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(54) Title: SUBSTITUTED TRICYCLIC PYRIDINE OR PYRIMIDINE VANILLOID RECEPTOR LIGANDS

(57) Abstract: The present invention relates to substituted tricyclic compounds, which can be used as vanilloid receptor ligands. In particular, compounds described herein are useful for treating or preventing diseases, conditions and/or disorders modulated by vanilloid receptor-1 (VRl). Also provided herein are pharmaceutical compositions and methods for treating or preventing diseases, conditions and/or disorders modulated by VRl.

SUBSTITUTED TRICYCLIC PYRIDINE OR PYRIMIDINE VANILLOID RECEPTOR LIGANDS

Field of the Invention

The present invention relates to substituted tricyclic compounds, which can be used as vanilloid receptor ligands. In particular, compounds described herein are useful for treating or preventing diseases, conditions and/or disorders modulated by vanilloid receptor-1 (VR1). Also provided herein are pharmaceutical compositions and methods for treating or preventing diseases, conditions and/or disorders modulated by VR1.

Background of the Invention

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

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

The lipophillic vanilloid, Capsaicin (8-methyl-N-vanillyl-6-nonenamides; CAP) is known to stimulate pain pathways through the release of a variety of sensory afferent neurotransmitters via a specific cell surface capsaicin receptor, cloned as the first vanilloid receptor (VR1 now known as TRPV1) (Caterina MJ, *et.al.*, Science , Apr 14; 288 (5464): 306-13, 2000). 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 analgesic component of VR1 receptor activation is thought to be mediated by a capsaicin-induced desensitization of the primary sensory afferent terminal. Based on this property, CAP and its analogues such as olvanil, nuvanil, DA-5018, SDZ-249482, and resiniferatoxin are either used or are under development as analgesic agents or therapeutic agents for urinary incontinence or skin disorders (Wrigglesworth and Walpole, Drugs of the Future, 23: pp 531-538, 1998).

VR1 is widely expressed in non-neuronal tissues in various organ systems, and the functional roles of VR1 in various systems are not properly understood at this time. An increasing number of animal studies have revealed the possible involvement of VR1 receptors in a number of pathologies. Based on this information VR1 is now being considered as a molecular target for various indications such as migraine, arthralgia, diabetic neuropathy, neurodegeneration, neurotic skin disorder, stroke, cardiac pain arising from an ischemic myocardium, Huntington's disease, memory deficits, restricted brain function, amyotrophic lateral sclerosis (ALS), dementia, urinary bladder hypersensitiveness, urinary incontinence, vulvodynia, pruritic conditions such as uremic pruritus, irritable bowel syndrome including gastro-esophageal reflux disease, enteritis, ileitis, stomach-duodenal ulcer, inflammatory bowel disease including Crohn’s disease, celiac disease and inflammatory diseases such as pancreatitis, and in respiratory disorders such as allergic and non-allergic rhinitis, asthma or chronic obstructive pulmonary disease, irritation of skin, eye or mucous membrane, dermatitis, and in non specific disorders such as fervescence, retinopathy, muscle spasms, emesis, dyskinesias and depression. Specifically, VR1 antagonists are likely to be useful in multiple sub-types of pain such as acute, chronic, neuropathic pain or post-operative pain, as well as in pain due to neuralgia (*e.g.*, post herpetic neuralgia 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 (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. VR1 antagonists at the clinical stages are for example, Amgen's AMG 571, Glaxo Smithkline's SB-705498, Merck's MK-2295 and Glenmark's GRC 6211.

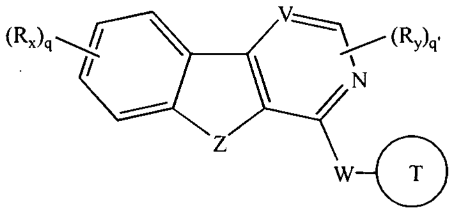
PCT Publications 2007/056155, 2006/041773, 93/14080 and U.S. Patent 5,753,663; discloses the pyrimidine derivatives.

Vanilloid receptor modulating compounds are disclosed in U.S. Patent Nos. 6,933,311, 6,939,891, and 7,037,927, U.S. Publication No. 2006/0100460, and PCT Publication Nos. WO 02/08221, 02/16317, 02/16318, 02/16319, 2004/103281, 2004/108133, 2004/111009, 2006/044527 and 2006/045498.

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

Summary of the Invention

The present invention relates to VR1 receptor ligands of formula (1):



(1)

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

Z is $-Y-(CR_1R_2)_n-$ or $-(CR_1R_2)_n-Y$;

Y is a bond, NR_1, -O-, or -S-;

n is an integer ranging from 0-3;

V is N or CR_1;

W is NR_1 or O;

Ring T is heteroaryl or heterocyclyl, optionally substituted with one or more R_y;

each occurrence of R_1, R_2, R_x and R_y is independently hydrogen, nitro, cyano, halogen, $-OR_3$, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted cycloalkenyl, substituted or unsubstituted cycloalkenylalkyl, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heteroarylalkyl, substituted or unsubstituted heterocyclic group, substituted or unsubstituted heterocyclylalkyl, $-NR_3R_4$, $-C(=L)-R_3$, $-C(O)O-R_3$, $-C(O)NR_3R_4$, $-S(O)_m-R_3$, $-S(O)_m-NR_3R_4$, $C(O)R_3$, $S(O)_2R_3$ or $COOR_3$;

each occurance of L is O, S or NR_a;

each occurrence of R_3 and R_4 may be the same or different and is independently hydrogen, $-OR^a$, $-SR^a$, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted cycloalkenyl, substituted or unsubstituted cycloalkenylalkyl, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heteroarylalkyl, substituted or unsubstituted heterocyclic group, substituted or unsubstituted heterocyclylalkyl, $-NR_aR_b$, $-C(=L)-R_a$, $-C(O)O-R_a$, $-C(O)NR_aR_b$, $-S(O)_m-R_a$ or $-S(O)_m-NR_aR_b$, or R_3 and R_4 taken together with the nitrogen atom to which they are attached are joined together to form an optionally substituted 3 to 7 membered saturated or unsaturated cyclic ring, which may optionally include at least two heteroatoms selected from O, NR_e or S;

each occurrence of R_a and R_b independently is hydrogen, $-OR_c$, $-SR_c$, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted cycloalkenyl, substituted or unsubstituted cycloalkenylalkyl, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heteroarylalkyl, substituted or unsubstituted heterocyclic group, substituted or unsubstituted heterocyclylalkyl, $-C(=L)-R_c$, $-C(O)O-R_c$, $-C(O)NR_cR_d$, $-S(O)_m-R_c$, $-S(O)_m-NR_cR_d$, $-NR_cR_d$, or a protecting group, or R_a and R_b taken together with the nitrogen atom to which they are attached are joined to form an optionally substituted 3 to 7 membered saturated or unsaturated cyclic ring, which may optionally include at least two heteroatoms selected from O, NR_e or S;

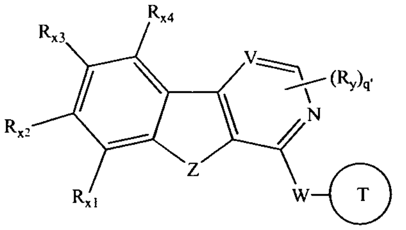
each occurrence of R_c and R_d is independently hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted cycloalkenyl, substituted or unsubstituted cycloalkenylalkyl, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heterocyclic group, substituted or unsubstituted heterocyclylalkyl, or a substituted or unsubstituted heteroarylalkyl or a protecting group, or R_c and R_d taken together with the nitrogen atom to which they are attached may be joined to form an optionally substituted 3 to 7 membered saturated or unsaturated cyclic ring, which may optionally include at least two heteroatoms selected from O, NR_e or S;

each occurrence of m is 0-2;

q is an integer ranging from 0-4; and

q' is an integer ranging from 0 or 1.

According to one embodiment the invention relates to compounds of formula (1a)



(1a)

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

Z is $-Y-(CR_1R_2)_n$, Y is -O-, n is 0.

V is N;

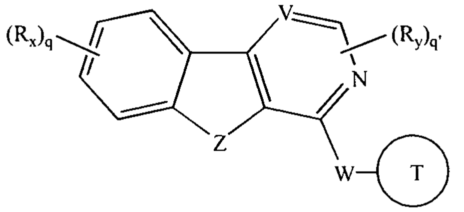
W is selected from NH or O; and

T is heteroaryl, optionally substituted with one or more R_y.

According to yet another embodiment ring T is selected from optionally substituted benzothiazolyl, benzodioxinyl, quinolinyl or indazolyl.

Further preferred is a compound of formula (1) wherein R_x (for all R_x substitutions) and R_y independently are selected from hydrogen, halogen, alkyl, NHCO-alkyl and $-OR_3$ (wherein R_3 is alkyl).

According to another embodiment the invention relates to compounds of formula (1b)



(1b)

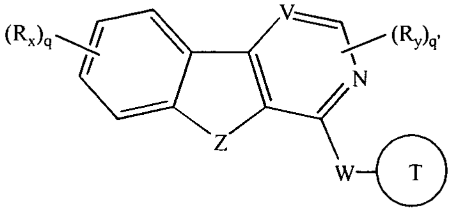
and pharmaceutically acceptable salts thereof, N-oxides thereof, and prodrugs thereof, wherein

Z is $-Y-(CR_1R_2)_n-$; Y is a bond; n is 2; V is N; W is NR_1;

Ring T is aryl, heteroaryl or heterocyclyl, optionally substituted with one or more alkyl or NHCO-alkyl groups with alkyl; and

R_1, R_2, R_x and R_y are hydrogen.

According to another embodiment the invention relates to compounds of formula (1c)



(1c)

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

Z is -Y-$(CR_1R_2)_n$-; Y is O; n is 2;

V is N; W is NR_1;

R_1, R_2, R_x and R_y are hydrogen; and

Ring T is heteroaryl or heterocyclyl, optionally substituted with one or more NHCO-alkyl.

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

N-{4-[(7-methyl[1]benzofuro[3,2-*d*]pyrimidin-4-yl)amino]-1,3-benzothiazol-2-yl}acetamide (Compound No. 1),

N-(2,3-dihydro-1,4-benzodioxin-6-yl)-7-methyl[1]benzofuro[3,2-*d*]pyrimidin-4-amine (Compound No. 2),

N-{4-[(7-tert-butyl[1]benzofuro[3,2-*d*]pyrimidin-4-yl)amino]-1,3-benzothiazol-2-yl}acetamide (Compound No. 3),

N-(2,3-dihydro-1,4-benzodioxin-6-yl)-7-tert-butyl[1]benzofuro[3,2-*d*]pyrimidin-4-amine (Compound No. 4),

N-[4-([1]benzofuro[3,2-*d*]pyrimidin-4-ylamino)-1,3-benzothiazol-2-yl]acetamide (Compound No. 5),

N-(2,3-dihydro-1,4-benzodioxin-6-yl)[1]benzofuro[3,2-*d*]pyrimidin-4-amine (Compound No. 6),

N-quinolin-7-yl[1]benzofuro[3,2-*d*]pyrimidin-4-amine (Compound No. 7),

N-1*H*-indazol-5-yl[1]benzofuro[3,2-*d*]pyrimidin-4-amine (Compound No. 8), *N*-(2,3-dihydro-1,4-benzodioxin-6-yl)-6-methoxy[1]benzofuro[3,2-*d*]pyrimidin-4-amine (Compound No. 9),

N-[4-([1]benzofuro[3,2-*d*]pyrimidin-4-yloxy)-1,3-benzothiazol-2-yl]acetamide (Compound No. 10),

N-[4-(7-*tert*-butyl[1]benzofuro[3,2-*d*]pyrimidin-4-yloxy)-1,3-benzothiazol-2-yl]acetamide (Compound No. 11),

N-{4-[(7-methyl[1]benzofuro[3,2-*d*]pyrimidin-4-yl)oxy]-1,3-benzothiazol-2-yl}acetamide (Compound No. 12),

N-{4-[(7-chloro[1]benzofuro[3,2-*d*]pyrimidin-4-yl)oxy]-1,3-benzothiazol-2-yl}acetamide (Compound No. 13),

N-(4-*tert*-butylphenyl)-5,6-dihydrobenzo[*h*]quinazolin-4-amine (Compound No. 14),

N-(2,3-dihydro-1,4-benzodioxin-6-yl)-5,6-dihydrobenzo[*h*]quinazolin-4-amine (Compound No. 15),

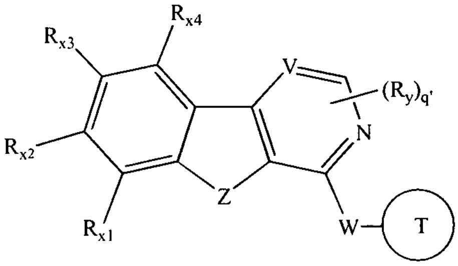
N-[4-(5,6-dihydrobenzo[*h*]quinazolin-4-ylamino)-1,3-benzothiazol-2-yl]acetamide (Compound No. 16),

N-(2,3-dihydro-1,4-benzodioxin-6-yl)-5,6-dihydro[1]benzoxepino[5,4-*d*]pyrimidin-4-amine (Compound No. 17),

N-[4-(5,6-dihydro[1]benzoxepino[5,4-*d*]pyrimidin-4-ylamino)-1,3-benzothiazol-2-yl]acetamide (Compound No. 18), and

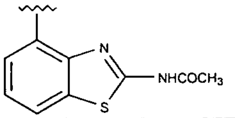
N-quinolin-7-yl-5,6-dihydro[1]benzoxepino[5,4-*d*]pyrimidin-4-amine (Compound No. 19).

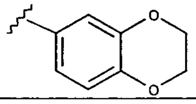
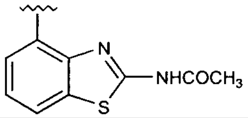
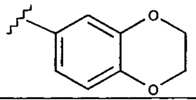
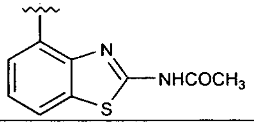
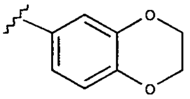
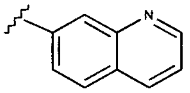
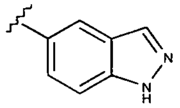
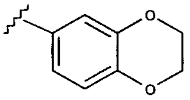
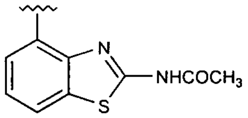
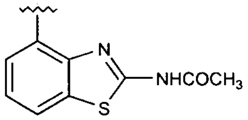
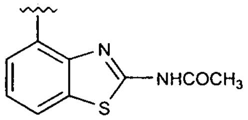
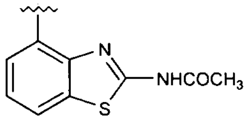
Table 1

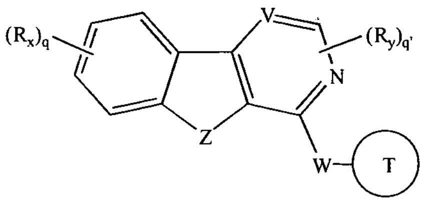


(1a)

(R_{x3}=R_{x4}= H, R_y =H, V=N, Z=O)

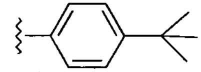
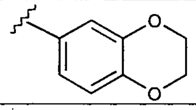
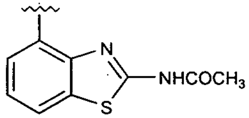
Compound No.	R_{x1}	R_{x2}	W	T
1	H	Me	-NH-	

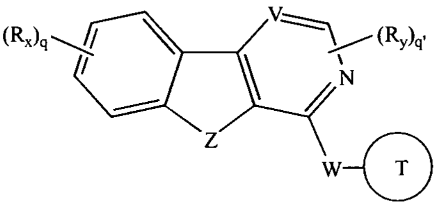
2	H	Me	-NH-	
3	H	-C(CH3)3	-NH-	
4	H	-C(CH3)3	-NH-	
5	H	H	-NH-	
6	H	H	-NH-	
7	H	H	-NH-	
8	H	H	-NH-	
9	OMe	H	-NH-	
10	H	H	-O-	
11	H	-C(CH3)3	-O-	
12	H	Me	-O-	
13	H	Cl	-O-	



(1b)

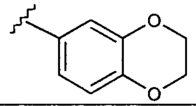
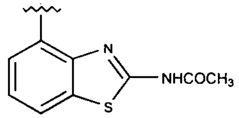
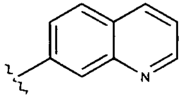
(R_x= R_y =H, V=N, Z=-CH_2-CH_2-)

Compound No.	W	T
14	-NH-	
15	-NH-	
16	-NH-	



(1c)

(R_x= R_y =H, V=N, Z=-O-CH_2-CH_2-)

Compound No.	W	T
17	-NH-	
18	-NH-	
19	-NH-	

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

The compounds and pharmaceutical compositions of the present invention are useful in the treatment of diseases, conditions and/or disorders modulated by vanilloid antagonists.

The present invention further provides a method of treating a disease, condition and/or disorder modulated by vanilloid VR1 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 present invention further provides a method of treating a disease, condition and/or disorder modulated by vanilloid VR1 receptor antagonists in a subject in need thereof by administering to the subject a therapeutically effective amount of a compound of formula 1.

Detailed Description of the Invention

Definitions

The term "alkyl" refers to an optionally substituted 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 "C_{1-6} alkyl" refers to an alkyl chain having 1 to 6 carbon atoms.

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

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

The term "alkoxy" denotes an optionally substituted alkyl group attached via an oxygen linkage to the rest of the molecule. Representative examples of such groups are $-OCH_3$ and $-OC_2H_5$.

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

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

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

The term "cycloalkenylalkyl" refers to an optionally substituted cycloalkenyl group as defined above directly bonded to an alkyl group as defined above. The term "aryl" refers to refers to an optionally substituted aromatic radical having 6 to 14 carbon atoms such as phenyl, naphthyl, tetrahydronapthyl, indanyl, and biphenyl.

The term "arylalkyl" refers to an optionally substituted aryl group as defined above directly bonded to an alkyl group as defined above, e.g., $-CH_2C_6H_5$ and $-C_2H_5C_6H_5$.

The term "heterocyclic ring" refers to an optionally substituted stable 3- to 15-membered ring radical which consists of carbon atoms and from one to five heteroatoms selected from nitrogen, phosphorus, oxygen and sulfur. For purposes of this invention, the heterocyclic ring radical may be a monocyclic, bicyclic or tricyclic ring system, which may include fused, bridged or spiro ring systems, and the nitrogen, phosphorus, carbon, oxygen or sulfur atoms in the heterocyclic ring radical may be optionally oxidized to various oxidation states. In addition, the nitrogen atom may be optionally quaternized; and the ring radical may be partially or fully saturated (i.e., heterocyclic or heteroaryl). Examples of such heterocyclic ring radicals include, but are not limited to, azetidinyl, acridinyl, benzodioxolyl, benzodioxanyl, benzofurnyl, carbazolyl, cinnolinyl, dioxolanyl, indolizinyl, naphthyridinyl, perhydroazepinyl, phenazinyl, phenothiazinyl, phenoxazinyl, phthalazinyl, pyridyl, pteridinyl, purinyl, quinazolinyl, quinoxalinyl, quinolinyl, isoquinolinyl, tetrazoyl, imidazolyl, tetrahydroisouinolyl, piperidinyl, piperazinyl, 2-oxopiperazinyl, 2-oxopiperidinyl, 2-oxopyrrolidinyl, 2-oxoazepinyl, azepinyl, pyrrolyl, 4-piperidonyl, pyrrolidinyl, pyrazinyl, pyrimidinyl, pyridazinyl, oxazolyl, oxazolinyl, oxasolidinyl, triazolyl, indanyl, isoxazolyl, isoxasolidinyl, morpholinyl, thiazolyl, thiazolinyl, thiazolidinyl, isothiazolyl, quinuclidinyl, isothiazolidinyl, indolyl, isoindolyl, indolinyl, isoindolinyl, octahydroindolyl, octahydroisoindolyl, quinolyl, isoquinolyl, decahydroisoquinolyl, benzimidazolyl, thiadiazolyl, benzopyranyl, benzothiazolyl, benzooxazolyl, furyl, tetrahydrofurtyl, tetrahydropyranyl, thienyl, benzothienyl, thiamorpholinyl, thiamorpholinyl sulfoxide, thiamorpholinyl sulfone, dioxaphospholanyl, 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 “heterocyclyl” refers to an optionally substituted heterocyclic ring radical as defined above. The heterocyclyl 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 an optionally substituted 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 optionally substituted aromatic heterocyclic ring radical. The heteroaryl ring radical may be attached to the main structure at any heteroatom or carbon atom that results in the creation of a stable structure.

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

Unless otherwise specified, the term "optionally substituted" as used herein refers to substitution with any one or any combination of the following substituents: hydrogen, 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 heteroarylalkyl, substituted or unsubstituted heterocyclic ring, substituted or unsubstiuted guanidine, $-COOR_a^x$, $-C(O)R_a^x$, $-C(S)R_a^x$, $-C(O)NR_a^xR_a^y$, $-C(O)ONR_a^xR_a^y$, $-NR_a^xCONR_a^yR_a^z$, $-N(R_a^x)SOR_a^y$, $-N(R_a^x)SO_2R_a^y$, $-(=N-N(R_a^x)R_a^y)$, $-NR_a^xC(O)OR_a^y$, $-NR_a^xR_a^y$, $-NR_a^xC(O)R_a^y$, $-NR_a^xC(S)R_a^y$, $-NR_a^xC(S)NR_a^yR_a^z$, $-SONR_a^xR_a^y$, $-SO_2NR_a^xR_a^y$, $-OR_a^x$, $-OR_a^xC(O)NR_a^yR_a^z$, $-OR_a^xC(O)OR_a^y$, $-OC(O)R_a^x$, $-OC(O)NR_a^xR_a^y$, $-R_a^xNR_a^yC(O)R_a^z$, $-R_a^xOR_a^y$, $-R_a^xC(O)OR_a^y$, $-R_a^xC(O)NR_a^yR_a^z$,

$-R_a^xC(O)R_a^y$, $-R_a^xOC(O)R_a^y$, $-SR_a^x$, $-SOR_a^x$, $-SO_2R_a^x$, and $-ONO_2$, wherein R_a^x, R_a^y and R_a^z are independently selected from hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkoxy, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkenyl, substituted or unsubstituted amino, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted heterocyclylalkyl ring, substituted or unsubstituted heteroarylalkyl, or substituted or unsubstituted heterocyclic ring. The substituents in the aforementioned "substituted" groups cannot be further substituted. For example, when the substituent on "substituted alkyl" is "substituted aryl", the substituent on "substituted aryl" cannot be "substituted alkenyl".

The term "protecting group" or "PG" refers to a substituent that is employed to block or protect a particular functionality while other functional groups on the compound may remain reactive. For example, an "amino-protecting group" is a substituent attached to an amino group that blocks or protects the amino functionality in the compound. Suitable amino-protecting groups include, but are not limited to, acetyl, trifluoroacetyl, t-butoxycarbonyl (BOC), benzyloxycarbonyl (CBz) and 9-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, tetrahydropyranyl and silyl. A "carboxy-protecting group" refers to a substituent of the carboxy group that blocks or protects the carboxy functionality. Suitable carboxy-protecting groups include, but are not limited to, $-CH_2CH_2SO_2Ph$, cyanoethyl, 2-(trimethylsilyl)ethyl, 2-(trimethylsilyl)ethoxymethyl, 2-(p-toluenesulfonyl)ethyl, 2-(p-nitrophenylsulfenyl)ethyl, 2-(diphenylphosphino)-ethyl, and nitroethyl. For a general description of protecting groups and their use, see, T. W. Greene, Protective Groups in Organic Synthesis, John Wiley & Sons, New York, 1991.

The term "prodrug" means a compound that is transformed in vivo to yield a compound of Formula (I) or a pharmaceutically acceptable salt, hydrate or solvate of the compound. The transformation may occur by various mechanisms, such as through hydrolysis in blood. A discussion of the use of prodrugs is provided by T. Higuchi and W. Stella, "Pro-drugs as Novel Delivery Systems," Vol. 14 of the A.C.S. Symposium Series, and in Bioreversible Carriers in Drug Design, *ed.* Edward B. Roche, American Pharmaceutical Association and Pergamon Press, 1987.

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

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

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

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

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

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

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

Pharmaceutically acceptable salts forming part of this invention include salts derived from inorganic bases (such as Li, Na, K, Ca, Mg, Fe, Cu, Zn, and Mn), salts of organic bases (such as N,N'-diacetylethylenediamine, 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 trifluroacetate), tartrates, maleates, citrates, fumarates, succinates, palmoates, methanesulphonates, benzoates, salicylates, benzenesulfonates, ascorbates, glycerophosphates, and ketoglutarates. Yet other pharmaceutically acceptable salts include, but are not limited to, quaternary ammonium salts of the compounds of invention with alkyl halides or alkyl sulphates (such as MeI or $(Me)_2SO_4$). The pharmaceutically acceptable salts of the present invention may be prepared by any conventional techniques known to a person of ordinary skill in the art, *e.g.,* as described in Handbook of Pharmaceutical Salts-Properties, Selection and Use", P. Heinrich Stahl, Camille G. Wermuth [Eds.], VHCA and WILEY-VCH [2002].

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

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

Pharmaceutical Compositions

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

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

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

The pharmaceutical composition may also include one or more pharmaceutically acceptable auxiliary agents, wetting agents, emulsifying agents, suspending agents, preserving agents, salts for influencing 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 pharmaceutical compositions may be in conventional forms, for example, capsules, tablets, aerosols, solutions, suspensions or products for topical application.

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

Solid oral formulations include, but are not limited to, tablets, capsules (soft or hard gelatin), dragees (containing the active ingredient in powder or pellet form), troches and lozenges. Tablets, dragees, or capsules having talc and/or a carbohydrate carrier or binder or the like are particularly suitable for oral application. Preferable carriers for tablets, dragees, or capsules include lactose, cornstarch, and/or potato starch. A syrup or elixir can be used in cases where a sweetened vehicle can be employed.

A typical tablet that may be prepared by conventional 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.

Methods of Treatment

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

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

Diseases, conditions, and/or disorders that are modulated by vanilloid receptor antagonists which may be treated by the compounds and compositions of the present invention include, but are not limited to, pain, urinary incontinence, 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. 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 retinopathy, muscle spasms, emesis, dyskinesias and depression.

Another embodiment is a method of treating or preventing a disease or disorder mediated or associated with the activity of the vanilloid receptor in a subject in need thereof (e.g., a mammal or human) by administering to the subject a therapeutically effective amount of the compound or pharmaceutical composition of the present invention. Such diseases and disorders include, but are not limited to, 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, ischemia, 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.

Yet another embodiment is a method of treating or preventing pain in a subject in need thereof by administering a therapeutically effective amount of the compound or pharmaceutical 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 vanilloid receptor.

The compounds of the present invention have potent analgesic and anti-inflammatory activity, and the pharmaceutical compositions of the present invention thus may be employed to alleviate or relieve acute, chronic or inflammatory pain, suppress inflammation, or treat urgent urinary incontinence.

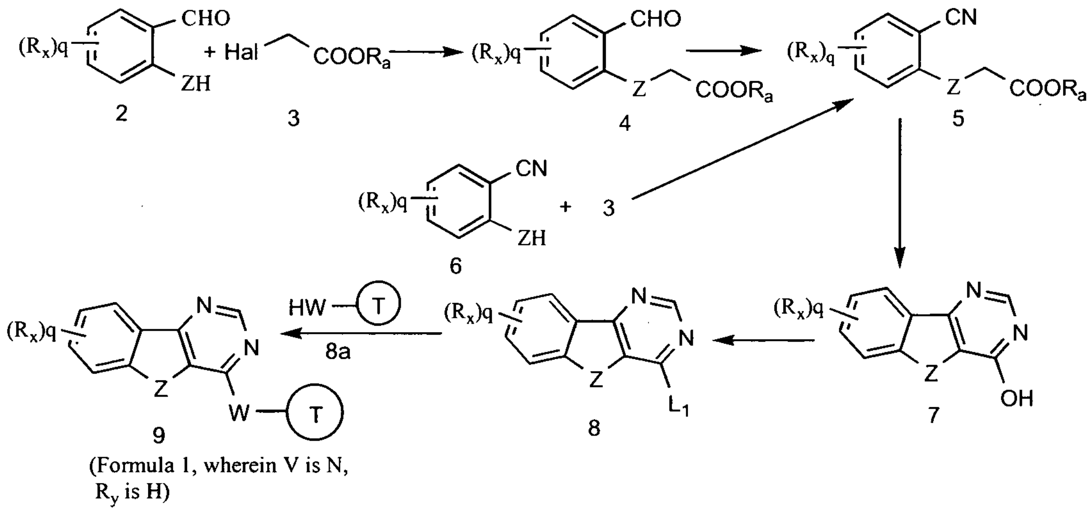
The compounds of the present invention may be used alone or in appropriate association, as well as in combination with other pharmaceutically active compounds.

The compounds and the pharmaceutical compositions of the present invention may be used alone or in combination with other pharmaceutically active compounds in the manufacture of a medicament for the therapeutic applications described herein.

Methods of Preparation

The compounds of the present invention, including compounds of formula 1 and specific examples, can be prepared by techniques known to one of ordinary skill in the art. The compounds of the present invention can be prepared through the reaction sequences shown in Schemes I-VIII. Where specific bases, acids, reagents, solvents, oxidizing agents, reducing agents, halogenating agents, dehydrating agents, fluorinating agents, coupling agents, etc., are mentioned, it is understood that other bases, acids, reagents, solvents, oxidizing agents, reducing agents, halogenating agents, dehydrating agents, fluorinating agents, coupling agents etc., known in the art, may also be used, and are included within the scope of the present invention. Modifications to reaction conditions, for example, temperature, duration of the reaction or a combination thereof, are envisioned as part of the present invention. All possible stereoisomers are also envisioned within the scope of this invention.

Scheme I



(Formula 1, wherein V is N, R_y is H)

According to one embodiment, a compound of formula 9 is prepared by the process described in Scheme I above. A compound of formula 2 (*Synthetic Communications* 24 (12), 1757-1760, 1994) is reacted with an ester of formula 3 (wherein Hal is halogen and R_a is alkyl) in the presence of one or more bases, for example, piperidine, pyridine, potassium hydroxide, sodium hydroxide, sodium methoxide, potassium methoxide, sodium carbonate, potassium carbonate or a mixture thereof, to form a compound of formula 4. The reaction can be performed in one or more solvents, for example, dimethylformamide, dimethylacetamide, dimethylsulfoxide, acetonitrile, tetrahydrofuran or a mixture thereof.

The compound of formula 4 is converted to a compound of formula 5, for example, by reaction with hydroxylamine hydrochloride to form an intermediary oxime which is dehydrated to form the compound of formula 5. The reaction can be performed in the presence of one or more bases, for example, piperidine, pyridine, dimethylaminopyridine, potassium hydroxide, sodium hydroxide, sodium methoxide, potassium methoxide, sodium carbonate, potassium carbonate or a mixture thereof in one or more solvents, for example, methanol, ethanol, isopropanol, dichloromethane, chloroform, dichloroethane, dibromoethane, dioxane, tetrahydrofuran, ethyl acetate, butyl acetate or a mixture thereof.

Alternatively, the compound of formula 6 (commercially available) can be reacted with a compound of formula 3 to form compound of formula 5. The reaction can be performed in one or more solvents, for example, dimethylformamide, dimethylacetamide, acetonitrile, dimethylsulfoxide, tetrahydrofuran or a mixture thereof.

The compound of formula 5 is reacted with an amide, for example formamide, optionally in the presence of one or more solvents, for example, dichloromethane, dichloroethane, dibromomethane, isopropanol, dioxane, tetrahydrofuran, *t*-butanol or a mixture thereof, to form a compound of formula 7.

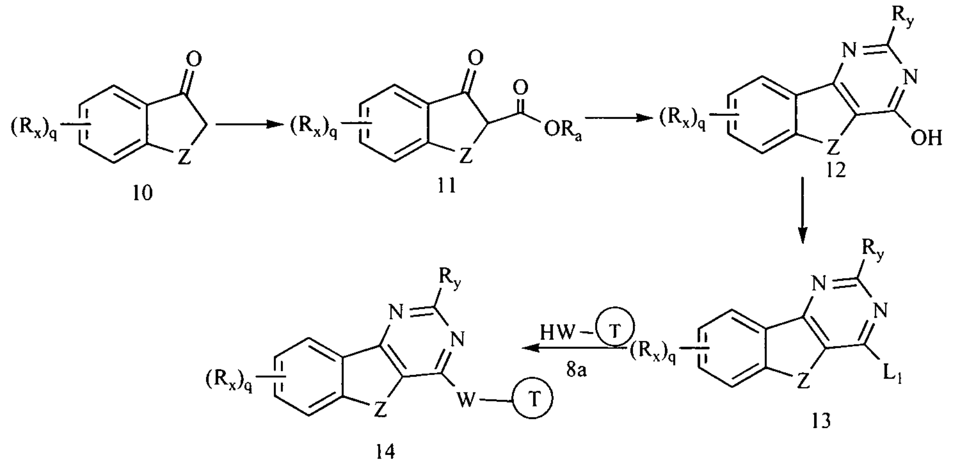
The compound of formula 7 is reacted with a halogenating agent, for example, phosphorous trichloride, phosphorous oxychloride, or thionyl chloride, to form a compound of formula 8, where L_1 is a halogen (e.g., chlorine).

The compound of formula 8 is reacted with a compound of formula 8a optionally in the presence of one or more bases, for example, cesium carbonate, sodium *t*-butoxide, triethylamine, diisopropylethyl amine, 1,8-Diazabicyclo[5.4.0]undec-7-ene or a mixture thereof, to form a compound of formula 9.

Alternatively, the reaction between the compounds of formulas 8 and 8a can be performed by a method described in "Metal-catalyzed cross-coupling reactions", F. Diederich and P. J. Stang (eds) Wiley-VCH, Weinheim, 1998. For example, the reaction can be performed in the presence of palladium catalysts (e.g., palladium acetate) and a ligand, for example, BINAP, tol-BINAP or 2-alkoxy BINAP.

The reaction between the compounds of formulas 8 and 8a can be performed in one or more solvents, for example, toluene, ethylenedichloride, methanol, ethanol, isopropanol, n-butyl alcohol, ethylene glycol, dioxane, tetrahydrofuran, ethyl acetate, butyl acetate, N,N-dimethylformamide, N-methylformamide, dimethylsulfoxide, or a mixture thereof.

Scheme II



(Formula 1, wherein V is N)

According to another embodiment, a compound of formula 14 is prepared using the process shown in Scheme II. The compound of formula 10 (*Journal of Organic Chemistry*, 1962, 27, 70-76; Tetrahedron, 2002, 58, 5203-5208) is treated with a compound of the formula $R_aOCOHal$ (wherein Hal is halogen and R_a is alkyl) or dialkyl carbonate to form a compound of formula 11. The reaction can be performed in the presence of one or more bases, for example, potassium hydroxide, sodium hydroxide, sodium hydride, potassium-t-butoxide, lithium diisopropylamide or lithium hexamethyldisilazide, in one or more solvents, for example, dimethylformamide, dimethylacetamide, acetonitrile, dimethylsulfoxide, tetrahydrofuran or a mixture thereof.

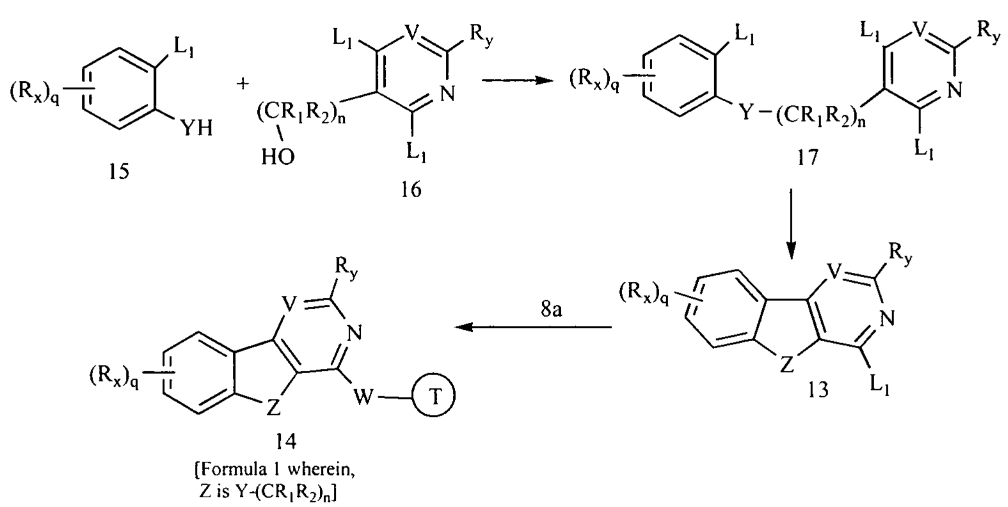
The compound of formula 11 is reacted with an amidine of the formula $R_y(C{=}NH)NH_2$ or a salt thereof to form a compound of formula 12. The reaction can be performed in the presence of one or more bases, for example, sodium carbonate, potassium carbonate, cesium carbonate, triethylamine, ammonia, pyridine or a mixture thereof optionally in the presence of one or more solvents, for example, methanol, ethanol, isopropanol, *t*-butanol, tetrahydrofuran, dimethylformamide or a mixture thereof.

Alternatively, the compound of formula 11 is converted to the corresponding enamine by reacting it with a source of ammonia, for example, ammonium hydroxide, ammonium formate, ammonium acetate or a mixture thereof, followed by reaction with an amide, for example, formamide, to form the compound of formula 12.

The compound of formula 12 is reacted with a halogenating agent (e.g., a chlorinating agent such as phosphorous oxychloride, thionyl chloride) to form a compound of formula 13. The reaction can be performed in one or more solvents, for example, carbon tetrachloride, dichloromethane, dichloroethane, dibromoethane, chloroform or a mixture thereof.

The compound of formula 13 is converted to a compound of formula 14 by following the procedure described in scheme I.

Scheme III

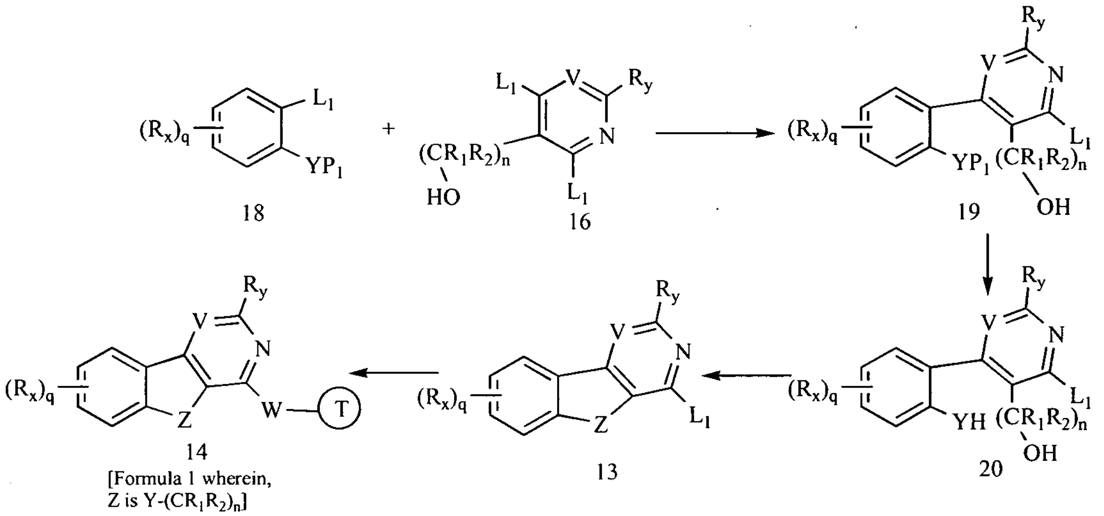


According to another embodiment, a compound of formula 14 is prepared using the process shown in Scheme III. The compound of formula 15 can be reacted with a compound of formula 16 in the presence of a nucleophile, for example, triarylphosphine and dialkylazodicarboxylate, to form a compound of formula 17 (wherein each occurrence of L_1 is independently a halogen). The reaction can be performed in one or more solvents, for example, methanol, ethanol, isopropanol, n-butyl alcohol, ethylene glycol, dioxane, tetrahydrofuran, ethyl acetate, butyl acetate or a mixture thereof.

The compound of formula 17 can be cyclized in the presence of one or more catalysts, for example, palladium acetate, nickel chloride, zinc or a mixture thereof in one or more solvents, for example, dimethylformamide, pyridine, acetonitrile, tetrahydrofuran, dichloroethane, dibromoethane or a mixture thereof.

The compound of formula 13 is converted to a compound of formula 14 by following the procedure described in scheme I.

Scheme IV

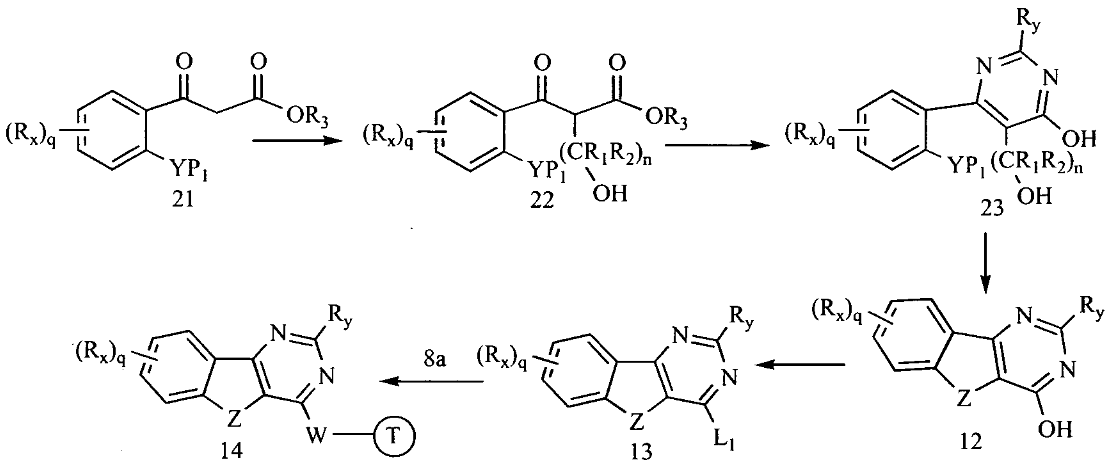


According to another embodiment, a compound of formula 14 is prepared using the process shown in Scheme IV. The compound of formula 18 (wherein P_1 is a protecting group, each occurrence of L_1 is independently a leaving group) can be reacted with the compound of formula 16 in the presence of one or more catalysts, for example, palladium acetate, nickel chloride, zinc or a mixture thereof in one or more solvents, for example, dimethylformamide, pyridine, acetonitrile, tetrahydrofuran, dichloroethane, dibromoethane or a mixture thereof, to form a compound of formula 19.

The compound of formula 19 is deprotected, for example, by reaction with a deprotecting agent (such as catalytic hydrogenation, hydrochloric acid, hydrobromic acid (e.g., in acetic acid), methane sufonic acid, and pyridimium hydrochloride) to form a compound of formula 20. The compound of formula 20 is cyclized, for example, in the presence of a reagent such as triarylphosphine and dialkylazodicarboxylate, to form a compound of formula 13. The reaction can be performed in one or more solvents, for example, methanol, ethanol, isopropanol, n-butyl alcohol, ethylene glycol, dioxane, tetrahydrofuran, ethyl acetate, butyl acetate or a mixture thereof.

The compound of formula 13 is converted to a compound of formula 14 by following the procedure described in scheme I.

Scheme V



Formula 1 wherein,
V is N, Z is Y-$(CR_1R_2)_n$

According to another embodiment, a compound of formula 14 is prepared using the process shown in Scheme V. The proton abstraction of a compound of formula 21 (wherein P_1 is a protecting group and R_3 is alkyl) is carried out with a base (preferably a strong base, for example, potassium hydroxide, sodium hydroxide, sodium hydride, potassium-t-butoxide, lithium diisopropylamide or lithium hexamethyldisilazide) and further reacted with a compound of the formula $OH\text{-}(CR_1R_2)\text{-}Hal$ (where Hal is a halogen) to form a compound of formula 22.

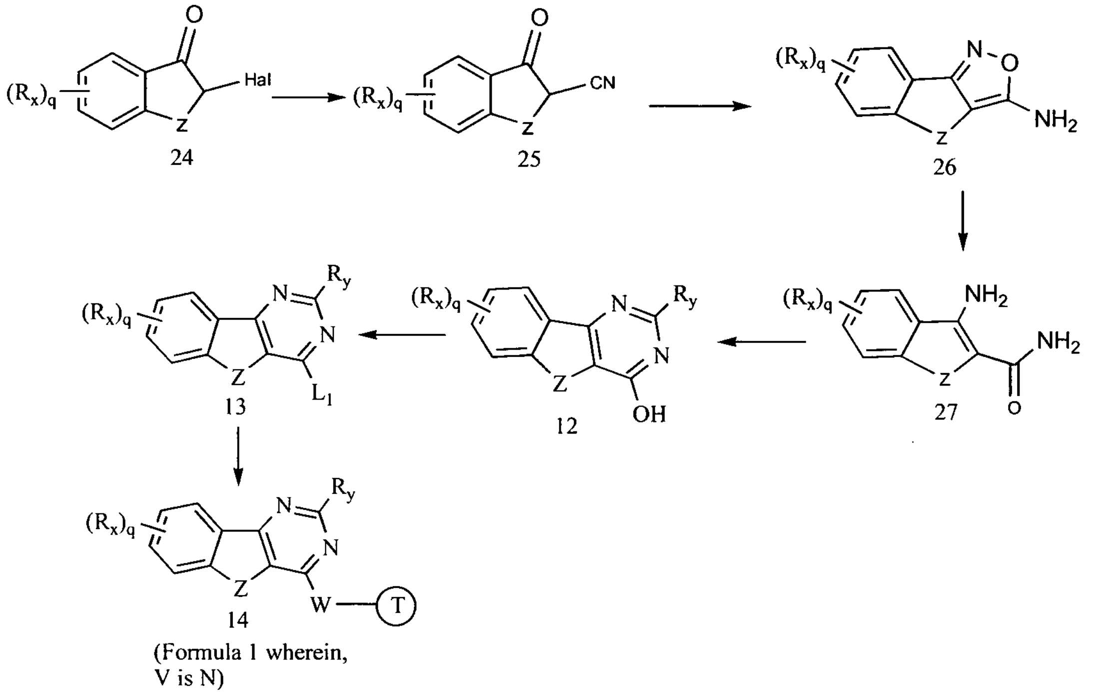
The compound of formula 22 is reacted with an amidine of the formula $R_y(C{=}NH_2)NH_2$ (or a salt thereof) to form a compound of formula 23 optionally in the presence of one or more bases, for example, sodium carbonate, potassium carbonate, cesium carbonate, triethylamine, ammonia, pyridine or a mixture thereof optionally in the presence of one or more solvents, for example, methanol, ethanol, isopropanol, *t*-butanol, tetrahydrofuran, dimethylformamide or a mixture thereof.

Alternatively, the compound of formula 22 is converted to the corresponding enamine by reacting it with a source of ammonia, for example, ammonium hydroxide, ammonium formate, ammonium acetate or a mixture thereof, followed by reaction with an amide, for example, formamide, to form a compound of formula 23.

The compound of formula 23 is deprotected (for example, by reaction with a deprotecting agent such as catalytic hydrogenation, hydrochloric acid, hydrobromic acid (e.g., in acetic acid), methane sufonic acid, and pyridimium hydrochloride) followed by cyclization, for example, in the presence of a reagent such as triarylphosphine and dialkylazodicarboxylate, to form a compound of formula 12. The reaction can be performed in one or more solvents, for example, methanol, ethanol, isopropanol, n-butyl alcohol, ethylene glycol, dioxane, tetrahydrofuran, ethyl acetate, butyl acetate or a mixture thereof.

The compound of formula 12 is converted to a compound of formula 14 by following the procedure described in scheme II.

Scheme VI



According to another embodiment, a compound of formula 14 is prepared using the process shown in Scheme VI. The compound of formula 24 (*Journal of American Chemical Society*, 1946, 68, 86-89) (wherein Hal is halogen) is converted to a compound of formula 25 by reaction with a cyanating agent, for example, sodium cyanide, trimethylsilyl cyanide, copper (I) cyanide or a mixture thereof optionally in one or more solvents, for example, dimethylformamide, dimethylacetamide, dimethylsulfoxide, acetonitrile, tetrahydrofuran or a mixture thereof.

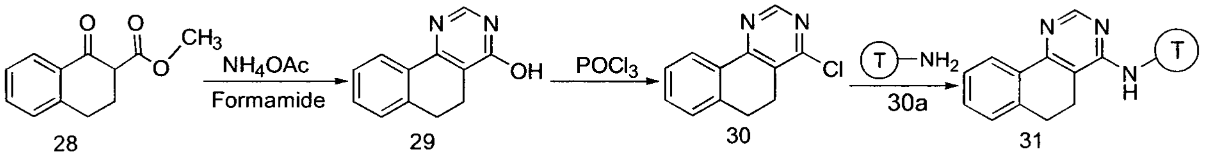
The compound of formula 25 is converted to a compound of formula 26, for example, by reaction with hydroxyl amine chloride or sulphate optionally in one or more solvents, for example, carbon tetrachloride, dichloromethane, dichloroethane, dibromoethane, chloroform or a mixture thereof, to form a compound of formula 26.

The compound of formula 26 is reduced to a compound of formula 27, for example, by reaction with a reducing agent (such as zinc/acetic acid, catalytic hydrogenation, iron / hydrochloric acid or a mixture thereof). The reaction can be performed in one or more solvents, for example, methanol, ethanol, isopropanol, n-butyl alcohol, ethylene glycol, dioxane, tetrahydrofuran, ethyl acetate, butyl acetate or a mixture thereof.

The compound of formula 27 is cyclized to form a compound of formula 12, for example, by reaction with a compound of formula $R_yCON(CH_3)_2$, optionally in one or more solvents, toluene, ethylene dichloride, methanol, ethanol, isopropanol, dichloromethane, chloroform, dichloroethane, dibromoethane, dioxane, tetrahydrofuran, ethyl acetate, butyl acetate or a mixture thereof.

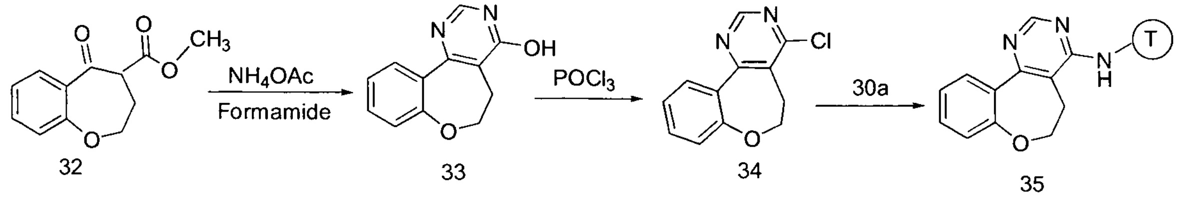
The compound of formula 12 is converted to a compound of formula 14 by following the procedure described in scheme II.

Scheme VII



According to another embodiment, a compound of formula 31 is prepared according to scheme VII. The compound of formula 28 (for example, prepared by a procedure described in *Tetrahedron*, vol. 51, No. 12, 3587-3606, 1995) is converted to a compound of formula 29, for example, by reaction with ammonium acetate in the presence of formamide to form a compound of formula 29. The compound of formula 29 is halogenated with a halogenating agent, for example, phosphorus oxychloride, to form a compound of formula 30. The compound of formula 30 is reacted with a compound of formula 30a to form a compound of formula 31 optionally in one or more solvents, for example, toluene, ethylenedichloride, methanol, ethanol, isopropanol, n-butyl alcohol, ethylene glycol, dioxane, tetrahydrofuran, ethyl acetate, butyl acetate, N,N-dimethylformamide, N-methylformamide, dimethylsulfoxide or a mixture thereof.

Scheme VIII



According to another embodiment, a compound of formula 35 is prepared according to scheme VIII. The compound of formula 32 (for example, prepared by a procedure described in *Tetrahedron* vol. 58, No. 12, 5203-5208, 2002) is converted to a compound of formula 33, for example, by reaction with ammonium acetate in the presence of formamide. The compound of formula 33 is halogenated with a halogenating agent, for example, phosphorus oxychloride, to form a compound of formula 34. The compound of formula 34 is reacted with a compound of formula 30a in one or more solvents, for example, toluene, ethylenedichloride, methanol, ethanol, isopropanol, n-butyl alcohol, ethylene glycol, dioxane, tetrahydrofuran, ethyl acetate, butyl acetate, N,N-dimethylformamide, N-methylformamide, dimethylsulfoxide or a mixture thereof, to form a compound of formula 35.

Experimental

Example 1: 2-hydroxy-4-methylbenzaldehyde

A solution of 3- methyl phenol (4.629mmol) in tetrahydrofuran (about 10 ml) was added dropwise to freshly prepared methyl magnesium bromide (4.629 mmol) at room temperature. After the phenoxide had completely precipitated, about 50 mL of benzene was added. Triethylamine (6.943 mmol) and paraformaldehyde (11.5 mmol) were added at once. The reaction mixture was refluxed for about 5-6 hrs at about 90 - 100^{0}C and then cooled to room temperature. The reaction mixture was then poured in 10% hydrochloric acid. Benzene and the aq. phases were separated and aq. layer was extracted with ethyl acetate . Organic phases were combined and dried over sodium sulphate. Solvent was removed under vacuum. Further purification was done by column chromatography to obtain the entitled compound.. ^{1}H NMR ($CDCl_3$): δ 2.37 (s, 3H); 6.81(s, 1H); 6.78 (d, 1H, J = 3.9 Hz); 7.40 (d, 1H, J =7.8Hz); 9.79 (s, 1H); 11.01 (s, 1H).IR (KBr) (cm^{-1}): 3564, 3050, 2864, 2761, 1654, 1573, 1508, 1446, 1320, 1289, 1204, 806, 738, 721.

The following compounds were prepared using the procedure described as described in Example 1 using appropriate phenol.

4-*tert*-butyl-2-hydroxybenzaldehyde

^{1}H NMR ($CDCl_3$): δ 1.31 (s, 9H); 6.98 (s, 1H); 7.03 (d, 1H, J = 7.2 Hz); 7.46 (d, 1H, J = 8.1 Hz); 9.81 (s, 1H); 10.97 (s, 1H). MS (M-H): 177.27

4-chloro-2-hydroxybenzaldehyde

^{1}H NMR ($CDCl_3$): δ 6.97- 6.99 (m, 2H); 7.47 (d, 1H, *J* = 8.7 Hz); 9.83 (s, 1H); 11.13 (s, 1H).

Example 2: Ethyl (2-formyl-5-methylphenoxy)acetate

Potassium carbonate (3.67 mmol) was added to the solution of 2-hydroxy-4-methylbenzaldehyde (1.838 mmol) in dimethylformamide (1 mL) and the mixture was stirred for about 30 minutes in nitrogen atmosphere. Ethyl bromoacetate (3.67 mmol) was added dropwise under cooling at about 10 – 20 ^{0}C. The reaction mixture was stirred at room temperature for about 2 hours. Cold water was added and then extracted with ethyl acetate. The extract was washed with water, dried over sodium sulphate. Solvent was removed under vacuum. Further purification was done by column chromatography to obtain the entitled compound. ^{1}H NMR (DMSO- d_6): δ 1.20 (t, 3H, J = 7.2 Hz); 2.26 (s, 3H); 4.16 (q, 2H, J = 6.3 Hz); 4.72 (s, 2H); 6.66- 6.76 (dd, 2H); 7.92 (s, 1H); 10.34 (s, 1H).

The following compounds were prepared using the procedure described as described in Example 2 using appropriate 2-hydroxy benzaldehyde.

Ethyl (5-*tert*-butyl-2-formylphenoxy)acetate

^{1}H NMR ($CDCl_3$): δ 1.28 (t, 3H, J = 4.8 Hz); 1.31 (s, 9H); 4.26 (q, 2H, J = 6.9 Hz); 4.74 (s, 2H); 6.83 (s, 1H); 7.10 (d, 1H, J = 8.4 Hz); 7.78 (d, 1H, J = 7.8 Hz); 10.47 (s, 1H).

Ethyl (5-chloro-2-formylphenoxy)acetate

Ethyl (2-formylphenoxy)acetate

^{1}H NMR ($CDCl_3$): δ 1.27 (t, 3H); 4.27 (q, 2H); 4.76 (s, 2H); 6.85 (d, 1H, J = 8.1 Hz); 7.07 (t, 1H, J = 7.2 Hz); 7.52 (t, 1H, J = 7.2 Hz); 7.84 (d, 1H, J = 7.2 Hz); 10.54 (s, 1H).

Example 3: Ethyl {2-[(hydroxyimino)methyl]-5-methylphenoxy}acetate

Hydroxyl amine hydrochloride (1.68 mmol) and sodium bicarbonate (1.68 mmol) were dissolved in water and stirred for about 15 minutes. Ethanolic solution of ethyl (2-formyl-5-methylphenoxy)acetate (1.126 mmol in 2.5 mL) and added dropwise to the above solution. The entire reaction mixture was stirred at room temperature for about 3– 4 hours. The solvent was evaporated under vacuum. Cold water was added to obtain a solid which was then filtered. The solid was washed with petroleum ether and dried to obtain the entitled compound. ^{1}H NMR ($CDCl_3$): δ 1.29 (t, 3H, J =7.2 Hz); 2.33 (s, 3H); 4.27 (q, 2H, J =6.9 Hz); 4.66 (s, 2H); 6.58 (s, 1H); 6.81 (d, 1H, J = 8.1 Hz); 7.61 (d, 1H, J =7.8 Hz); 8.55 (s, 1H).

The following compounds were prepared using the procedure described as described in Example 3 using appropriate ethyl (2-formylphenoxy)acetate

Ethyl {5-*tert*-butyl-2-[(hydroxyimino)methyl]phenoxy}acetate

^{1}H NMR ($CDCl_3$): δ 1.28 (t, 3H, J = 4.7 Hz); 1.29 (s, 9H); 4.26 (q, 2H, J = 7.5 Hz); 4.66 (s, 2H); 6.78 (s, 1H); 7.02(d, 1H, J = 8.1 Hz); 7.24 (s, 1H); 7.65 (d, 1H, J = 8.4 Hz); 8.58 (s, 1H). MS $(M+H)^+$: 280.75

Ethyl {2-[(hydroxyimino)methyl]phenoxy}acetate

^{1}H NMR ($CDCl_3$): δ 1.28 (t, 3H, J = 7.5 Hz); 4.25 (q, 2H, J = 7.2 Hz); 4.67(s, 2H); 6.7 (d, 1H, J = 8.4 Hz); 6.99 (d, 1H, J = 7.2 Hz); 7.30 (t, 1H, J = 7.8 Hz); 7.72 (d, 1H, J = 7.8 Hz); 8.45 (bs, 1H); 8.57 (s, 1H).

Ethyl {2-[(hydroxyimino)methyl]-5-chlorophenoxy}acetate

^{1}H NMR (DMSO- d_6): δ 3.70 (s, 3H); 4.93 (s, 2H); 7.05 (d, 1H, *J* = 8.4 Hz); 7.17 (s, 1H); 7.66 (d, 1H, *J* = 8.1 Hz); 8.27 (s, 2H); 11.38 (s, 1H).

Example 4: Ethyl (2-cyano-5-methylphenoxy)acetate

Dimethylaminopyridine (2.625 mmol) was dissolved in dichloromethane (5 mL) and cooled to about 0 to - 5^{0}C under nitrogen atmosphere. The solution was stirred for about 30 minutes. To this was added thionyl chloride (2.32 mmol) at about - 5^{0}C followed by ethyl {2-[(hydroxyimino)methyl]-5-methylphenoxy}acetate dropwise. The reaction mixture was neutralized with dilute hydrochloric acid. The product was extracted with dichloromethane. The remaining solution was washed with water, dried over sodium sulphate. The solvent was removed under vacuum. The compound so obtained was purified by column chromatography to obtain the desired product. ^{1}H NMR ($CDCl_3$): δ 1.26 (t, 3H, J = 6.9 Hz); 2.37 (s, 3H); 4.24 (q, 2H, J = 6.9 Hz); 4.73 (s, 2H); 6.63 (s, 1H); 6.85 (d, 1H, J = 7.8 Hz); 7.43 (d, 1H, J = 7.8 Hz). MS $(M+H)^+$: 220.07

The following compounds were prepared using the procedure described as described in Example 4 using appropriate {2-[(hydroxyimino)methyl]phenoxy}acetate

Ethyl (5-*tert*-butyl-2-cyanophenoxy)acetate

^{1}H NMR ($CDCl_3$): δ 1.28 (t, 3H, J = 7.5 Hz); 1.29 (s, 9H); 4.26 (q, 2H, J = 6.9 Hz); 4.75 (s, 2H); 6.81 (s, 1H); 7.06(d, 1H, J = 8.1 Hz); 7.4 (d, 1H, J = 8.4 Hz).

Ethyl (2-cyanophenoxy)acetate

^{1}H NMR ($CDCl_3$): δ 1.28 (t, 3H, J = 6.9 Hz); 4.25 (q, 2H, J = 6.9 Hz); 4.75 (s, 2H); 6.83 (d, 1H, J = 8.7 Hz); 7.04 (t, 1H, J = 7.8 Hz); 7.50 (t, 1H, J = 8.4 Hz); 7.58 (d, 1H, J = 7.8 Hz).

Ethyl (5-chloro-2-cyano phenoxy)acetate

^{1}H NMR (DMSO- d_6): δ 3.73 (s, 3H); 5.08 (s, 2H); 7.22 (d, 1H); 7.41 (s, 1H); 7.79 (d, 1H, *J* = 8.1 Hz).

Example 5: 7-methyl[1]benzofuro[3,2-*d*]pyrimidin-4-ol

The solution of ethyl (2-cyano-5-methylphenoxy)acetate (1.126 mmol) in formamide (2.81 mmol) was refluxed at about 170 – 180^{0}C for about 12 – 16 hrs. Cold water was added slowly to this solution. Aqueous layer was extracted in dichloromethane. The remnant solution was washed with water, dried over anhydrous sodium sulphate. The solvent was removed under vacuum and the solid so obtained was further purified by column chromatography. ^{1}H NMR (CD_3OD): δ 2.27 (s, 3H); 4.62 (bs, 1H); 7.35 (d, 1H, J =8.7 Hz); 7.55(s, 1H); 7.95 (d, 1H, J = 8.1 Hz); 8.21 (s, 1H). MS $(M+H)^+$: 201.32

The following compounds were prepared using the procedure described as described in Example 5 using appropriate ethyl (2-cyanophenoxy)acetate.

7-*tert*-butyl[1]benzofuro[3,2-*d*]pyrimidin-4-ol

^{1}H NMR (CD_3OD): δ 1.41 (s, 9H); 4.61 (bs, 1H); 7.56 (d, 1H, J = 10.2 Hz); 7.70(s, 1H); 7.96 (d, 1H, J = 8.4 Hz); 8.18 (s, 1H).

[1]benzofuro[3,2-*d*]pyrimidin-4-ol

^{1}H NMR (DMSO- d_6): δ 4.67 (s, 1H); 7.07 (t, 1H); 7.49 (d, 1H); 7.56 (t, 1H); 7.73 (d, 1H); 7.93 (s, 1H).

7- chloro[1]benzofuro[3,2-*d*]pyrimidin-4-ol

^{1}H NMR ($CDCl_3$): δ 7.22 (d, 1H); 7.37 (d, 1H, J = 8.7 Hz); 7.72 – 7.82 (m, 2H); 11.93 (bs, 1H).

Example 6: 4-chloro-7-methyl[1]benzofuro[3,2-*d*]pyrimidine

A solution of 7-methyl[1]benzofuro[3,2-*d*]pyrimidin-4-ol (0.231 mmol) in phosphorous oxychloride (5 mL) was refluxed at about 80 -90 ^{0}C for about12-14 hrs. The phosphorous oxychloride was distilled out. The residue so obtained was slowly added to cold water and the extraction was done with ethyl acetate. The solution was washed with water, dried over sodium sulphate. Solvent was removed under vacuum and the solid so obtained was purified by column chromatography to obtain the desired compound. ^{1}H NMR ($CDCl_3$): δ 2.60 (s, 3H); 7.34 (d, 1H, J = 7.2 Hz); 7.51 (s, 1H); 8.09 (d, 1H, J = 8.4 Hz); 8.92 (s, 1H). MS $(M+H)^+$: 219.55

The following compounds were prepared using the procedure described as described in Example 6 using appropriate benzofuro[3,2-*d*]pyrimidin-4-ol.

7-*tert*-butyl-4-chloro[1]benzofuro[3,2-*d*]pyrimidine

^{1}H NMR ($CDCl_3$): δ 1.43 (s, 9H); 7.59 (d, 1H, J = 8.1); 7.72 (s, 1H); 8.14 (d, 1H, J = 8.7 Hz); 8.93 (s, 1H).

4-chloro[1]benzofuro[3,2-*d*]pyrimidine

^{1}H NMR ($CDCl_3$): δ 7.53 (t, 1H, J = 6.3 Hz); 7.73 (m, 2H); 8.24 (d, 1H, J = 7.8 Hz); 8.97 (s, 1H).

4-chloro-6-methoxy[1]benzofuro[3,2-*d*]pyrimidine

The entitled compound is prepared by following the procedures as described in WO 2006064355
^{1}H NMR (DMSO- d_6): δ 4.04 (s, 3H); 7.47 – 7.56 (m, 2H); 7.77 (d, 1H, J = 7.5 Hz); 9.04 (s, 1H).

4,7-dichloro[1]benzofuro[3,2-*d*]pyrimidine

^{1}H NMR (DMSO- d_6): δ 7.67 (dd, 1H); 8.26 (d, 1H); 8.29 (s, 1H); 9.06 (s, 1H).

Example 7: 5,6-dihydrobenzo[*h*]quinazolin-4-ol

Ammonium acetate (5 mmol.) was added to the stirred solution of methyl 1-oxo-1,2,3,4-tetrahydronaphthalene-2-carboxylate (1 mmol) (Tetrahedron vol. 51, No. 12, 3587- 3606, 1995) in formamide (8 volume) and heated to about 160^{0}C for about 20 hours. The reaction mixture was then poured in ice water, solid obtained was dissolved in ethyl acetate. This layer was collected and washed with water, brine and dried over sodium sulphate. Solvent was evaporated to get the product. ^{1}H NMR (DMSO- d_6): δ 2.63 – 2.68 (m, 2H); 3.81 – 2.86 (m, 2H); 7.25 – 7.35 (m, 3H); 8.02 (dd, 1H); 8.14 (s, 1H); 12.42 (bs, 1H).
MS $[M+1]^+$: 199.638.

Example 8: 4-chloro-5,6-dihydrobenzo[*h*]quinazoline

The stirred solution of 5,6-dihydrobenzo[*h*]quinazolin-4-ol (1 mmol) in phosphoric trichloride was refluxed for about 1 hour. Phosphorous oxychloride was distilled off and residue was taken in ethyl acetate and water. Organic layer was separated and washed with saturated sodium bicarbonate solution, water and finally with brine. Dried over anhydrous sodium sulphate and solvent was evaporated to get the product. ^{1}H NMR (DMSO- d_6): δ 3.01 (s, 4H); 7.34 – 7.51 (m, 3H); 8.22 (d, 1H, *J*= 7.8 Hz); 8.89 (s, 1H).
MS $[M+1]^+$: -217.34

Example 9: 5,6-dihydro[1]benzoxepino[5,4-*d*]pyrimidin-4-ol

To the stirred solution of ethyl 5-oxo-2,3,4,5-tetrahydro-1-benzoxepine-4-carboxylate

(1 mmol) in formamide was added ammonium acetate (5 mmol.) and heated to 160^{0}C for 16 h. then reaction mixture was poured in ice water, extracted in ethyl acetate. This layer was collected and washed with water and dried over sodium sulphate. Solvent was evaporated to get the crude product. Further purified by column chromatography.

^{1}H NMR (CDCl$_3$): δ 2.75–2.79 (m, 2H); 4.40-4.44 (m, 2H); 7.06 (d, 1H, J = 7.8 Hz); 7.18 (t, 1H, J = 7.8 Hz); 7.39 (t, 1H, J = 7.8 Hz), 7. 48 (d, 1H, J = 7.8 Hz); 8.18 (s, 1H); 12.54 (brs, 1H), MS [M-1]$^-$: 233

Example 10: 4-chloro-5,6-dihydro[1]benzoxepino[5,4-*d*]pyrimidine

The stirred solution of 5,6-dihydro[1]benzoxepino[5,4-*d*]pyrimidin-4-ol (1 mmol) in phosphoric trichloride (10 volume) was refluxed for about 18 hours. Phosphoric trichloride was distilled off and water was added slowly. Extracted in dichloromethane. Organic layer was separated, washed with water and dried over anhydrous sodium sulphate and solvent was evaporated to get the product. Further purified by column chromatography.

^{1}H NMR (CDCl$_3$): δ 3.04–3.08 (m, 2H); 4.53-4.57 (m, 2H); 7.17 (d, 1H, J = 7.8 Hz); 7.30 (t, 1H, J = 7.8 Hz); 7.54 (t, 1H, J = 7.8 Hz), 7. 96 (d, 1H, J = 7.8 Hz); 8.99 (s, 1H)
MS [M+1]$^+$: 233

Example 11: *N*-{4-[(7-methyl[1]benzofuro[3,2-*d*]pyrimidin-4-yl)amino]-1,3-benzothiazol-2-yl}acetamide (Compound No. 1)

A solution of 4-chloro-7-methyl[1]benzofuro[3,2-*d*]pyrimidine (0.336 mmol) in isopropyl alcohol (15 mL) was stirred for about 2 -3 minutes. To this was added an isopropanolic solution of *N*-(4-amino-1,3-benzothiazol-2-yl)acetamide (0.40 mmol) at once. The solution was refluxed for about 12-15 hrs. The solvent was removed under vacuum. Water was added and the solid was extracted in chloroform. The chloroform layer was washed and dried over sodium sulphate. The solvent was concentrated to obtain a solid which was further purified by column chromatography to obtain the desired compound.^{1}H NMR (DMF): δ 2.35 (s, 3H); 2.59 (s, 3H), 7.40 (m, 2H); 7.69 (s, 1H); 7.75 (d, 1H, J =7.8 Hz); 8.07 (d, 1H, J = 9 Hz); 8.54 (d, 1H, J = 8.4 Hz); 8.73 (s, 1H); 8.92 (s, 1H); 12.51 (s, 1H). IR (KBr) (cm^{-1}): 3393, 1632, 1615, 1581, 1553, 1495, 1408, 1293, 1246, 1094, 986, 742, 713. MS (M+H)$^+$: 390.62
M. P. - > 250^{0}C

The following compounds were prepared using the procedure described as described in Example 7 using appropriate 4-chloro[1]benzofuro[3,2-*d*]pyrimidine.

Example 12: *N*-(2,3-dihydro-1,4-benzodioxin-6-yl)-7-methyl[1]benzofuro[3,2-*d*]pyrimidin-4-amine (Compound No. 2)

^{1}H NMR ($CDCl_3$): δ 2.55 (s, 3H), 4.27 (m, 4H); 6.88 (d, 1H, J =8.4 Hz); 6.94 (s, 1H); 7.06 (d, 1H, J = 9 Hz); 7.24 (s, 1H); 7.39 (m, 2H); 8.00 (d, 1H, J = 7.8 Hz); 8.66 (s, 1H). IR (KBr) (cm^{-1}): 3435, 3300, 2925, 1637, 1571, 1507, 1454, 1300, 1201, 1072, 1050, 788. MS $(M+H)^+$: 334.71 M. P: 195 - 197^{0}C.

Example 13: *N*-{4-[(7-tert-butyl[1]benzofuro[3,2-*d*]pyrimidin-4-yl)amino]-1,3-benzothiazol-2-yl}acetamide (Compound No. 3)

^{1}H NMR ($CDCl_3$): δ 1.42 (s, 9H); 2.35 (s, 3H), 7.39 (t, 1H, J = 8.1 Hz); 7.49 (m, 2H); 7.63 (s, 1H); 8.09 (d, 1H, J = 8.4 Hz); 8.39 (s, 1H); 8.80 (s, 2H); 9.20 (s, 1H).
IR (KBr) (cm^{-1}): 3444, 2962, 1634, 1618, 1508, 1408, 1319, 1249, 1071, 984, 785, 722.
MS $(M)^-$: 430.95 M. P. - > 250^{0}C.

Example 14: *N*-(2,3-dihydro-1,4-benzodioxin-6-yl)-7-tert-butyl[1]benzofuro[3,2-*d*]pyrimidin-4-amine (Compound No. 4)

^{1}H NMR (DMSO- d_6): δ 1.39 (s, 9H); 4.42 (s, 4H); 6.87 (d, 1H, J = 8.4 Hz); 7.28(d, 1H, J = 8.1 Hz); 7.44 (s, 1H); 7.59 (s, 1H); 7.70 (s, 1H); 8.50 (d, 1H); 8.84 (d, 1H); 10.39 (bs, 1H).
IR (KBr) (cm^{-1}): 3435, 2969, 1645, 1594, 1503, 1478, 1301, 1280, 1200, 1173, 1073, 868, 804.
MS $(M+H)^+$: 376.39 M. P: 200 - 203^{0}C.

Example 15: *N*-[4-([1]benzofuro[3,2-*d*]pyrimidin-4-ylamino)-1,3-benzothiazol-2-yl]acetamide (Compound No. 5)

^{1}H NMR (DMF): δ 2.35 (s, 3H); 7.41 (t, 1H); 7.58 (t, 1H); 7.77 (m, 2H); 7.88 (d, 1H); 8.22 (d, 1H); 8.55 (d, 1H); 8.77 (s, 1H); 9.06 (s, 1H); 12.55 (s, 1H).
IR (KBr) (cm^{-1}): 3358, 1690, 1636, 1557, 1513, 1416, 1278, 1091, 988, 743.
MS $(M+H)^+$: 376.33 M. P: > 250^{0}C.

Example 16: *N*-(2,3-dihydro-1,4-benzodioxin-6-yl)[1]benzofuro[3,2-*d*]pyrimidin-4-amine (Compound No. 6)

^{1}H NMR (DMSO- d_6): δ 4.23 (m, 4H); 6.84 (d, 1H, J =8.7 Hz); 7.32 (d, 1H, J =9.3 Hz); 7.51 (m, 2H); 7.71 (t, 1H, J =6.6 Hz); 7.82 (d, 1H, J = 8.1 Hz); 8.12 (d, 1H, J = 8.4 Hz); 8.58 (s, 1H); 9.97 (s, 1H).
IR (KBr) (cm^{-1}): 3434, 2928, 1650, 1508, 1305, 1201, 1101, 1055, 950, 740.
MS $(M+H)^+$: 320.74 M. P: 191 - 193^{0}C.

Example 17: *N*-quinolin-7-yl[1]benzofuro[3,2-*d*]pyrimidin-4-amine (Compound No. 7)

^{1}H NMR (DMSO- d_6): δ 7.41 (d, 1H); 7.57 (t, 1H, J = 7.2 Hz); 7.77 (t, 1H, J = 7.8 Hz); 7.88 (d, 1H, J = 8.1 Hz); 7.95 (d, 1H, J = 8.7 Hz); 8.11 (d, 1H, J = 8.7 Hz); 8.18 (d, 1H, J = 7.8 Hz); 8.27 (d, 1H, J = 7.8 Hz); 8.77 (s, 1H); 8.82 (s, 2H); 10.55

(bs, 1H).
IR (KBr) (cm^{-1}): 3435, 2929, 1642, 1579, 1499, 1436, 1304, 1201, 988, 839, 754.
MS $(M+H)^+$: 313.75 M. P: > 250^0C.

Example 18: *N*-1*H*-indazol-5-yl[1]benzofuro[3,2-*d*]pyrimidin-4-amine (Compound No. 8)

^{1}H NMR (DMSO- d_6): δ 7.57 (m, 2H), 7.73 (m, 3H); 7.88 (d, 1H, J = 8.4 Hz); 8.09 (s, 1H); 8.22 (s, 1H); 8.27 (s, 1H); 8.77 (s, 1H); 10.77 (s, 1H).
IR (KBr) (cm^{-1}): 3418, 3045, 1650, 1570, 1504, 1445, 1349, 1308, 1085, 946, 937, 750.
MS $(M+H)^+$: 302.33 M. P: > 250^0C.

Example 19: *N*-(2,3-dihydro-1,4-benzodioxin-6-yl)-6-methoxy[1]benzofuro[3,2-*d*]pyrimidin-4-amine (Compound No. 9)
^{1}H NMR ($CDCl_3$): δ 4.09(s, 3H); 4.28 (m, 4H); 6.87 (d, 1H, J = 8.4 Hz); 7.07 – 7.13 (m, 3H); 7.31(t, 1H, J = 7.8 Hz); 7.44 (d, 1H); 7.74 (d, 1H, J = 7.2 Hz); 8.69 (s, 1H).
IR (KBr) (cm^{-1}): 3363, 1637, 1606, 1509, 1470, 1416, 1307, 1276, 1162, 1063, 995, 773.
MS $(M+H)^+$: 350.61 M. P. 182-184 °C.

Example 20: *N*-[4-([1]benzofuro[3,2-*d*]pyrimidin-4-yloxy)-1,3-benzothiazol-2-yl]acetamide (Compound No. 10)

^{1}H NMR ($CDCl_3$): δ 2.23 (s, 3H); 7.39 (m, 4H); 7.70 (m, 4H); 9.57 (s, 1H).
IR (KBr) (cm^{-1}): 3434, 2923, 1707, 1643, 1602, 1523, 1463, 1393, 1276, 1248, 1180, 1092, 762, 740.
MS $(M-H)^-$: 375.29 M. P. 182 -184^0C.

Example 21: *N*-[4-(7-*tert*-butyl[1]benzofuro[3,2-*d*]pyrimidin-4-yloxy)-1,3-benzothiazol-2-yl]acetamide (Compound No. 11)

^{1}H NMR (DMSO- d_6): δ 1.41 (s, 9H); 2.93 (s, 3H); 7.41 (m, 2H); 7.67 (d, 1H, J = 8.1 Hz); 7.94 (m, 2H); 8.14 (d, 1H, J = 9 Hz); 8.60 (s, 1H); 12.31 (s, 1H).
IR (KBr) (cm^{-1}): 3440, 2960, 1693, 1636, 1592, 1549, 1456, 1391, 1270, 1221, 1184, 1070, 971, 873, 741.
MS $(M-H)^-$: 431.21 M. P. > 250 °C.

Example 22: *N*-{4-[(7-methyl[1]benzofuro[3,2-*d*]pyrimidin-4-yl)oxy]-1,3-benzothiazol-2-yl}acetamide (Compound No. 12)

^{1}H NMR (DMSO- d_6): δ 2.09 (s, 3H); 2.58 (s, 3H); 7.44 (m, 3H); 7.80 (s, 1H); 7.94 (d, 1H); 8.09 (d, 1H); 8.60 (s, 1H).
IR (KBr) (cm^{-1}): 3428, 2924, 1637, 1602, 1550, 1454, 1378, 1260, 1221, 1165, 1098, 1052, 971, 864, 781, 722.
MS $(M-H)^-$: 389.27 M. P: 240 - 242^0C.

Example 23: *N*-{4-[(7-chloro[1]benzofuro[3,2-*d*]pyrimidin-4-yl)oxy]-1,3-benzothiazol-2-yl}acetamide (Compound No. 13)

^{1}H NMR (DMSO- d_6): δ 2.10 (s, 3H); 7.40- 7.46 (m, 2H); 7.65 (d, 1H, *J* = 8.7 Hz); 7.95 (d, 1H, *J* = 7.2 Hz); 8.23- 8.27 (m, 2H); 8.66 (s, 1H); 12.36 (bs, 1H).
IR (KBr) (cm^{-1}): 3368, 2944, 1709, 1608, 1593, 1489, 1456, 1372, 1244, 1105, 1028, 933, 866, 753.
MS (M-H)$^-$: 409.26 M. P: > 250 ^{0}C.

Example 24: *N*-(4-*tert*-butylphenyl)-5,6-dihydrobenzo[*h*]quinazolin-4-amine (Compound No. 14)

To the stirred solution of 4-chloro-5,6-dihydrobenzo[*h*]quinazoline (1 mmol) in ethanol was added 4-*tert*-butylaniline (1 mmol) and refluxed for about 3 hours. Then solvent was evaporated to get crude product which was purified bi titurated with diethyl ether.

^{1}H NMR (DMSO- d_6): *δ* 1.30 (s, 9H); 2.93 (m, 4H); 7.39 – 7.51 (m, 7H); 8.0 (d, 1H, *J* = 7.2 Hz); 8.67 (s, 1H); 9.72 (bs, 1H). IR (KBr) (cm^{-1}): 3420, 2962, 2637, 1747, 1718, 1626, 1578, 1551, 1411, 1334, 1241, 1152, 841, 747. MS [M-1]$^-$: 328.48 M.P. 243 - 245^{0}C

The following compounds were prepared using the procedure described as described in Example 24 using appropriate heteroaryl-amine

Example 25: *N*-(2,3-dihydro-1,4-benzodioxin-6-yl)-5,6-dihydrobenzo[*h*]quinazolin-4-amine (Compound No. 15)

^{1}H NMR (DMSO- d_6): *δ* 2.91 – 3.01 (m, 4H); 4.25 (s, 4H); 6.88 (d, 1H, *J* = 8.7 Hz); 7.02 (dd, 1H); 7.15 (s, 1H); 7.41 – 7.55 (m, 3H); 8.11 (d, 1H, *J* = 7.5 Hz); 8.69 (s, 1H); 9.83 (bs, 1H).
IR (KBr)(cm^{-1}): 34 20, 2595, 1628, 1576, 1505, 1431, 1308, 1208, 1068, 882, 751
MS [M+1]+ : -332.34 M.P. >250^{0}C

Example 26: *N*-[4-(5,6-dihydrobenzo[*h*]quinazolin-4-ylamino)-1,3-benzothiazol-2-yl]acetamide (Compound No. 16)

^{1}H NMR ($CDCl_3$): *δ* 2.34 (s, 3H); 2.91 – 3.05 (m, 4H); 7.20 – 7.43 (m, 5H); 8.0 (s, 1H); 8.29 (m, 1H); 8.67 (d, 1H, *J* = 7.8 Hz); 8.80 (s, 1H); 8.96 (bs, 1H).
IR (KBr)(cm^{-1}): 3392, 2920, 1687, 1608, 1584, 1547, 1507, 1415, 1370, 1297, 1282, 1256, 1001, 757
MS [M+1]$^+$: -388.19 M.P: >250^{0}C

Example 27: *N*-(2,3-dihydro-1,4-benzodioxin-6-yl)-5,6-dihydro[1]benzoxepino[5,4-*d*]pyrimidin-4-amine (Compound No. 17)

To the stirred solution of 4-chloro-5,6-dihydro[1]benzoxepino[5,4-*d*]pyrimidine (1 mmol.) in ethanol was added 2,3-dihydro-1,4-benzodioxin-6-amine. (1 mmol) and refluxed for about 3 hours. Then solvent was evaporated to get crude product which was purified by column chromatography.

^{1}H NMR ($CDCl_3$): δ 2.86-2.90 (m, 2H); 4.22 (s, 2H); 4.52-4.56 (m, 2H); 6.80 (d, 1H, J = 8.4 Hz); 7.03-7.11 (m, 2H); 7.22-7.24 (m, 2H, J = 7.8 Hz), 7. 86 (d, 1H, J = 7.8 Hz); 8.51 (s, 1H); 8.70 (s, 1H).
IR (KBr)(cm^{-1}): 3420, 2962, 2637, 1747, 1718, 1626, 1578, 1551, 1411, 1334, 1241, 1152, 841, 747.
MS $[M+1]^+$: 248; M.P: 243 - 245^{0}C
The following compounds were prepared using the procedure described as described in Example 27 using appropriate heteroaryl-amine

Example 28: *N*-[4-(5,6-dihydro[1]benzoxepino[5,4-*d*]pyrimidin-4-ylamino)-1,3-benzothiazol-2-yl]acetamide (Compound No. 18)

^{1}H NMR ($CDCl_3$): δ 2.17 (s, 3H); 2.97 (m, 2H); 4.59 (s, 2H); 7.13 (d, 1H, J = 8.4 Hz); 7.23-7.34 (m, 2H); 7.45 (t, 1H, J = 7.8 Hz), 7. 72-7.78 (m, 2H); 7.92 (d, 1H, J = 6.9 Hz) 8.45 (s, 1H); 8.96 (s, 1H).
MS $[M+1]^+$: 403

Example 29: *N*-quinolin-7-yl-5,6-dihydro[1]benzoxepino[5,4-*d*]pyrimidin-4-amine (Compound No. 19)

^{1}H NMR ($CDCl_3$): δ 2.99-3.30 (m, 2H); 4.60-4.64 (s, 2H); 7.14 (d, 1H, J = 8.4 Hz); 7.8 (t, 1H, J = 7.2 Hz); 7.37-7.47 (m, 2H), 7.87-7.93 (m, 2H); 8.26 (d, 1H, J = 7.2 Hz) 8.46 (s, 1H); 8.70 (s, 1H), 8.81 (d, 1H, J = 2.4 Hz); 9.22 (s, 1H).
MS $[M+1]^+$: 341

Example 30: Screening for TRPV1 antagonist using ^{45}Calcium uptake assay:

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

Materials:

A stock solution of capsaicin was made in ethanol and test compounds were prepared in 100% DMSO. Stock solutions were diluted to appropriate final concentrations in assay buffer keeping the final DMSO concentration between 0.1% and 0.55%. ^{45}Ca was used at a final concentration of 2.5 μCi/ml (^{45}Ca, ICN).Assay buffer was composed of F-12 DMEM medium supplemented with 1.8 mM $CaCl_2$ (final conc.) and 0.1% Bovine serum albumin.(BSA from SIGMA) The wash buffer was Tyrodes solution supplemented with 0.1% BSA and 1.8 mM calcium. Lysis buffer contained 50 mM Tris-HCl, pH7.5, 150 mM NaCl, 1% Triton X-100, 0.5% deoxycholate and 0.1% Sodium dodecyl sulphate (SDS,SIGMA).

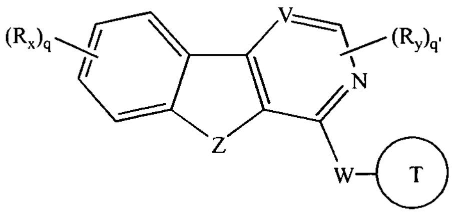
Method:

The assay was carried out with some modifications of the procedure as described by Toth et.al. (***See*** Toth A *et. al.*, *Life Sciences* **73** p 487-498, ***2003***). Human TRPV1 expressing CHO cells were grown in F-12 DMEM (Dulbecco's modified Eagle's medium –GIBCO) medium with 10% FBS (fetal bovine serum Hyclone), 1% penicillin-streptomycin solution, and 400 μg / ml of G-418. Cells were seeded 48 h prior to the assay in 96 well plates to obtain ~ 50,000 cells per well on the day of experiment. Plates were incubated at 37°C in the presence of 5 % CO_2. Cells were then washed twice with 200 μl of assay buffer and re-suspended in 144 μl of the same. Assay was carried out at 30°C in total volume of 200 μl. Test compounds were added to the cells fifteen minutes before addition of capsaicin. The final concentration of capsaicin in the assay was 250 nM. After 5 minutes of agonist treatment, the drug was washed out and the wells were rinsed with 300 μl of ice cold wash buffer 3X. The cells were lysed in 50 μl lysis buffer for 20 min. 40 μl of cell lysate was mixed with 150 μl of Microscint PS, left overnight for equilibration. Radioactivity in samples was measured as counts per minute (cpm) using Packard Biosciences Top Count. The drug / vehicle / capsaicin treated ^{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. IC_{50} value was calculated from dose response curve by nonlinear regression analysis using GraphPadPRISM software. Results were expressed as percent inhibition at various concentrations.

% inhibition of the test compounds at 300 nM ranged from between about 20% to about 25%; at 1 μM ranged from between about 2% to about 20%, from between about 20% to about 75%; at 3 μM ranged from between about 50% to about 100%.

We Claim:

1. A compound of the formula (1)



(1)

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

Z is $-Y-(CR_1R_2)_n-$ or $-(CR_1R_2)_n-Y$;

Y is a bond, NR_1, -O-, or -S-;

n is an integer ranging from 0-3;

V is N or CR_1; W is NR_1 or O;

Ring T is heteroaryl or heterocyclyl, optionally substituted with one or more R_y;

each occurrence of R_1, R_2, R_x and R_y is independently hydrogen, nitro, cyano, halogen, $-OR_3$, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted cycloalkenyl, substituted or unsubstituted cycloalkenylalkyl, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heteroarylalkyl, substituted or unsubstituted heterocyclic group, substituted or unsubstituted heterocyclylalkyl, $-NR_3R_4$, $-C(=L)-R_3$, $-C(O)O-R_3$, $-C(O)NR_3R_4$, $-S(O)_m-R_3$, $-S(O)_m-NR_3R_4$, $C(O)R_3$, $S(O)_2R_3$ or $COOR_3$;

each occurrence of L is O, S or NR_a

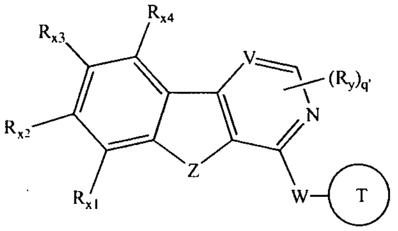
each occurrence of R_3 and R_4 may be the same or different and is independently hydrogen, $-OR^a$, $-SR^a$, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted cycloalkenyl, substituted or unsubstituted cycloalkenylalkyl, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heteroarylalkyl, substituted or unsubstituted heterocyclic group, substituted or unsubstituted heterocyclylalkyl, $-NR_aR_b$, $-C(=L)-R_a$, $-C(O)O-R_a$, $-C(O)NR_aR_b$, $-S(O)_m-R_a$ or $-S(O)_m-NR_aR_b$, or R_3 and R_4 taken together with the nitrogen atom to which they are attached are joined together to form an optionally substituted 3 to 7 membered saturated or unsaturated cyclic ring, which may optionally include at least two heteroatoms selected from O, NR_e or S;

each occurrence of R_a and R_b independently is hydrogen, $-OR_c$, $-SR_c$, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted cycloalkenyl, substituted or unsubstituted cycloalkenylalkyl, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heteroarylalkyl, substituted or unsubstituted heterocyclic group, substituted or unsubstituted heterocyclylalkyl, $-C(=L)-R_c$, $-C(O)O-R_c$, $-C(O)NR_cR_d$, $-S(O)_m-R_c$, $-S(O)_m-NR_cR_d$, $-NR_cR_d$, or a protecting group, or R_a and R_b taken together with the nitrogen atom to which they are attached are joined to form an optionally substituted 3 to 7 membered saturated or unsaturated cyclic ring, which may optionally include at least two heteroatoms selected from O, NR_e or S;

each occurrence of R_c and R_d is independently hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted cycloalkenyl, substituted or unsubstituted cycloalkenylalkyl, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heterocyclic group, substituted or unsubstituted heterocyclylalkyl, or a substituted or unsubstituted heteroarylalkyl or a protecting group, or R_c and R_d taken together with the nitrogen atom to which they are attached may be joined to form an optionally substituted 3 to 7 membered saturated or unsaturated cyclic ring, which may optionally include at least two heteroatoms selected from O, NR_e or S;

q is an integer ranging from 0-4, and q' is 0 or 1.

2. The compound of claim 1, wherein the compound has the formula (1a)



(1a)

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

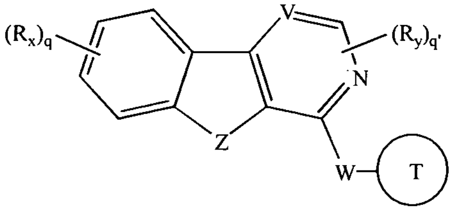
Z is -Y-$(CR_1R_2)_n$ wherein Y is -O-, n is 0;

V is N; W is selected from NH and O;

T is heteroaryl selected from benzothiazolyl, benzodioxinyl, quinolinyl and indazolyl, optionally substituted with one or more R_y,

R_{x1}-R_{x4} and R_y independently are selected from hydrogen, halogen, alkyl, NHCO-alkyl and -OR_3, wherein R_3 is alkyl.

3. The compound of claim 1, wherein the compound has the formula (1b)



(1b)

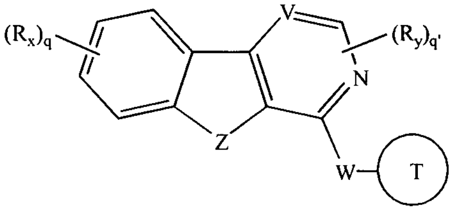
and pharmaceutically acceptable salts thereof, N-oxides thereof, and prodrugs thereof, wherein

Z is -Y-$(CR_1R_2)_n$- ; Y is a bond; n is 2; V is N; W is NR_1

Ring T is aryl, heteroaryl or heterocyclyl, optionally substituted with alkyl or NHCO-alkyl; and

R_1, R_2, R_x and R_y are hydrogen.

4. The compound of claim 1, wherein the compound has the formula (1c)



(1c)

prodrugs, pharmaceutically acceptable salts, N-oxides, esters, solvates, tautomers or stereoisomers thereof, wherein

Z is -Y-$(CR_1R_2)_n$- ; Y is O; n is 2; V is N; W is NR_1;

R_1, R_2, R_x and R_y are hydrogen; and

Ring T is heteroaryl or heterocyclyl, optionally substituted with NHCO-alkyl.

5. A compound selected from:

N-{4-[(7-methyl[1]benzofuro[3,2-*d*]pyrimidin-4-yl)amino]-1,3-benzothiazol-2-yl}acetamide, *N*-(2,3-dihydro-1,4-benzodioxin-6-yl)-7-methyl[1]benzofuro[3,2-*d*]pyrimidin-4-amine,

N-{4-[(7-tert-butyl[1]benzofuro[3,2-*d*]pyrimidin-4-yl)amino]-1,3-benzothiazol-2-yl}acetamide,

N-(2,3-dihydro-1,4-benzodioxin-6-yl)-7-tert-butyl[1]benzofuro[3,2-*d*]pyrimidin-4-amine,

N-[4-([1]benzofuro[3,2-*d*]pyrimidin-4-ylamino)-1,3-benzothiazol-2-yl]acetamide,

N-(2,3-dihydro-1,4-benzodioxin-6-yl)[1]benzofuro[3,2-*d*]pyrimidin-4-amine,

N-quinolin-7-yl[1]benzofuro[3,2-*d*]pyrimidin-4-amine,

N-1*H*-indazol-5-yl[1]benzofuro[3,2-*d*]pyrimidin-4-amine,

N-(2,3-dihydro-1,4-benzodioxin-6-yl)-6-methoxy[1]benzofuro[3,2-*d*]pyrimidin-4-amine,

N-[4-([1]benzofuro[3,2-*d*]pyrimidin-4-yloxy)-1,3-benzothiazol-2-yl]acetamide,

N-[4-(7-*tert*-butyl[1]benzofuro[3,2-*d*]pyrimidin-4-yloxy)-1,3-benzothiazol-2-yl]acetamide,

N-{4-[(7-methyl[1]benzofuro[3,2-*d*]pyrimidin-4-yl)oxy]-1,3-benzothiazol-2-yl}acetamide,

N-{4-[(7-chloro[1]benzofuro[3,2-*d*]pyrimidin-4-yl)oxy]-1,3-benzothiazol-2-yl}acetamide,

N-(4-*tert*-butylphenyl)-5,6-dihydrobenzo[*h*]quinazolin-4-amine,

N-(2,3-dihydro-1,4-benzodioxin-6-yl)-5,6-dihydrobenzo[*h*]quinazolin-4-amine,

N-[4-(5,6-dihydrobenzo[*h*]quinazolin-4-ylamino)-1,3-benzothiazol-2-yl]acetamide,

N-(2,3-dihydro-1,4-benzodioxin-6-yl)-5,6-dihydro[1]benzoxepino[5,4-*d*]pyrimidin-4-amine,

N-[4-(5,6-dihydro[1]benzoxepino[5,4-*d*]pyrimidin-4-ylamino)-1,3-benzothiazol-2-yl]acetamide,

N-quinolin-7-yl-5,6-dihydro[1]benzoxepino[5,4-*d*]pyrimidin-4-amine and

prodrugs, pharmaceutically acceptable salts, N-oxides, esters, solvates, tautomers or stereoisomers thereof.

6. A pharmaceutical composition comprising one or more compounds of claim 1 and one or more pharmaceutically acceptable excipients.

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 of claims 1.

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 8, 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, gastrointestinal disorders such as irritable bowel syndrome, gastro-esophageal reflux disease, enteritis, ileitis, stomach-duodenal ulcer, inflammatory bowel disease, Crohn's disease, celiac disease, an inflammatory disease such as pancreatitis, a respiratory disorder such as allergic and non-allergic rhinitis, asthma or chronic obstructive pulmonary disease, irritation of skin, eye or mucous membrane, dermatitis, pruritic conditions such as uremic pruritus, fervescence, muscle spasms, emesis, dyskinesias, depression, Huntington's disease, memory deficits, restricted brain function, amyotrophic lateral sclerosis (ALS), dementia, arthritis, osteoarthritis, diabetes, obesity, urticaria, actinic keratosis, keratocanthoma, alopecia, Meniere's disease, tinnitus, hyperacusis, anxiety disorders and benign prostate hyperplasia.

10. A method of treating neuropathic pain in a subject in need thereof comprising administering to the subject a therapeutically effective amount of a compound of claim 1-6.

11. 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 one of claims 1-6.

12. 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 one of claims 1-6.

13. 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 one of claims 1-6.

14. 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 one of claims 1-6.

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2007/004076

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D491/04 C07D405/12 C07D417/12 C07D239/94 A61K31/519
A61K31/517 A61P29/00 A61P25/02

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

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, BEILSTEIN Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2005/227992 A1 (HURLEY, LAURENCE H. ET AL) 13 October 2005 (2005-10-13) see compounds 32-87 to 32-89 and compounds 32-89 to 32-91,	1,6
X	WO 01/87845 A2 (FUJISAWA PHARMACEUTICAL CO., LTD., JAPAN) 22 November 2001 (2001-11-22) see compounds of example 50 (2) and (3) on p. 106	1,3,6
X	WO 99/06396 A1 (WARNER-LAMBERT COMPANY, USA) 11 February 1999 (1999-02-11) see first 2 compounds on p. 29, the last 2 compounds on p. 34 and the two compounds in l. 23 to 26 on p. 39	1,6
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☒ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search 29 January 2009	Date of mailing of the international search report 05/02/2009
Name and mailing address of the ISA/ European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Authorized officer Traegler-Goeldel, M

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	JP 06 220059 A (TANABE SEIYAKU CO, JAPAN) 9 August 1994 (1994-08-09) see e.g. compounds 156 (p. 33), 165, 166 (p. 35), 167 (p. 36), 193, 194 (p. 42), 35, 36 (p. 49), 79 (p. 55) and 90 and 91 (p. 57)	1,6
X	MULAGI, S. M. ET AL: "Synthesis of 2-phenylbenzofuro[3,2-d]pyrimidine and its derivatives" INDIAN JOURNAL OF CHEMISTRY, SECTION B: ORGANIC CHEMISTRY INCLUDING MEDICINAL CHEMISTRY , 32B(9), 965-8 CODEN: IJSBDB; ISSN: 0376-4699, 1993, XP009110873 see compound (12) in scheme 1	1
X	SASAKI, KENJI ET AL: "Polycyclic N-hetero compounds. XXXIII. Syntheses of 4-substituted 6,7-dihydro-5H-benzo[6,7]cyclohepta[1,2-d] pyrimidines and their inhibitory activities on platelet aggregation and on reserpine-induced hypothermia" JOURNAL OF HETEROCYCLIC CHEMISTRY , 27(6), 1771-6 CODEN: JHTCAD; ISSN: 0022-152X, 1990, XP009110878 see compound IIId in scheme 1	1,6
X	US 3 755 583 A (DE ANGELIS, GERALD GEORGE ET AL) 28 August 1973 (1973-08-28) see all compounds of example XIII in column 15	1,6
E	WO 2008/074445 A1 (UCB PHARMA, S. A., BELG.) 26 June 2008 (2008-06-26) see examples 24 and 30 as claimed in claim 22	1,6
E	WO 2008/060767 A2 (ABBOTT LABORATORIES, USA) 22 May 2008 (2008-05-22) see e.g. compounds on p. 94 (3 compounds), 95 (1st), 98 (last), 99 (2nd), 100 (3rd), 101 (3), 104 (last), 108 (1st, 3rd), 109 (3), 110 (2) and examples 65, 66, 68 to 72, 72A, 72B, 121 ans 122	1,6
E	WO 2008/008359 A2 (JANSSEN PHARMACEUTICA, N.V., BELG.) 17 January 2008 (2008-01-17) see e.g. examples 41 and 111 and their trifluoroacetic acid salts	1,6

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INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2007/004076

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2005/016922 A (GLAXO GROUP LTD [GB]; RAMI HARSHAD KANTILAL [GB]; THOMPSON MERVYN [GB]) 24 February 2005 (2005-02-24) see structure and activity as vanilloid receptor anatgonists -----	1-14
A	WO 2005/070929 A (AMGEN INC [US]) 4 August 2005 (2005-08-04) see structure and activity as vanilloid receptor ligands -----	1-14

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB2007/004076

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

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

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

Although claims 7 to 14 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

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

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

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

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

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers allsearchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search reportcovers only those claims for which fees were paid, specifically claims Nos.:

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

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/IB2007/004076

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		CA 2553969 A1	04-08-2005
		EP 1713807 A1	25-10-2006
		JP 2007524673 T	30-08-2007
		MX PA06008257 A	31-08-2006