hz); 7.43 (s, IH); 7.90 (s, IH); 8.65 (s, IH); 12.76 (s, IH). \]

IR (KBr) (cm\(^{-1}\)): 3306, 2938, 1633, 1563, 1483, 1453, 1317, 1274, 1236, 1205, 1149, 1069, 947, 847, 754.
MS [M+H]^+ : -379.37  M.P. -243 - 244°C

(+)-(6,8-difluoro-3,4-dihydrospiro[chromene-2,r-cyclobutan]-4-yl)-3-(1H-indazol-4-yl)urea (Compound No. 30)

This compound was prepared by using the same procedure described in example 2 using (+)-(6,8-difluoro-3,4-dihydrospiro[chromene-2,r-cyclobutan]-4-yl)-3-(1-ethoxycarbonyl-1H-indazol-4-yl)urea(1mmol) and sodium hydroxide (2.8 mmol)

$^1$H NMR (DMSO- $d_6$): $\delta$ 1.74-2.49 (m, 8H); 4.98 (m, IH); 6.83-6.93 (m, 2H); 7.08 (d, IH, J = 7.8 Hz); 7.18-7.24 (m, 2H); 7.64 (d, IH, J = 7.8 Hz); 8.06 (s, IH); 8.76 (s, IH); 12.99 (s, IH)

M.P. - 219 - 221°C

(-)-(6,8-difluoro-3,4-dihydrospiro[chromene-2, 1'-cyclobutan]-4-yl)-3-(1H-indazol-4-yl)urea (Compound No. 33)

This compound was prepared by using the same procedure described in example 2 using (-)-(6,8-difluoro-3,4-dihydrospiro[chromene-2,1'-cyclobutan]-4-yl)-3-(1-ethoxycarbonyl-1H-indazol-4-yl)urea(1mmol) and sodium hydroxide (2.8 mmol)

$^1$H NMR (DMSO- $d_6$): $\delta$ 1.73-2.42 (m, 8H); 4.99 (m, IH); 6.83-6.93 (m, 2H); 7.08 (d, IH, J = 8.4 Hz); 7.15-7.24 (m, 2H); 7.65 (d, IH, J = 7.5 Hz); 8.06 (s, IH); 8.77 (s, IH); 13.00 (s, IH)

M.P. - 225 - 227°C

(±)-(6-pyrrolidin-2-one -1H-indazol-4-yl) -3-(3,4-dihydrospiro[chromene-2,1'-cyclobutan]-4-yl)urea (Compound No. 35)

To the stirred solution of (±)-(6-pyrrolidin-2-one-1-ethoxycarbonyl-1H-indazol-4-yl) -3-(3,4-dihydrospiro[chromene-2,1'-cyclobutan]-4-yl)urea in THF was added 5M NaOH/MeOH slowly at room temperature and stirred for 2 h. The solvent was evaporated, and the precipitate was dissolved in ethyl acetate. The product was washed with distilled water followed by a brine solution. The crude product was further purified by column chromatography.

$^1$H NMR (DMSO- $d_6$): $\delta$ 1.75-2.49 (m, 10H); 3.32 (m, 2H); 3.87 (m, 2H); 5.00 (m, IH); 6.74-6.80 (m, 2H); 6.89 (t, IH, J= 7.2 Hz); 7.14(t, IH, J= 7.2 Hz); 7.26 (d, IH, J= 6.32 Hz); 7.54 (s, IH); 7.94-7.98 (d, 2H); 8.75 (s, IH); 12.90 (s, IH)

M.P. - 244 - 245°C
Example 3: Screening for TRPV1 antagonist using the $^{45}$Ca 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:

Stock solutions of capsaicin were made in ethanol, and test compounds 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, MP Biomedicals, formerly ICN Biomedicals, Irvine, CAICN, ).

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-ALDRICH, St. Louis, MO).

Wash buffer was Tyrodes solution supplemented with 0.1% BSA and 1.8 mM calcium. Lysis buffer contained 50 mM Tris-HCl, pH 7.5, 150 mM NaCl, 1% Triton X-100, 0.5% deoxycholate and 0.1% Sodium dodecyl sulphate (SDS, SIGMA-ALDRICH, St. Louis, MO).

Method:

The assay was carried out with some modifications of the procedure 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, 400 µg/ml of G-418. Cells were seeded 48 h prior to the assay in 96 well plates so as to get ~ 50,000 cells per well on the day of experiment. Plates were incubated at 37°C in the presence of 5% CO$_2$. Cells were then washed twice with 200 µl of assay buffer and re-suspended in 144 µl of the same. Assays were carried out at 30°C in a total volume of 200 µl. Test compounds were added to the cells fifteen minutes before the addition of capsaicin. The final concentration of capsaicin used in the assay was 250 nM. After 5 minutes of agonist treatment, the drug was washed out and the wells were rinsed 3X with 300 µl of ice cold wash buffer. The cells were lysed in 50 µl of lysis buffer for 20 min. 40 µl of cell lysate was mixed with 150 µl of Microscint PS, and the mixture was left overnight for equilibration. Radioactivity in samples was measured as counts per minute (cpm) using a Packard Biosciences Top Count. The drug / vehicle / capsaicin treated $^{45}$Ca uptake values were normalized over basal $^{45}$Ca value. Data was expressed as % inhibition of $^{45}$Ca uptake by test
compound with respect to maximum $^{45}$Ca uptake induced by capsaicin alone. An IC$_{50}$ value was calculated from the dose response curve by nonlinear regression analysis using GraphPad PRISM software (GraphPad Software, Inc., San Diego, CA).

Results were expressed as IC$_{50}$ ranged from between about 0.9 nM to about 60 nM; from between about 0.9 nM to about 30 nM; from between about 0.9 nM to about 20 nM; from between about 0.9 nM to about 10 nM; from between about 0.9 nM to about 2.5 nM.

All references and patent publications cited herein are incorporated by reference in their entireties.
We Claim

1. A compound of Formula I

   or a pharmaceutically acceptable salt thereof, N-oxide thereof, or prodrug thereof, wherein:

   each occurrence of \( R^1 \), \( R^3 \) and \( R^4 \) is independently hydrogen, hydroxy, halogen, cyano, nitro, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted alkoxy, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted cycloalkenyl, substituted or unsubstituted cycloalkenylalkyl substituted or unsubstituted heterocyclyl, substituted or unsubstituted heterocyclylalkyl, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heteroarylalkyl, substituted or unsubstituted amino, COOR\( ^x \), C(O)R\( ^y \), C(S)R\( ^z \), C(0)NR\( ^x \)R\( ^y \), C(O)ONR\( ^x \)R\( ^y \), NR\( ^x \)CONR\( ^y \)R\( ^z \), N(R\( ^x \))SOR\( ^y \), N(R\( ^x \))SO\( ^y \)R\( ^z \), (=N-N(R\( ^x \))R\( ^y \)), NR\( ^x \)C(O)OR\( ^y \), NR\( ^x \)R\( ^y \), NR\( ^x \)C(O)R\( ^y \), NR\( ^x \)C(S)R\( ^y \), NR\( ^x \)C(S)NR\( ^y \)R\( ^z \), SONR\( ^y \)R\( ^z \), SO\( ^x \)NR\( ^x \)R\( ^y \), OR\( ^y \), OR\( ^y \)C(O)NR\( ^x \)R\( ^y \), OR\( ^y \)C(O)OR\( ^y \), OC(O)R\( ^y \), OC(O)NR\( ^x \)R\( ^y \), R\( ^y \)NR\( ^x \)C(O)R\( ^z \), R\( ^y \)OR\( ^y \), R\( ^y \)C(O)OR\( ^y \), R\( ^x \)C(0)NR\( ^y \)R\( ^z \), R\( ^x \)C(O)R\( ^y \), R\( ^y \)OC(O)R\( ^y \), SR\( ^x \), SOR\( ^y \)or SO\( ^y \)R\( ^z \);

   \( R^2 \) is hydrogen, alkoxy carbonyl, nitro, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted amino, substituted or unsubstituted heteroaryl, substituted or unsubstituted heterocyclyl, SONR\( ^y \)R\( ^y \), SO\( ^x \)NR\( ^x \)R\( ^y \), C(O)NR\( ^y \)R\( ^z \), SOR\( ^y \)or SO\( ^y \)R\( ^z \);

   \( m \) is 0, 1, 2, 3 or 4;

   \( n \) is 0, 1, 2 or 3; and

   each occurrence of \( R^x \), \( R^y \) and \( R^z \) is independently 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 cycloalkylalkyl, substituted or unsubstituted cycloalkenyl, substituted or unsubstituted cycloalkenylalkyl substituted or unsubstituted heterocyclyl, substituted or unsubstituted heterocyclylalkyl, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heteroarylalkyl, substituted or unsubstituted amino, COOR\( ^x \), C(O)R\( ^y \), C(S)R\( ^z \), C(0)NR\( ^x \)R\( ^y \), C(O)ONR\( ^x \)R\( ^y \), NR\( ^x \)CONR\( ^y \)R\( ^z \), N(R\( ^x \))SOR\( ^y \), N(R\( ^x \))SO\( ^y \)R\( ^z \), (=N-N(R\( ^x \))R\( ^y \)), NR\( ^x \)C(O)OR\( ^y \), NR\( ^x \)R\( ^y \), NR\( ^x \)C(O)R\( ^y \), NR\( ^x \)C(S)R\( ^y \), NR\( ^x \)C(S)NR\( ^y \)R\( ^z \), SONR\( ^y \)R\( ^z \), SO\( ^x \)NR\( ^x \)R\( ^y \), OR\( ^y \), OR\( ^y \)C(O)NR\( ^x \)R\( ^y \), OR\( ^y \)C(O)OR\( ^y \), OC(O)R\( ^y \), OC(O)NR\( ^x \)R\( ^y \), R\( ^y \)NR\( ^x \)C(O)R\( ^z \), R\( ^y \)OR\( ^y \), R\( ^y \)C(O)OR\( ^y \), R\( ^x \)C(0)NR\( ^y \)R\( ^z \), R\( ^x \)C(O)R\( ^y \), R\( ^y \)OC(O)R\( ^y \), SR\( ^x \), SOR\( ^y \)or SO\( ^y \)R\( ^z \);
cycloalkylalkyl, substituted or unsubstituted cycloalkenyl, substituted or unsubstituted amino, substituted or unsubstituted heteroaryl, substituted or unsubstituted heterocyclylalkyl, substituted or unsubstituted heteroaryllalkyl, or substituted or unsubstituted heterocyclyl.

2. A compound of claim 1, wherein R^1 is hydrogen, R^2 is selected from hydrogen, benzyl and ethoxycarbonyl, R^3 is selected from hydrogen, bromo, fluoro and pyrrolidin-2-one and R^4 is fluorine.

3. A compound of Formula II

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or a pharmaceutically acceptable salt thereof or N-oxide thereof, and prodrugs thereof, wherein:

each occurrence of R^1, R^3 and R^4 is independently hydrogen, hydroxy, halogen, cyano, nitro, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted alkoxy, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted cycloalkenyl, substituted or unsubstituted cycloalkenylalkyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted heterocyclylalkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heteroaryllalkyl, substituted or unsubstituted amino, COOR^X, C(O)R^Y, C(S)R^X, C(O)NR^R^Z, C(O)NR^2R^Z, NR^XCONR^YR^Z, N(R^3)SOR^Y, N(R^3)SO^2R^Y, (=N-N(R^3)R^Y), NR^X(C)(O)OR^Y, NR^X(R^Y), NR^X(C)(O)R^Y, NR^X(C)(S)R^Y, NR^X(C)(S)NR^YR^Z, SONR^YR^Z, SO^2NR^YR^Z, OR^X, OR^X(C)(O)NR^YR^Z, OR^X(C)(O)OR^Y, OC(O)R^Z, OC(O)NR^YR^Z, R^XNR^Y(C)(O)R^Z, R^XOR^Y, R^X(C)(O)OR^Y, R^X(C)(O)NR^YR^Z, R^X(C)(O)R^Y, R^XOC(O)R^Y, SR^X, SOR^X or SO^2R^X.

R^2 is hydrogen or alkoxy carbonyl;
m is 0, 1, 2, 3 or 4;

n is 0, 1, 2 or 3; and

each occurrence of R^3, R^Y and R^Z is independently hydrogen, 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 amino, substituted or unsubstituted heteroaryl, substituted or unsubstituted heterocyclylalkyl, substituted or unsubstituted heteroarylalkyl, or substituted or unsubstituted heterocyclyl.

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

(±) - 1-(3,4-dihydrospiro [chromene-2, 1'-cyclobutanol]-4-yl)-3-(1-ethoxycarbonyl-1H-indazol-4-yl)urea (Compound No. 1),

(±) - 1-(3,4-dihydrospiro [chromene-2, 1'-cyclobutanol]-4-yl)-3-(1H-indazol-4-yl)urea (Compound No. 2),

(±) - 1-(3,4-dihydrospiro [chromene-2, 1'-cyclobutanol]-4-yl)-3-(I-ethoxycarbonyl-1H-indazol-4-yl)urea (Compound No. 3)

(±) - 1-(3,4-dihydrospiro [chromene-2, 1'-cyclobutanol]-4-yl)-3-(1H-indazol-4-yl)urea (Compound No. 4),

(±) - 1-(3,4-dihydrospiro [chromene-2, 1'-cyclobutanol]-4-yl)-3-(1-ethoxycarbonyl-1H-indazol-4-yl)urea (Compound No. 5),

(±) - 1-(6-fluoro-3,4-dihydrospiro [chromene-2, r-cyclobutanol]-4-yl)-3-(1-ethoxycarbonyl-1H-indazol-4-yl)urea (Compound No. 7),

(±) - 1-(6-fluoro-3,4-dihydrospiro [chromene-2, r-cyclobutanol]-4-yl)-3-(1H-indazol-4-yl)urea (Compound No. 8),

(±) - 1-(7-fluoro-3,4-dihydrospiro [chromene-2, 1'-cyclobutanol]-4-yl)-3-(1-ethoxycarbonyl-1H-indazol-4-yl)urea (Compound No. 9),

(±) - 1-(7-fluoro-3,4-dihydrospiro [chromene-2, 1'-cyclobutanol]-4-yl)-3-(1H-indazol-4-yl)urea (Compound No. 10),

(±) - 1-(6,8-difluoro-3,4-dihydrospiro [chromene-2, 1'-cyclobutanol]-4-yl)-3-(1-ethoxycarbonyl-1H-indazol-4-yl)urea (Compound No. 11),

(±) - 1-(6,8-difluoro-3,4-dihydrospiro [chromene-2, 1'-cyclobutanol]-4-yl)-3-(1H-indazol-4-yl)urea (Compound No. 12),

(±) - 1-(6,8-difluoro-3,4-dihydrospiro [chromene-2, r-cyclobutanol]-4-yl)-3-(1-ethoxycarbonyl-1H-indazol-4-yl)urea (Compound No. 13),

(±) - 1-(6,8-difluoro-3,4-dihydrospiro [chromene-2, r-cyclobutanol]-4-yl)-3-(1H-indazol-4-yl)urea (Compound No. 14),

(±) - 1-(1-ethoxycarbonyl-1H-indazol-4-yl)-3-(7-methyl-3,4-dihydrospiro [chromene-2, 1'-cyclobutanol]-4-yl)urea. (Compound No. 15),
(±)-1-(1H-indazol-4-yl)-3-(7-methyl-3,4-dihydropyrrolo[chromene-2,r-cyclobutan]-4-yl)urea.

(Compound No. 16),

(±)-1-(1-ethoxycarbonyl-1H-indazol-4-yl)-3-(7-methoxy-3,4-dihydropyrrolo[chromene-2,l'-cyclobutan]-4-yl)urea. (Compound No. 17),

(±)-1-(1H-indazol-4-yl)-3-(7-methoxy-3,4-dihydropyrrolo[chromene-2,l'-cyclobutan]-4-yl)urea. (Compound No. 18),

(±)-1-(1-ethoxycarbonyl-1H-indazol-4-yl)-3-(7-chloro-3,4-dihydropyrrolo[chromene-2,l'-cyclobutan]-4-yl)urea. (Compound No. 19),

(±)-1-(1H-indazol-4-yl)-3-(7-chloro-3,4-dihydropyrrolo[chromene-2,l'-cyclobutan]-4-yl)urea. (Compound No. 20),

(±)-1-(1-ethoxycarbonyl-6-bromo-1H-indazol-4-yl)-3-(3,4-dihydropyrrolo[chromene-2,l'-cyclobutan]-4-yl)urea. (Compound No. 21),

(±)-1-(3,4-dihydropyrrolo[chromene-2,l'-cyclobutan]-4-yl)-3-(6-bromo-1H-indazol-4-yl)urea (Compound No. 22),

(±)-1-(1-ethoxycarbonyl-6-fluoro-1H-indazol-4-yl)-3-(3,4-dihydropyrrolo[chromene-2,l'-cyclobutan]-4-yl)urea. (Compound No. 23),

(±)-1-(3,4-dihydropyrrolo[chromene-2,r-cyclobutan]-4-yl)-3-(6-fluoro-1H-indazol-4-yl)urea (Compound No. 24),

(±)-1-(1-benzyl-6-pyrrolidin-2-one-1H-indazol-4-yl)-3-(3,4-dihydropyrrolo[chromene-2,l'-cyclobutan]-4-yl)urea. (Compound No. 25),

(+)-1-(1-ethoxycarbonyl-6-fluoro-1H-indazol-4-yl)-3-(3,4-dihydropyrrolo[chromene-2,l'-cyclobutan]-4-yl)urea. (Compound No. 26),

(+)-1-(3,4-dihydropyrrolo[chromene-2,l'-cyclobutan]-4-yl)-3-(6-fluoro-1H-indazol-4-yl)urea (Compound No. 27),

(±)-1-(1-ethoxycarbonyl-6-methoxy-1H-indazol-4-yl)-3-(3,4-dihydropyrrolo[chromene-2,l'-cyclobutan]-4-yl)urea. (Compound No. 28),

(±)-1-(3,4-dihydropyrrolo[chromene-2,l'-cyclobutan]-4-yl)-3-(6-methoxy-1H-indazol-4-yl)urea (Compound No. 29),

(+)-1-(6,8-difluoro-3,4-dihydropyrrolo[chromene-2,r-cyclobutan]-4-yl)-3-(1-ethoxycarbonyl-1H-indazol-4-yl)urea (Compound No. 30),

(+)-1-(6,8-difluoro-3,4-dihydropyrrolo[chromene-2,r-cyclobutan]-4-yl)-3-(1H-indazol-4-yl)urea (Compound No. 31),

(-)-1-(6,8-difluoro-3,4-dihydropyrrolo[chromene-2,r-cyclobutan]-4-yl)-3-(1-ethoxycarbonyl-1H-indazol-4-yl)urea (Compound No. 32),
(-) 1-(6,8-difluoro-3,4-dihydrospiro[chromene-2, 1'-cyclobutan]-4-yl)-3-(1H-indazol-4-yl)urea (Compound No. 33),

(±) 1-(6- pyrrolidin-2-one-l-ethoxycarbonyl-l H-indazol-4-yl) -3-(3,4-dihydrospiro [chromene-2,l'-cyclobutan]-4-yl)urea. (Compound No. 34),

(±) 1-(6- pyrrolidin-2-one -1H-indazol-4-yl) -3-(3,4-dihydrospiro[chromene-2,l'-cyclobutan]-
4-yl)urea. (Compound No.35) and

pharmaceutically acceptable salts thereof.

5. A pharmaceutical composition comprising a compound according to any one of claims 1-4 and a pharmaceutically acceptable excipient.

6. The pharmaceutical composition according to claim 5, wherein the pharmaceutically acceptable excipient is a carrier or diluent.

7. 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 1-4.

8. The method according to claim 7, wherein the vanilloid receptor mediated disease, disorder or syndrome is a pain or inflammatory disease, disorder or syndrome mediated by vanilloid receptor 1 (VR1).

9. The method according to claim 7, 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, gastroesophageal 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.
10. 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 1-4.

11. The method of claim 10, wherein the pain is acute pain.

12. The method of claim 10, wherein the pain is chronic pain.

13. The method of claim 10, wherein the pain is post-operative pain.

14. 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 1-4.

15. 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 1-4.

16. 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 1-4.

17. 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 1-4.

18. 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 1-4.

19. A process for the preparation of a compound of formula

\[
\text{I}
\]

or a pharmaceutically acceptable salt thereof, wherein:

- each occurrence of R₁, R₃ and R₄ is independently hydrogen, hydroxy, halogen, cyano, nitro, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted alkoxy, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted cycloalkenyl, substituted or unsubstituted cycloalkenylalkyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted heterocyclylalkyl, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted arylalkenyl, substituted or unsubstituted arylalkynyl, substituted or unsubstituted arylalkoxy, substituted or unsubstituted arylalkylalkyl, substituted or unsubstituted arylalkenylalkyl, substituted or unsubstituted arylalkynylalkyl, substituted or unsubstituted arylalkoxyalkyl, substituted or unsubstituted arylalkylalkoxy, substituted or unsubstituted arylalkenylalkoxy, substituted or unsubstituted arylalkynylalkoxy, substituted or unsubstituted arylalkoxyalkyl, substituted or unsubstituted arylalkylalkoxyalkyl, substituted or unsubstituted arylalkenylalkoxyalkyl, substituted or unsubstituted arylalkynylalkoxyalkyl, substituted or unsubstituted arylalkoxyalkylalkyl, substituted or unsubstituted arylalkylalkoxyalkylalkyl, substituted or unsubstituted arylalkenylalkoxyalkylalkyl, substituted or unsubstituted arylalkynylalkoxyalkylalkyl, substituted or unsubstituted arylalkoxyalkylalkoxy, substituted or unsubstituted arylalkylalkoxyalkylalkoxy, substituted or unsubstituted arylalkenylalkoxyalkylalkoxy, substituted or unsubstituted arylalkynylalkoxyalkylalkoxy, substituted or unsubstituted arylalkoxyalkylalkoxyalkyl, substituted or unsubstituted arylalkylalkoxyalkylalkoxyalkyl, substituted or unsubstituted arylalkenylalkoxyalkylalkoxyalkyl, substituted or unsubstituted arylalkynylalkoxyalkylalkoxyalkyl, substituted or unsubstituted arylalkoxyalkylalkoxyalkylalkyl, substituted or unsubstituted arylalkylalkoxyalkylalkoxyalkylalkyl, substituted or unsubstituted arylalkenylalkoxyalkylalkoxyalkylalkyl, substituted or unsubstituted arylalkynylalkoxyalkylalkoxyalkylalkyl, substituted or unsubstituted arylalkoxyalkylalkoxyalkylalkylalkyl, substituted or unsubstituted arylalkylalkoxyalkylalkoxyalkylalkylalkyl, substituted or unsubstituted arylalkenylalkoxyalkylalkoxyalkylalkylalkyl, substituted or unsubstituted arylalkynylalkoxyalkylalkoxyalkylalkylalkyl, substituted or unsubstituted arylalkoxyalkylalkoxyalkylalkylalkylalkyl, substituted or unsubstituted arylalkylalkoxyalkylalkoxyalkylalkylalkylalkyl.
heteroaryl, substituted or unsubstituted heteroarylalkyl, substituted or unsubstituted amino,
COOR<sup>x</sup>, C(O)R<sup>x</sup>, C(S)R<sup>y</sup>, C(O)NR<sup>y</sup>R<sup>z</sup>, C(O)ONR<sup>y</sup>R<sup>z</sup>, NR<sup>y</sup>CONR<sup>y</sup>R<sup>z</sup>, N(R<sup>y</sup>)SOR<sup>y</sup>, 
N(R<sup>y</sup>)SO<sub>2</sub>R<sup>y</sup>, (=N-N(R<sup>y</sup>))R<sup>y</sup>, NR<sup>y</sup>C(O)OR<sup>y</sup>, NR<sup>y</sup>R<sup>y</sup>, NR<sup>y</sup>C(O)R<sup>y</sup>, NR<sup>y</sup>C(S)R<sup>y</sup>, 
NR<sup>y</sup>C(S)NR<sup>y</sup>R<sup>y</sup>, SONR<sup>y</sup>R<sup>y</sup>, SO<sub>2</sub>NR<sup>y</sup>R<sup>y</sup>, OR<sup>x</sup>, OR<sup>y</sup>C(O)NR<sup>y</sup>R<sup>z</sup>, OR<sup>y</sup>C(O)OR<sup>y</sup>, OC(O)R<sup>y</sup>, 
OC(O)NR<sup>y</sup>R<sup>y</sup>, R<sup>z</sup>NR<sup>y</sup>C(O)R<sup>y</sup>, R<sup>z</sup>OOR<sup>y</sup>, R<sup>z</sup>C(O)OR<sup>y</sup>, R<sup>z</sup>C(O)NR<sup>y</sup>R<sup>z</sup>, R<sup>z</sup>OC(O)R<sup>y</sup>, 
SR<sup>x</sup>, SOR<sup>y</sup> or SO<sub>2</sub>R<sup>y</sup>.

R<sup>2</sup> is hydrogen, alkoxy carbonyl, nitro, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted amino, substituted or unsubstituted heteroaryl, substituted or unsubstituted heterocyclyl,
SONR<sup>y</sup>R<sup>y</sup>, SO<sub>2</sub>NR<sup>y</sup>R<sup>y</sup>, C(O)NR<sup>y</sup>R<sup>z</sup>, SOR<sup>y</sup> or SO<sub>2</sub>R<sup>y</sup>;

m is 0, 1, 2, 3 or 4;
n is 0, 1, 2 or 3; and

each occurrence of R<sup>y</sup>, R<sup>y</sup> and R<sup>z</sup> is independently 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 cycloalkylalkyl, substituted or unsubstituted cycloalkenyl, substituted or unsubstituted amino, substituted or unsubstituted heteroaryl, substituted or unsubstituted heterocyclylalkyl, substituted or unsubstituted heteroarylalkyl, or substituted or unsubstituted heterocyclyl,

the process comprising the steps of:

(a) reacting the compound of formula (I) with a ketone of formula (2)

![Diagram](image1)

(1)

(2)

(3)

to form a compound of formula (3)

(b) converting the compound of formula (4) to a compound of formula (5)
reducing the compound of formula (4) to form a compound of formula (5)

(d) reacting the compound of formula (5) with a compound of formula (7), wherein X' is a leaving group and Rp is hydrogen, alkyl or aryl,

\[ \text{XCOORP} \]

(6)

to form a compound of formula (7)

(c) reacting the compound of formula (7) with a compound of formula (8)

(7)

(8)

to form the compound of formula I and optionally converting the compound to a pharmaceutically acceptable salt.

20. A process for the preparation of a compound of formula
or a pharmaceutically acceptable salt thereof, wherein:

each occurrence of $R^1$, $R^3$ and $R^4$ is independently hydrogen, hydroxy, halogen, cyano, nitro, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted alkoxy, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted cycloalkenyl, substituted or unsubstituted cycloalkenylalkyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted heterocyclylalkyl, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heteroarylalkyl, substituted or unsubstituted amino, $\text{COOR}^x$, $\text{C(OR)}^x$, $\text{C(S)R}^x$, $\text{C(ONR)}^x\text{R}^x$, $\text{NR}^x\text{CONR}^x\text{R}^x$, $\text{N(R}^x)\text{SOR}^x$, $\text{N(R}^x)\text{SO}_2\text{R}^x$, ($\text{N}=\text{N(R}^x)\text{R}^x$), $\text{NR}^x\text{C(O)OR}^x$, $\text{NR}^x\text{R}^x$, $\text{NR}^x\text{C(O)R}^x$, $\text{NR}^x\text{C(S)R}^x$, $\text{NR}^x\text{C(S)NR}^x\text{R}^x$, $\text{SONR}^x\text{R}^x$, $\text{SO}_2\text{NR}^x\text{R}^x$, $\text{OR}^x$, $\text{OR}^x\text{C(O)NR}^x\text{R}^x$, $\text{OR}^x\text{C(O)OR}^x$, $\text{OC(O)R}^x$, $\text{OC(O)NR}^x\text{R}^x$, $\text{R}^x\text{NR}^x\text{C(OR)}^x\text{R}^x$, $\text{R}^x\text{OR}^x$, $\text{R}^x\text{C(O)OR}^x$, $\text{R}^x\text{C(OR)}^x\text{R}^x$, $\text{R}^x\text{C(O)R}^x$, $\text{R}^x\text{OC(O)R}^x$:

$R^2$ is hydrogen, alkoxy carbonyl, nitro, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted amino, substituted or unsubstituted heteroaryl, substituted or unsubstituted heterocyclyl, $\text{SONR}^x\text{R}^x$, $\text{SO}_2\text{NR}^x\text{R}^x$, $\text{C(ONR)}^x\text{R}^x$, $\text{SOR}^x$ or $\text{SO}_2\text{R}^x$;

$m$ is 0, 1, 2, 3 or 4;

$n$ is 0, 1, 2 or 3; and

each occurrence of $R^x$, $R^y$ and $R^z$ is independently 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 cycloalkylalkyl, substituted or unsubstituted cycloalkenyl, substituted or unsubstituted amino, substituted or unsubstituted heteroaryl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted heterocyclylalkyl, or substituted or unsubstituted heteroarylalkyl, or the process comprising the steps of:
(a) reacting an amine of formula (8) with a compound of formula (6), wherein $X'$ is a leaving group and $R^p$ is hydrogen, alkyl or aryl,

![Diagram](image)

(8) $XCOORP$

(6)

to form a compound of formula (9)

![Diagram](image)

(9)

(b) reacting the compound of formula (9) with a compound of formula (5)

![Diagram](image)

(5)

to form the compound of formula I and optionally converting the compound to a pharmaceutically acceptable salt.

21. A process for the preparation of a compound of formula

![Diagram](image)

or a pharmaceutically acceptable salt thereof, wherein:

- each occurrence of $R^1$, $R^3$ and $R^4$ is independently hydrogen, hydroxy, halogen, cyano, nitro, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted alkoxy, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted cycloalkenyl, substituted or unsubstituted cycloalkenylalkyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted heterocyclylalkyl, substituted or
unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heteroarylalkyl, substituted or unsubstituted amino, 
\( \text{COOR}^\chi, \text{C(O)R}^\chi, \text{C(S)R}^\chi, \text{C(O)NR}^\chi \text{R}^\gamma, \text{C(O)ONR}^\chi \text{R}^\gamma, \text{NR}^\chi \text{CONR}^\gamma \text{R}^z, \text{N(R}^\chi \text{)SOR}^\gamma, \text{N(R}^\chi \text{)SO}_2 \text{R}^\gamma, \text{=N-N(R}^\chi \text{)R}^\gamma, \text{NR}^\chi \text{C(O)OR}^\gamma, \text{NR}^\chi \text{R}^\gamma, \text{NR}^\chi \text{C(O)R}^\gamma, \text{NR}^\chi \text{C(S)R}^\gamma, \text{NR}^\chi \text{C(S)NR}^\gamma \text{R}^z, \text{SONR}^\gamma \text{R}^\gamma, \text{SO}_2 \text{NR}^\chi \text{R}^\gamma, \text{OR}^\chi, \text{OR}^\gamma \text{C(O)NR}^\chi \text{R}^z, \text{OR}^\chi \text{C(O)OR}^\gamma, \text{OC(O)R}^\chi, \text{OC(O)NR}^\gamma \text{R}^\gamma, \text{R}^\chi \text{NR}^\chi \text{C(O)R}^\gamma, \text{R}^\gamma \text{OR}^\gamma, \text{R}^\gamma \text{C(O)OR}^\gamma, \text{R}^\gamma \text{C(O)NR}^\chi \text{R}^z, \text{R}^\gamma \text{C(O)R}^\gamma, \text{R}^\gamma \text{OC(O)R}^\gamma, \text{SR}^\chi, \text{SOR}^\gamma \text{or SO}_2 \text{R}^\chi \text{.}
\)

\( R^2 \) is hydrogen, alkoxycarbonyl, nitro, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted amino, substituted or unsubstituted heteroaryl, substituted or unsubstituted heterocyclyl, 
\( \text{SONR}^\chi \text{R}^\gamma, \text{SO}_2 \text{NR}^\chi \text{R}^\gamma, \text{C(O)NR}^\chi \text{R}^z, \text{SOR}^\gamma \text{or SO}_2 \text{R}^\chi \text{.}
\)

\( m \) is 0, 1, 2, 3 or 4;
\( n \) is 0, 1, 2 or 3; and
each occurrence of \( R^\chi, \text{R}^\gamma \text{ and } R^z \) is independently 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 cycloalkylalkyl, substituted or unsubstituted cycloalkenyl, substituted or unsubstituted amino, substituted or unsubstituted heteroaryl, substituted or unsubstituted heterocyclylalkyl, substituted or unsubstituted heteroarylalkyl, or substituted or unsubstituted heterocyclyl,

the process comprising the steps of:

reacting a compound of formula (10)

```
NCO
(R^4)^n
(5)
```

with a compound of formula (8)

```
R_2
(R^3)^n
(8)
```
to form the compound of formula I and optionally converting the compound to a pharmaceutically acceptable salt.

22. A process for the preparation of a compound of formula

\[ \text{I} \]

or a pharmaceutically acceptable salt thereof, wherein:

each occurrence of \( R^1 \), \( R^3 \) and \( R^4 \) is independently hydrogen, hydroxy, halogen, cyano, nitro, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted alkoxy, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted cycloalkenyl, substituted or unsubstituted cycloalkenylalkyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted heterocyclylalkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heteroarylalkyl, substituted or unsubstituted amino, \( \text{COOR}^x \), \( \text{C(O)R}^x \), \( \text{C(S)R}^x \), \( \text{C(0)NR}^x \text{R}^y \), \( \text{C(0)NR}^x \text{C(0)NR}^x \text{R}^y \), \( \text{NR}^x \text{CONR}^x \text{R}^y \), \( \text{N(R}^x)\text{SOR}^y \), \( \text{N(R}^x)\text{SO}_2\text{R}^y \), \( \text{C}(\text{S})\text{R}^x \), \( \text{NR}^x \text{C}(\text{0})\text{R}^y \), \( \text{NR}^x \text{R}^y \), \( \text{NR}^x \text{C}(\text{0})\text{R}^y \), \( \text{NR}^x \text{C}(\text{S})\text{R}^y \), \( \text{NR}^x \text{C}(\text{S})\text{NR}^y \text{R}^z \), \( \text{SONR}^x \text{R}^y \), \( \text{S}_2 \text{NR}^x \text{R}^y \), \( \text{OR}^x \), \( \text{OC}(\text{0})\text{NR}^x \text{R}^y \), \( \text{R}^x \text{OR}^y \), \( \text{R}^x \text{C}(\text{0})\text{OR}^y \), \( \text{R}^x \text{C}(\text{0})\text{NR}^x \text{R}^y \), \( \text{R}^x \text{C}(\text{0})\text{R}^y \), \( \text{R}^x \text{OC}(\text{0})\text{R}^y \), \( \text{SR}^x \), \( \text{SOR}^x \) or \( \text{SO}_2\text{R}^y \).

\( R^2 \) is hydrogen, alkoxycarbonyl, nitro, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted amino, substituted or unsubstituted heteroaryl, substituted or unsubstituted heterocyclyl, \( \text{SONR}^x \text{R}^y \), \( \text{SO}_2 \text{NR}^x \text{R}^y \), \( \text{C}(\text{0})\text{NR}^x \text{R}^y \), \( \text{SOR}^x \) or \( \text{SO}_2\text{R}^y \).

\( m \) is 0, 1, 2, 3 or 4;
\( n \) is 0, 1, 2 or 3; and

each occurrence of \( R^3 \), \( R^y \) and \( R^z \) is independently 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 cycloalkylalkyl, substituted or unsubstituted cycloalkenyl, substituted or unsubstituted amino,
substituted or unsubstituted heteroaryl, substituted or unsubstituted heterocyclylalkyl, substituted or unsubstituted heteroarylalkyl, or substituted or unsubstituted heterocyclyl.

the process comprising the steps of:

a) reducing compound of formula (3)

\[
\text{(3)}
\]

5
to form a compound of formula (11)

\[
\text{(11)}
\]

\[
\text{OH}
\]

\[
\text{NCOCH}_3
\]

(12)

reacting the compound of formula (11) with acetonitrile in sulphuric acid to form a compound of formula (12)

\[
\text{(12)}
\]

10

(c) hydrolyzing the compound of formula (12) to form a compound of formula (5)

\[
\text{(5)}
\]

15

(d) reacting the compound of formula (5) with a compound of formula (9)

\[
\text{(9)}
\]

wherein \( R^p \) is hydrogen, alkyl, or aryl, to form a compound of formula I and optionally converting the compound to a pharmaceutically acceptable salt.
**INTERNATIONAL SEARCH REPORT**

**A. CLASSIFICATION OF SUBJECT MATTER**

INV. C07D 405/12 A61K31/416 A61P29/00

According to International Patent Classification (IPC) or to both national classification and IPC

**B. FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)
C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, CHEM ABS Data, WPI Data

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

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X Further documents are listed in the continuation of Box C.

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Authorized officer
Lauro, Paola

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<td>WO 2005075463 A</td>
<td>18-08-2005</td>
<td>CA 2551575 A1</td>
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