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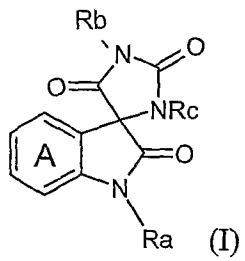
(54) **Title:** USE OF SPIRO [IMIDAZOLIDINE-4, 3'-INDOLE] 2, 2', 5' (1H) TRIONES FOR TREATMENT OF CONDITIONS ASSOCIATED WITH VANILLOID RECEPTOR 1



(I)

(57) **Abstract:** The present invention relates to a new use of spiro-hydantoin derivatives of formula (I), or salts, solvates or solvated salts thereof, as well as to new compounds, a process for their preparation and new intermediates used in the preparation thereof, pharmaceutical compositions containing said therapeutically active compounds and to the use of said active compounds in therapy.

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Use of spiro[imidazolidine-4,3´-indole]2,2´,5´(1H)triones for treatment of conditions associated with vanilloid receptor 1.

FIELD OF THE INVENTION

The present invention relates to a new use of spiro-hydantoin derivatives of formula I, or salts, solvates or solvated salts thereof, as well as to new compounds, a process for their preparation and new intermediates used in the preparation thereof, pharmaceutical compositions containing said therapeutically active compounds and to the use of said active compounds in therapy.

BACKGROUND OF THE INVENTION

Compounds of general formula I below are disclosed in EP 66378 and EP 28906. EP 66378 and EP 28906 further describe the use of these compounds for inhibition of the enzyme aldose reductase.

It has now been found that the spiro-hydantoin derivatives as decribed in EP 66378 and EP 28906 are well suited for inhibiting vanilloid receptor 1 (VR1). These inhibitors inhibitors are suitable in the treatment of conditions associated with vanilloid receptor 1 in the central and peripheral nervous system. In particular, the compounds of the invention are expected to be suitable for treatment of especially pain.

Functional studies using VR1 indicate that it is also activated by noxious heat, tissue acidification and other inflammatory mediators (Tominaga, M., Caterina, M.J. et.al. Neuron (1998) v. 21, p. 531-543). Expression of VR1 is also regulated after peripheral nerve damage of the type that leads to neuropathic pain. These properties of VR1 make it a highly relevant target for pain and for diseases involving inflammation. While agonists of the VR1 receptor can act as analgesics through nociceptor destruction, the use of agonists, such as capsaicin and its analogues, is limited due to their pungency, neurotoxicity and induction of hypothermia. Instead, agents that block the activity of VR1 should prove more useful. Antagonists would maintain the analgesic properties, but avoid pungency and neurotoxicity side effects.

Compounds with VR1 inhibitor activity are believed to be of potential use for the treatment and/or prophylaxis of disorders such as pain, especially that of inflammatory or traumatic origin such as arthritis, ischaemia, cancer, fibromyalgia, low back pain and post-operative pain (Walker et al J Pharmacol Exp Ther. (2003) Jan; 304(1):56-62). In addition

to this visceral pains such as chronic pelvic pain, cystitis, irritable bowel syndrome (IBS), pancreatitis and the like, as well as neuropathic pain such as sciatia, diabetic neuropathy, HIV neuropathy, multiple sclerosis, and the like (Walker et al *ibid*, Rashid et al J Pharmacol Exp Ther. (2003) Mar; 304(3):940-8), are potential pain states that could be treated with VR1 inhibitonThese compounds are also believed to be potentially useful for inflammatory disorders like asthma, cough, inflammatory bowel disease (IBD) (Hwang and Oh Curr Opin Pharmacol (2002) Jun; 2(3):235-42). Compounds with VR1 blocker activity are also useful for itch and skin diseases like psoriasis and for gastro-esophageal reflux disease (GERD), emesis, cancer, urinary incontinence and hyperactive bladder (Yiangou et al BJU Int (2001) Jun; 87(9):774-9, Szallasi Am J Clin Pathol (2002) 118: 110-21). VR1 inhibitors are also of potential use for the treatment and/or prophylaxis of the effects of exposure to VR1 activators like capsaicin or tear gas, acids or heat (Szallasi ibid).

A further portential use relates to the treatment of tolerance to VR1 activators.

VR1 inhibitors may also be useful in the treatment of interstitial cystitis and pain related to interstitial cystitis.

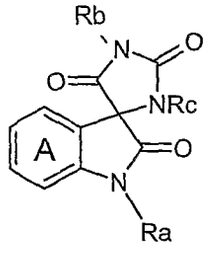
VR1 inhibitors may also be useful in the treatment of obesity and migraine;

WO2006/007851 discloses the use of VR1 antagonists for the treatment of obesity.

WO 92/07830 describes spiro-hydantoin derivatives and their use as antagonists for gastrin releasing peptide.

DETAILED DESCRIPTION OF THE INVENTION

In the present invention a compound of the general formula I, or salts, solvates or solvated salts thereof, may be used, in the manufacturing of a medicament for the treatment of conditions associated with vanilloid receptor 1:



(I)

wherein:

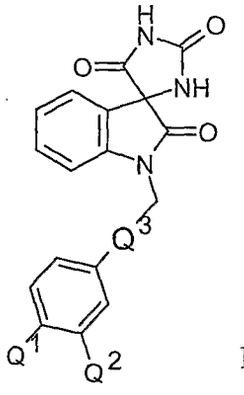
Ra is a C_{1-12}alkyl radical, a phenyl, naphthylmethyl, cinnamyl radical or a benzyl radical optionally substituted by one or more groups selected from halogen, cyano, nitro,

CF_3, OCF_3, trimethylsilyl, hydroxy, $-NR^6R^7$, SO_2R^7, R^6O-C_{1-6} alkyl, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{6-10}aryl and C_{5-10}heteroaryl;

Rb and Rc are independently selected from H, C_{1-10}alkyl, C_{2-10}alkenyl, C_{2-10}alkynyl, C_{3-10}cycloalkyl, C_{3-10}cycloalkyl-C_{1-6}alkyl, C_{4-8}cycloalkenyl-C_{1-6}alkyl, C_{3-6}heterocycloalkyl-C_{1-6}alkyl, C_{4-8}cycloalkenyl, C_{3-5}heteroaryl, C_{6-10}aryl and C_{3-6}heterocycloalkyl, C_{3-6}heteroaryl-C_{1-6}alkyl, C_{6-10}aryl-C_{1-6}alkyl and C_{1-6} alkyl-oxy-C_{1-5}alkyl,
optionally substituted by one or more groups selected from halogen, cyano, nitro, methoxy, ethoxy, methyl, ethyl, hydroxy and $-NR^6R^7$;

benzene ring A optionally substituted by one or more groups selected from H, halogen, C_{1-10}alkyl, haloalkyl, haloalkylO, C_{2-10}alkenyl, C_{2-10}alkynyl, C_{3-10}cycloalkyl, C_{3-10}cycloalkyl-C_{1-6}alkyl and C_{4-8}cycloalkenyl-C_{1-6}alkyl; and

R^6 and R^7 are independently selected from H, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, substituted or unsubstituted C_{6-10}aryl, substituted or unsubstituted C_{3-6}heteroaryl and a divalent C_{1-6}group that together with another divalent Ra, R^6 or R^7 forms a portion of a ring, or salts, solvates or solvated salts thereof, with the proviso that the compound does not have the formula III:



III

where Q^1 and Q^2 are independently halo or C_{1-3}haloalkyl and
Q^3 is ethenyl or ethynyl.

One embodiment of the invention relates to the use of compounds of formula I as described above wherein;

Ra is a C_{1-6}alkyl radical, a phenyl or a benzyl radical optionally substituted by one or more groups selected from halogen, CF_3, methoxy, ethoxy, OCF_3, methyl, ethyl, *tert*-butyl, hydroxy, SO_2R^7, R^6O-C_{1-6}alkyl, C_{1-6}alkyl, C_{2-6}alkenyl, C_{6-10}aryl and C_{5-10}heteroaryl

Rb and Rc are independently selected from H, C_{1-10}alkyl and C_{1-6} alkyl-oxy-C_{1-5}alkyl;

benzene ring A optionally substituted by one or more groups selected from H, halogen, C_{1-10}alkyl, haloalkyl and haloalkylO; and

R^6 and R^7 are independently selected from H, C_{1-6}alkyl, substituted or unsubstituted C_{6-10}aryl and substituted or unsubstituted C_{3-6}heteroaryl.

In another embodiment of the invention benzene ring A may be substituted by hydrogen, bromo, chloro, fluoro, methyl, ethyl, propyl, fluoromethyl, difluoromethyl, trifluoromethyl, fluoromethoxy, difluoromethoxy or trifluoromethoxy.

In one embodiment relates to the use of compounds of formula I whereby the benzene ring A is substituted by chloro.

Another embodiment of the invention relates the use to compounds of formula I whereby the benzene ring A is substituted by fluoro.

A further embodiment relates to the use of compounds of formula I whereby the benzene ring A is substituted by methyl.

Yet another embodiment relates to the use of compounds of formula I whereby the benzene ring A is substituted by hydrogen.

In another embodiment the benzene ring A is substituted on position 5.

In a further embodiment the benzene ring A is substituted on position 7.

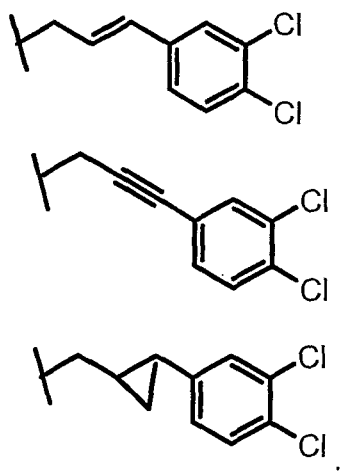
In yet a further embodiment the benzene ring A is substituted on position 5 and 7.

In one embodiment Rb is hydrogen or methyl; and Rc is hydrogen or methyl.

In another embodiment Rb and Rc are methyl. In yet another embodiment Rb and Rc are hydrogen. In a further embodiment Ra is methyl and Rb is hydrogen

In yet a further embodiment Ra is C_{1-6}alkyl radical is, for example, a methyl, ethyl, propyl, butyl, pentyl or hexyl radical, which alkyl radical may be straight or branched.

In another embodiment of the invention Ra is selected from the group consisting of



One embodiment of the invention relates to the use of a compound selected from the group consisting of

1'-(3,4-dichlorobenzyl)-1-pivaloyloxymethyl-spiro(imidazolidine-4,3'-indoline]-2,2',5-trione,

1'-(3,4-dichlorobenzyl)-3-formyl-spiro(imidazolidine-4,3'-indoline]-2,2',5-trione,

1'-(3,4-dichlorobenzyl)-1,3-di(ethoxycarbonyl)-spiro[imidazolidine-4,3'-indoline]-2,2',5-trione

3-ethoxycarbonyl-l'-(3,4-dichlorobenzyl)-spiro[imidazolidine-4,3'-indoline]-2,2',5-trione

3-benzoyl-l'-(3,4-dichlorobenzyl)-spiro[imidazolidine-4,3'-indoline]-2,2',5-trione

1'-(3,4-dichlorobenzyl)-3-(3-oxo-1,3-dihydro-2-benzofuran-1-yl)-2*H*,5*H*-spiro[imidazolidine-4,3'-indole]-2,2',5(1'*H*)-trione

3-benzyloxycarbonyl-l'-(3,4-dichlorobenzyl)-spiro(imidazolidine-4,3'-indoline)-2,2',5-trione,

3-benzyloxycarbonyl-l-ethoxycarbonyl-1'-(3,4-dichlorobenzyl)-spiro[imidazolidine-4,3'-indoline]-2,2',5-trione,

l-ethoxycarbonyl-l'-(3,4-dichlorobenzyl)-spiro[imidazolidine-4,3'-indoline]-2,2',5-trione,

l-acetyl-3-benzyloxycarbonyl-l'-(3,4-dichlorobenzyl)-spiro[imidazolidine-4,3'-indoline]-2,2',5-trione,

1-acetyl-l'-(3,4-dichlorobenzyl)-spiro[imidazolidine-4,3'-indoline]-2,2',5-trione,

ethyl [1'-(3,4-dichlorobenzyl)-2,2',5-trioxo-1',2'-dihydro-3*H*-spiro[imidazolidine-4,3'-indol]-3-yl](oxo)acetate

l'-(4-bromo-2-fluorobenzyl)-1-(pivaloyloxymethyl)-spiro[imidazolidine-4,3'-indoline]-2,2',5-trione,

(+)-l'-(3,4-dichlorobenzyl)-1-(pivaloyloxymethyl)-spiro[imidazolidine-4,3'-indoline]-2,2',5-trione, and

l'-(3,4-dichlorobenzyl)-7'-fluoro-l-(pivaloyloxymethyl)-spiro[imidazolidine-4,3'-indoline]-2,2',5-trione

or salts, solvates or solvated salts thereof,

in the manufacturing of a medicament for the treatment of conditions associated with vanilloid receptor 1.

Another embodiment of the invention relates to novel compounds selected from the group consisting of

1'-(2-methylpropyl)-2H,5H-spiro[imidazolidine-4,3'-indole]-2,2',5(1'H)-trione,

1'-(2-ethylbutyl)-2H,5H-spiro[imidazolidine-4,3'-indole]-2,2',5(1'H)-trione,

1'-{[4-(methylsulfonyl)phenyl]methyl}-2H,5H-spiro[imidazolidine-4,3'-indole]-2,2',5(1'H)-trione,

1'-(phenylmethyl)-2H,5H-spiro[imidazolidine-4,3'-indole]-2,2',5(1'H)-trione,

5'-chloro-1'-(3-methylbutyl)-2H,5H-spiro[imidazolidine-4,3'-indole]-2,2',5(1'H)-trione,

1'-[(2E)-2-butenyl]-5'-chloro-2H,5H-spiro[imidazolidine-4,3'-indole]-2,2',5(1'H)-trione,

1'-[(2-bromophenyl)methyl]-5'-fluoro-2H,5H-spiro[imidazolidine-4,3'-indole]-2,2',5(1'H)-trione,

5'-fluoro-1'-(2-methylpropyl)-2H,5H-spiro[imidazolidine-4,3'-indole]-2,2',5(1'H)-trione,

5'-fluoro-1'-{[4-(1-methylethyl)phenyl]methyl}-2H,5H-spiro[imidazolidine-4,3'-indole]-2,2',5(1'H)-trione,

5'-fluoro-1'-{[3-(methyloxy)phenyl]methyl}-2H,5H-spiro[imidazolidine-4,3'-indole]-2,2',5(1'H)-trione,

5'-fluoro-1'-(4-methyl-3-pentenyl)-2H,5H-spiro[imidazolidine-4,3'-indole]-2,2',5(1'H)-trione,

5'-fluoro-1'-{[2-(trifluoromethyl)phenyl]methyl}-2H,5H-spiro[imidazolidine-4,3'-indole]-2,2',5(1'H)-trione,

1'-(2-ethylbutyl)-5'-fluoro-2H,5H-spiro[imidazolidine-4,3'-indole]-2,2',5(1'H)-trione,

1'-(1,1'-biphenyl-2-ylmethyl)-5'-fluoro-2H,5H-spiro[imidazolidine-4,3'-indole]-2,2',5(1'H)-trione,

5'-fluoro-1'-{[4-(methylsulfonyl)phenyl]methyl}-2H,5H-spiro[imidazolidine-4,3'-indole]-2,2',5(1'H)-trione,

1'-{[2-chloro-5-(trifluoromethyl)phenyl]methyl}-5'-fluoro-2H,5H-spiro[imidazolidine-4,3'-indole]-2,2',5(1'H)-trione,
5'-fluoro-1'-[(2,4,6-trimethylphenyl)methyl]-2H,5H-spiro[imidazolidine-4,3'-indole]-2,2',5(1'H)-trione,
1'-[(2-chloro-6-fluorophenyl)methyl]-5'-fluoro-2H,5H-spiro[imidazolidine-4,3'-indole]-2,2',5(1'H)-trione,
1'-[(2,3-dichlorophenyl)methyl]-5'-fluoro-2H,5H-spiro[imidazolidine-4,3'-indole]-2,2',5(1'H)-trione,
5'-fluoro-1'-(3-methylbutyl)-2H,5H-spiro[imidazolidine-4,3'-indole]-2,2',5(1'H)-trione,
5'-fluoro-1'-pentyl-2H,5H-spiro[imidazolidine-4,3'-indole]-2,2',5(1'H)-trione,
5'-fluoro-1'-{[4-(1,2,3-thiadiazol-4-yl)phenyl]methyl}-2H,5H-spiro[imidazolidine-4,3'-indole]-2,2',5(1'H)-trione,
5'-fluoro-1'-(phenylmethyl)-2H,5H-spiro[imidazolidine-4,3'-indole]-2,2',5(1'H)-trione,
1'-[(2E)-2-butenyl]-5'-fluoro-2H,5H-spiro[imidazolidine-4,3'-indole]-2,2',5(1'H)-trione,
5'-fluoro-1'-(2-propenyl)-2H,5H-spiro[imidazolidine-4,3'-indole]-2,2',5(1'H)-trione,
5'-fluoro-1'-[(2E)-3-phenyl-2-propenyl]-2H,5H-spiro[imidazolidine-4,3'-indole]-2,2',5(1'H)-trione,
5'-chloro-7'-methyl-1'-{[3-(methyloxy)phenyl]methyl}-2H,5H-spiro[imidazolidine-4,3'-indole]-2,2',5(1'H)-trione,
5'-chloro-1'-{[2-fluoro-4-(trifluoromethyl)phenyl]methyl}-7'-methyl-2H,5H-spiro[imidazolidine-4,3'-indole]-2,2',5(1'H)-trione,
5'-chloro-1'-{[4-fluoro-3-(trifluoromethyl)phenyl]methyl}-7'-methyl-2H,5H-spiro[imidazolidine-4,3'-indole]-2,2',5(1'H)-trione,
5'-chloro-1'-[(2-chloro-6-fluorophenyl)methyl]-7'-methyl-2H,5H-spiro[imidazolidine-4,3'-indole]-2,2',5(1'H)-trione,
5'-chloro-7'-methyl-1'-{[3-(trifluoromethyl)phenyl]methyl}-2H,5H-spiro[imidazolidine-4,3'-indole]-2,2',5(1'H)-trione,
5'-chloro-7'-methyl-1'-{[4-(trifluoromethyl)phenyl]methyl}-2H,5H-spiro[imidazolidine-4,3'-indole]-2,2',5(1'H)-trione,
5'-chloro-7'-methyl-1'-(3-methylbutyl)-2H,5H-spiro[imidazolidine-4,3'-indole]-2,2',5(1'H)-trione,
5'-chloro-7'-methyl-1'-pentyl-2H,5H-spiro[imidazolidine-4,3'-indole]-2,2',5(1'H)-trione,

5'-chloro-7'-methyl-1'-(phenylmethyl)-2H,5H-spiro[imidazolidine-4,3'-indole]-2,2',5(1'H)-trione,
1'-[(2E)-2-butenyl]-5'-chloro-7'-methyl-2H,5H-spiro[imidazolidine-4,3'-indole]-2,2',5(1'H)-trione,
5'-chloro-7'-methyl-1'-(2-propenyl)-2H,5H-spiro[imidazolidine-4,3'-indole]-2,2',5(1'H)-trione,
5'-methyl-1'-(2-methylpropyl)-2H,5H-spiro[imidazolidine-4,3'-indole]-2,2',5(1'H)-trione,
1'-[(2-chloro-6-fluorophenyl)methyl]-2H,5H-spiro[imidazolidine-4,3'-indole]-2,2',5(1'H)-trione,
1'-(3-methylbutyl)-2H,5H-spiro[imidazolidine-4,3'-indole]-2,2',5(1'H)-trione,
1'-[(2E)-2-butenyl]-2H,5H-spiro[imidazolidine-4,3'-indole]-2,2',5(1'H)-trione,
1'-(2-propenyl)-2H,5H-spiro[imidazolidine-4,3'-indole]-2,2',5(1'H)-trione,
1'-[(4-fluorophenyl)methyl]-5'-methyl-2H,5H-spiro[imidazolidine-4,3'-indole]-2,2',5(1'H)-trione,
1'-[(2-bromophenyl)methyl]-5'-methyl-2H,5H-spiro[imidazolidine-4,3'-indole]-2,2',5(1'H)-trione,
5'-methyl-1'-{[4-(1-methylethyl)phenyl]methyl}-2H,5H-spiro[imidazolidine-4,3'-indole]-2,2',5(1'H)-trione,
5'-methyl-1'-{[3-(methyloxy)phenyl]methyl}-2H,5H-spiro[imidazolidine-4,3'-indole]-2,2',5(1'H)-trione,
5'-methyl-1'-(4-methyl-3-pentenyl)-2H,5H-spiro[imidazolidine-4,3'-indole]-2,2',5(1'H)-trione,
1'-{[2-fluoro-4-(trifluoromethyl)phenyl]methyl}-5'-methyl-2H,5H-spiro[imidazolidine-4,3'-indole]-2,2',5(1'H)-trione,
5'-methyl-1'-({4-[(trifluoromethyl)oxy]phenyl}methyl)-2H,5H-spiro[imidazolidine-4,3'-indole]-2,2',5(1'H)-trione,
1'-(1,1'-biphenyl-2-ylmethyl)-5'-methyl-2H,5H-spiro[imidazolidine-4,3'-indole]-2,2',5(1'H)-trione,
1'-{[2-chloro-5-(trifluoromethyl)phenyl]methyl}-5'-methyl-2H,5H-spiro[imidazolidine-4,3'-indole]-2,2',5(1'H)-trione,
1'-[(2-chloro-6-fluorophenyl)methyl]-5'-methyl-2H,5H-spiro[imidazolidine-4,3'-indole]-2,2',5(1'H)-trione,

1'-[(4-chlorophenyl)methyl]-5'-methyl-2H,5H-spiro[imidazolidine-4,3'-indole]-2,2',5(1'H)-trione,

1'-{[4-(1,1-dimethylethyl)phenyl]methyl}-5'-methyl-2H,5H-spiro[imidazolidine-4,3'-indole]-2,2',5(1'H)-trione,

5'-methyl-1'-{[4-(trifluoromethyl)phenyl]methyl}-2H,5H-spiro[imidazolidine-4,3'-indole]-2,2',5(1'H)-trione,

1'-[(2,4-dichlorophenyl)methyl]-5'-methyl-2H,5H-spiro[imidazolidine-4,3'-indole]-2,2',5(1'H)-trione,

1'-[(2,3-dichlorophenyl)methyl]-5'-methyl-2H,5H-spiro[imidazolidine-4,3'-indole]-2,2',5(1'H)-trione,

5'-methyl-1'-(3-methylbutyl)-2H,5H-spiro[imidazolidine-4,3'-indole]-2,2',5(1'H)-trione,

5'-methyl-1'-pentyl-2H,5H-spiro[imidazolidine-4,3'-indole]-2,2',5(1'H)-trione,

1'-[(2-iodophenyl)methyl]-5'-methyl-2H,5H-spiro[imidazolidine-4,3'-indole]-2,2',5(1'H)-trione,

1'-[(4-ethenylphenyl)methyl]-5'-methyl-2H,5H-spiro[imidazolidine-4,3'-indole]-2,2',5(1'H)-trione,

5'-methyl-1'-(phenylmethyl)-2H,5H-spiro[imidazolidine-4,3'-indole]-2,2',5(1'H)-trione,

1'-[(2E)-2-butenyl]-5'-methyl-2H,5H-spiro[imidazolidine-4,3'-indole]-2,2',5(1'H)-trione,

5'-methyl-1'-(2-propenyl)-2H,5H-spiro[imidazolidine-4,3'-indole]-2,2',5(1'H)-trione,

5'-methyl-1'-[(2E)-3-phenyl-2-propenyl]-2H,5H-spiro[imidazolidine-4,3'-indole]-2,2',5(1'H)-trione,

5'-methyl-1'-{[2-(trifluoromethyl)phenyl]methyl}-2H,5H-spiro[imidazolidine-4,3'-indole]-2,2',5(1'H)-trione,

1'-(2-ethylbutyl)-5'-methyl-2H,5H-spiro[imidazolidine-4,3'-indole]-2,2',5(1'H)-trione,

1'-{[4-fluoro-3-(trifluoromethyl)phenyl]methyl}-5'-methyl-2H,5H-spiro[imidazolidine-4,3'-indole]-2,2',5(1'H)-trione,

5'-methyl-1'-{[4-(methylsulfonyl)phenyl]methyl}-2H,5H-spiro[imidazolidine-4,3'-indole]-2,2',5(1'H)-trione,

5'-methyl-1'-[(2,4,6-trimethylphenyl)methyl]-2H,5H-spiro[imidazolidine-4,3'-indole]-2,2',5(1'H)-trione,

5'-methyl-1'-{[3-(trifluoromethyl)phenyl]methyl}-2H,5H-spiro[imidazolidine-4,3'-indole]-2,2',5(1'H)-trione,

5'-methyl-1'-({3-[(trifluoromethyl)oxy]phenyl}methyl)-2H,5H-spiro[imidazolidine-4,3'-indole]-2,2',5(1'H)-trione,

1'-[(4-bromo-2-fluorophenyl)methyl]-5'-methyl-2H,5H-spiro[imidazolidine-4,3'-indole]-2,2',5(1'H)-trione,

5'-methyl-1'-{[4-(1,2,3-thiadiazol-4-yl)phenyl]methyl}-2H,5H-spiro[imidazolidine-4,3'-indole]-2,2',5(1'H)-trione,

5'-chloro-1'-(4-methyl-3-pentenyl)-2H,5H-spiro[imidazolidine-4,3'-indole]-2,2',5(1'H)-trione,

5'-chloro-1'-(phenylmethyl)-2H,5H-spiro[imidazolidine-4,3'-indole]-2,2',5(1'H)-trione,

5'-chloro-1'-pentyl-2H,5H-spiro[imidazolidine-4,3'-indole]-2,2',5(1'H)-trione,

5'-fluoro-1'-{[2-fluoro-4-(trifluoromethyl)phenyl]methyl}-2H,5H-spiro[imidazolidine-4,3'-indole]-2,2',5(1'H)-trione,

5'-fluoro-1'-{[4-fluoro-3-(trifluoromethyl)phenyl]methyl}-2H,5H-spiro[imidazolidine-4,3'-indole]-2,2',5(1'H)-trione,

5'-chloro-7'-methyl-1'-(2-methylpropyl)-2H,5H-spiro[imidazolidine-4,3'-indole]-2,2',5(1'H)-trione,

5'-chloro-7'-methyl-1'-(4-methyl-3-pentenyl)-2H,5H-spiro[imidazolidine-4,3'-indole]-2,2',5(1'H)-trione,

5'-chloro-1'-(2-ethylbutyl)-7'-methyl-2H,5H-spiro[imidazolidine-4,3'-indole]-2,2',5(1'H)-trione, and

5'-chloro-7'-methyl-1'-[(2E)-3-phenyl-2-propenyl]-2H,5H-spiro[imidazolidine-4,3'-indole]-2,2',5(1'H)-trione,

or salts, solvates or solvated salts thereof.

A further embodiment of the invention relates to the use of the above listed compounds in the manufacturing of a medicament for the treatment of conditions associated with vanilloid receptor 1.

Listed below are definitions of various terms used in the specification and claims to describe the present invention.

For the avoidance of doubt it is to be understood that where in this specification a group is qualified by 'hereinbefore defined', 'defined hereinbefore' or 'defined above' the said group encompasses the first occurring and broadest definition as well as each and all of the other definitions for that group.

Unless specified otherwise within this specification, the nomenclature used in this specification generally follows the examples and rules stated in *Nomenclature of Organic Chemistry, Sections A, B, C, D, E, F, and H*, Pergamon Press, Oxford, 1979, which is incorporated by references herein for its exemplary chemical structure names and rules on naming chemical structures.

The term "C_{m-n}" or "C_{m-n} group" used alone or as a prefix, refers to any group having m to n carbon atoms.

The term "hydrocarbon" used alone or as a suffix or prefix, refers to any structure comprising only carbon and hydrogen atoms up to 14 carbon atoms.

The term "hydrocarbon radical" or "hydrocarbyl" used alone or as a suffix or prefix, refers to any structure as a result of removing one or more hydrogens from a hydrocarbon.

The term "alkyl" used alone or as a suffix or prefix, refers to monovalent straight or branched chain hydrocarbon radicals comprising 1 to about 12 carbon atoms.

The term "alkenyl" used alone or as suffix or prefix, refers to a monovalent straight or branched chain hydrocarbon radical having at least one carbon-carbon double bond and comprising at least 2 up to about 12 carbon atoms.

The term "alkynyl" used alone or as suffix or prefix, refers to a monovalent straight or branched chain hydrocarbon radical having at least one carbon-carbon triple bond and comprising at least 2 up to about 12 carbon atoms.

The term "cycloalkyl," used alone or as suffix or prefix, refers to a monovalent ring-containing hydrocarbon radical comprising at least 3 up to about 12 carbon atoms.

The term "cycloalkenyl" used alone or as suffix or prefix, refers to a monovalent ring-containing hydrocarbon radical having at least one carbon-carbon double bond and comprising at least 3 up to about 12 carbon atoms.

The term "aryl" used alone or as suffix or prefix, refers to a hydrocarbon radical having one or more polyunsaturated carbon rings having aromatic character, (*e.g.*, 4n + 2 delocalized electrons) and comprising 5 up to about 14 carbon atoms, wherein the radical is located on a carbon of the aromatic ring. Said heteroaryl may be substituted or unsubstituted.

The term "non-aromatic group" or "non-aromatic" used alone, as suffix or as prefix, refers to a chemical group or radical that does not contain a ring having aromatic character (*e.g.*, 4n + 2 delocalized electrons).

The term "heteroalkyl" used alone or as a suffix or prefix, refers to a radical formed as a result of replacing one or more carbon atom of an alkyl with one or more heteroatoms selected from N, O, P and S.

The term "heteroaromatic" used alone or as a suffix or prefix, refers to a ring-containing structure or molecule having one or more multivalent heteroatoms, independently selected from N, O, P and S, as a part of the ring structure and including at least 3 and up to about 20 atoms in the ring(s), wherein the ring-containing structure or molecule has an aromatic character (*e.g.*, 4n + 2 delocalized electrons).

The term "heterocyclic," or "heterocyclo" used alone or as a suffix or prefix, refers to a radical derived from a heterocycle by removing one or more hydrogens therefrom.

The term "heterocyclyl" used alone or as a suffix or prefix, refers a radical derived from a heterocycle by removing at least one hydrogen from a carbon of a ring of the heterocycle.

The term "heteroaryl" used alone or as a suffix or prefix, refers to a heterocyclyl having aromatic character, wherein the radical of the heterocyclyl is located on either a carbon or a heteroatom of an aromatic ring of the heterocyclyl. Said heteroaryl may be substituted or unsubstituted.

The term "heterocycloalkyl" used alone or as a suffix or prefix, refers to a heterocyclyl that does not have aromatic character.

The term "six-membered" used as prefix refers to a group having a ring that contains six ring atoms.

The term "five-membered" used as prefix refers to a group having a ring that contains five ring atoms.

A five-membered ring heteroaryl is a heteroaryl with a ring having five ring atoms wherein 1, 2 or 3 ring atoms are independently selected from N, O and S.

Exemplary five-membered ring heteroaryls are thienyl, furyl, pyrrolyl, imidazolyl, thiazolyl, oxazolyl, pyrazolyl, isothiazolyl, isoxazolyl, 1,2,3-triazolyl, tetrazolyl, 1,2,3-thiadiazolyl, 1,2,3-oxadiazolyl, 1,2,4-triazolyl, 1,2,4-thiadiazolyl, 1,2,4-oxadiazolyl, 1,3,4-triazolyl, 1,3,4-thiadiazolyl, and 1,3,4- oxadiazolyl.

A six-membered ring heteroaryl is a heteroaryl with a ring having six ring atoms wherein 1, 2 or 3 ring atoms are independently selected from N, O and S.

Exemplary six-membered ring heteroaryls are pyridyl, pyrazinyl, pyrimidinyl, triazinyl and pyridazinyl.

The term "substituted" used as a prefix refers to a structure, molecule or group, wherein one or more hydrogens are replaced with one or more C_{1-12}hydrocarbon groups, or one or more chemical groups containing one or more heteroatoms selected from N, O, S, F, Cl, Br, I, and P. Exemplary chemical groups containing one or more heteroatoms include heterocyclyl, $-NO_2$, -OR, -Cl, -Br, -I, -F, $-CF_3$, -C(=O)R, -C(=O)OH, $-NH_2$, -SH, -NHR, $-NR_2$, -SR, $-SO_3H$, $-SO_2R$, -S(=O)R, -CN, -OH, -C(=O)OR, $-C(=O)NR_2$, -NRC(=O)R, oxo (=O), imino (=NR), thio (=S), and oximino (=N-OR), wherein each "R" is a C_{1-12}hydrocarbyl. For example, substituted phenyl may refer to nitrophenyl, pyridylphenyl, methoxyphenyl, chlorophenyl, aminophenyl, etc., wherein the nitro, pyridyl, methoxy, chloro, and amino groups may replace any suitable hydrogen on the phenyl ring.

The term "substituted" used as a suffix of a first structure, molecule or group, followed by one or more names of chemical groups refers to a second structure, molecule or group, which is a result of replacing one or more hydrogens of the first structure, molecule or group with the one or more named chemical groups. For example, a "phenyl substituted by nitro" refers to nitrophenyl.

The term "optionally substituted" refers to both groups, structures, or molecules that are substituted and those that are not substituted.

Heterocycle includes, for example, monocyclic heterocycles such as: aziridine, oxirane, thiirane, azetidine, oxetane, thietane, pyrrolidine, pyrroline, imidazolidine, pyrazolidine, pyrazoline, dioxolane, sulfolane 2,3-dihydrofuran, 2,5-dihydrofuran tetrahydrofuran, thiophane, piperidine, 1,2,3,6-tetrahydro-pyridine, piperazine, morpholine, thiomorpholine, pyran, thiopyran, 2,3-dihydropyran, tetrahydropyran, 1,4-dihydropyridine, 1,4-dioxane, 1,3-dioxane, dioxane, homopiperidine, 2,3,4,7-tetrahydro-1*H*-azepine homopiperazine, 1,3-dioxepane, 4,7-dihydro-1,3-dioxepin, and hexamethylene oxide.

In addition, heterocycle includes aromatic heterocycles, for example, pyridine, pyrazine, pyrimidine, pyridazine, thiophene, furan, furazan, pyrrole, imidazole, thiazole, oxazole, pyrazole, isothiazole, isoxazole, 1,2,3-triazole, tetrazole, 1,2,3-thiadiazole, 1,2,3-

oxadiazole, 1,2,4-triazole, 1,2,4-thiadiazole, 1,2,4-oxadiazole, 1,3,4-triazole, 1,3,4-thiadiazole, and 1,3,4- oxadiazole.

Additionally, heterocycle encompass polycyclic heterocycles, for example, indole, indoline, isoindoline, quinoline, tetrahydroquinoline, isoquinoline, tetrahydroisoquinoline, 1,4-benzodioxan, coumarin, dihydrocoumarin, benzofuran, 2,3-dihydrobenzofuran, isobenzofuran, chromene, chroman, isochroman, xanthene, phenoxathiin, thianthrene, indolizine, isoindole, indazole, purine, phthalazine, naphthyridine, quinoxaline, quinazoline, cinnoline, pteridine, phenanthridine, perimidine, phenanthroline, phenazine, phenothiazine, phenoxazine, 1,2-benzisoxazole, benzothiophene, benzoxazole, benzthiazole, benzimidazole, benztriazole, thioxanthine, carbazole, carboline, acridine, pyrolizidine, and quinolizidine.

In addition to the polycyclic heterocycles described above, heterocycle includes polycyclic heterocycles wherein the ring fusion between two or more rings includes more than one bond common to both rings and more than two atoms common to both rings. Examples of such bridged heterocycles include quinuclidine, diazabicyclo[2.2.1]heptane and 7-oxabicyclo[2.2.1]heptane.

Heterocyclyl includes, for example, monocyclic heterocyclyls, such as: aziridinyl, oxiranyl, thiiranyl, azetidinyl, oxetanyl, thietanyl, pyrrolidinyl, pyrrolinyl, imidazolidinyl, pyrazolidinyl, pyrazolinyl, dioxolanyl, sulfolanyl, 2,3-dihydrofuranyl, 2,5-dihydrofuranyl, tetrahydrofuranyl, thiophanyl, piperidinyl, 1,2,3,6-tetrahydro-pyridinyl, piperazinyl, morpholinyl, thiomorpholinyl, pyranyl, thiopyranyl, 2,3-dihydropyranyl, tetrahydropyranyl, 1,4-dihydropyridinyl, 1,4-dioxanyl, 1,3-dioxanyl, dioxanyl, homopiperidinyl, 2,3,4,7-tetrahydro-1*H*-azepinyl, homopiperazinyl, 1,3-dioxepanyl, 4,7-dihydro-1,3-dioxepinyl, and hexamethylene oxidyl.

In addition, heterocyclyl includes aromatic heterocyclyls or heteroaryl, for example, pyridinyl, pyrazinyl, pyrimidinyl, pyridazinyl, thienyl, furyl, furazanyl, pyrrolyl, imidazolyl, thiazolyl, oxazolyl, pyrazolyl, isothiazolyl, isoxazolyl, 1,2,3-triazolyl, tetrazolyl, 1,2,3-thiadiazolyl, 1,2,3-oxadiazolyl, 1,2,4-triazolyl, 1,2,4-thiadiazolyl, 1,2,4-oxadiazolyl, 1,3,4-triazolyl, 1,3,4-thiadiazolyl, and 1,3,4 oxadiazolyl.

Additionally, heterocyclyl encompasses polycyclic heterocyclyls (including both aromatic or non-aromatic), for example, indolyl, indolinyl, isoindolinyl, quinolinyl, tetrahydroquinolinyl, isoquinolinyl, tetrahydroisoquinolinyl, 1,4-benzodioxanyl, coumarinyl,

dihydrocoumarinyl, benzofuranyl, 2,3-dihydrobenzofuranyl, isobenzofuranyl, chromenyl, chromanyl, isochromanyl, xanthenyl, phenoxathiinyl, thianthrenyl, indolizinyl, isoindolyl, indazolyl, purinyl, phthalazinyl, naphthyridinyl, quinoxalinyl, quinazolinyl, cinnolinyl, pteridinyl, phenanthridinyl, perimidinyl, phenanthrolinyl, phenazinyl, phenothiazinyl, phenoxazinyl, 1,2-benzisoxazolyl, benzothiophenyl, benzoxazolyl, benzthiazolyl, benzimidazolyl, benztriazolyl, thioxanthinyl, carbazolyl, carbolinyl, acridinyl, pyrolizidinyl, and quinolizidinyl.

In addition to the polycyclic heterocyclyls described above, heterocyclyl includes polycyclic heterocyclyls wherein the ring fusion between two or more rings includes more than one bond common to both rings and more than two atoms common to both rings. Examples of such bridged heterocycles include quinuclidinyl, diazabicyclo[2.2.1]heptyl; and 7-oxabicyclo[2.2.1]heptyl.

The term "alkoxy" used alone or as a suffix or prefix, refers to radicals of the general formula –O-R, wherein -R is selected from a hydrocarbon radical. Exemplary alkoxy includes methoxy, ethoxy, propoxy, isopropoxy, butoxy, t-butoxy, isobutoxy, cyclopropylmethoxy, allyloxy, and propargyloxy.

The term "aryloxy" used alone or as suffix or prefix, refers to radicals of the general formula –O-Ar, wherein -Ar is an aryl.

The term "heteroaryloxy" used alone or as suffix or prefix, refers to radicals of the general formula –O-Ar', wherein -Ar' is a heteroaryl.

The term "amine" or "amino" used alone or as a suffix or prefix, refers to radicals of the general formula –NRR', wherein R and R' are independently selected from hydrogen or a hydrocarbon radical.

"Halogen" includes fluorine, chlorine, bromine and iodine.

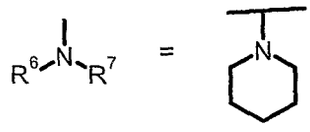
"Halogenated," used as a prefix of a group, means one or more hydrogens on the group is replaced with one or more halogens.

"RT" or "rt" means room temperature.

"Saturated carbon" means a carbon atom in a structure, molecule or group wherein all the bonds connected to this carbon atom are single bond. In other words, there is no double or triple bonds connected to this carbon atom and this carbon atom generally adopts an sp^3 atomic orbital hybridization.

"Unsaturated carbon" means a carbon atom in a structure, molecule or group wherein at least one bond connected to this carbon atom is not a single bond. In other words, there is at least one double or triple bond connected to this carbon atom and this carbon atom generally adopts a *sp* or sp^2 atomic orbital hybridization.

The term 'a divalent C_{1-6}group that together with another divalent R^5, R^6 or R^7 forms a portion of a ring' means that Ra, R^6 or R^7 can be cyclic e.g.



4, 5, 6, 7 membered rings with and without heteroatoms (O,N).

The present invention relates to the compounds of the invention as hereinbefore defined as well as to the salts, solvates or solvated salts thereof. Salts for use in pharmaceutical formulations will be pharmaceutically acceptable salts, but other salts may be useful in the production of the compounds of the invention.

A suitable pharmaceutically acceptable salt of the compounds of the invention is, for example, an acid-addition salt, for example a salt with an inorganic or organic acid. In addition, a suitable pharmaceutically acceptable salt of the compounds of the invention is an alkali metal salt, an alkaline earth metal salt or a salt with an organic base.

Other pharmaceutically acceptable salts and methods of preparing these salts may be found in, for example, Remington's Pharmaceutical Sciences (18^{th} Edition, Mack Publishing Co.).

Some compounds of the invention may have chiral centres and/or geometric isomeric centres (E- and Z- isomers), and it is to be understood that the invention encompasses all such optical, diastereoisomeric and geometric isomers.

The invention also relates to any and all tautomeric forms of the compounds of the invention.

Methods of Preparation

One embodiment of the present invention provides processes for preparing compounds of the invention, or salts, solvates or solvated salts thereof.

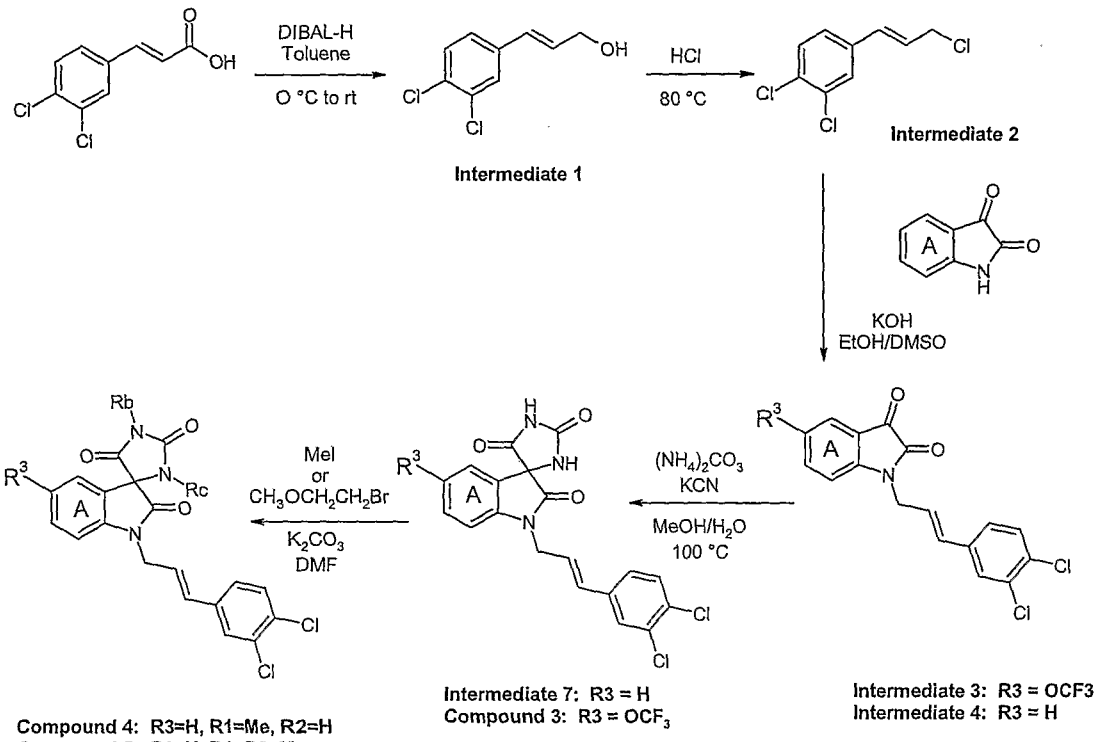
Many of the compounds of the invention can be made according to the preparation methods described in patent EP 66378.

Throughout the following description of such processes it is to be understood that, where appropriate, suitable protecting groups will be added to, and subsequently removed from, the various reactants and intermediates in a manner that will be readily understood by one skilled in the art of organic synthesis. Conventional procedures for using such protecting groups as well as examples of suitable protecting groups are described, for example, in "Protective Groups in Organic Synthesis", T.W. Green, P.G.M. Wuts, Wiley-Interscience, New York, (1999). References and descriptions of other suitable reactions are described in textbooks of organic chemistry, for example, "Advanced Organic Chemistry", March, 4th ed. McGraw Hill (1992) or, "Organic Synthesis", Smith, McGraw Hill, (1994). For representative examples of heterocyclic chemistry see for example "Heterocyclic Chemistry", J. A. Joule, K. Mills, G. F. Smith, 3rd ed. Chapman and Hall (1995), p. 189-224 and "Heterocyclic Chemistry", T. L. Gilchrist, 2nd ed. Longman Scientific and Technical (1992), p. 248-282.

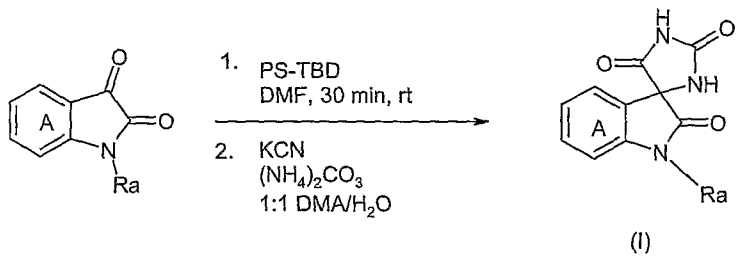
The term "room temperature" and "ambient temperature" shall mean, unless otherwise specified, a temperature between 16 and 25 °C.

Schemes

Scheme 1



Scheme 2



Pharmaceutical composition

According to one embodiment of the present invention there is provided a pharmaceutical composition comprising as active ingredient a therapeutically effective amount of the compound of the invention, or salts, solvates or solvated salts thereof, in association with one or more pharmaceutically acceptable diluents, excipients and/or inert carriers.

The composition may be in a form suitable for oral administration, for example as a tablet, pill, syrup, powder, granule or capsule, for parenteral injection (including intravenous, subcutaneous, intramuscular, intravascular or infusion) as a sterile solution, suspension or emulsion, for topical administration e.g. as an ointment, patch or cream, for rectal administration e.g. as a suppository or for inhalation.

In general the above compositions may be prepared in a conventional manner using one or more conventional excipients, pharmaceutical acceptable diluents and/or inert carriers.

Suitable daily doses of the compounds of formula I in the treatment of a mammal, including man, are approximately 0.01 to 250 mg/kg bodyweight at peroral administration and about 0.001 to 250 mg/kg bodyweight at parenteral administration.

The typical daily dose of the active ingredient varies within a wide range and will depend on various factors such as the relevant indication, severity of the illness being treated, the route of administration, the age, weight and sex of the patient and the particular compound being used, and may be determined by a physician.

The above compositions may be obtained by conventional procedures well known in the pharmaceutical art.

Medical use

It has been found that the compounds according to the present invention are useful in therapy. The compounds of the invention, or salts, solvates or solvated salts thereof, as well as their corresponding active metabolites, exhibit a high degree of potency and selectivity for individual vanilloid receptor 1 (VR1) groups. Accordingly, the compounds of the present invention are expected to be useful in the treatment of conditions associated with excitatory activation of vanilloid receptor 1 (VR1).

The compounds may be used to produce an inhibitory effect of VR1 in mammals, including man.

VR1 are highly expressed in the peripheral nervous system and in other tissues. Thus, it is expected that the compounds of the invention are well suited for the treatment of VR1 mediated disorders.

The compounds of the invention are expected to be suitable for the treatment of acute and chronic pain, acute and chronic neuropathic pain and acute and chronic inflammatory pain.

Examples of such disorder may be selected from the group comprising low back pain, post-operative pain, visceral pains like chronic pelvic pain and the like.

The compounds of the invention are also expected to be suitable for the treatment of acute and chronic nociceptive pain.

Further relevant disorders may be selected from the group comprising cystitis, including interstitial cystitis and pain related thereto, ischeamic, sciatia, multiple sclerosis, arthritis, osteoarthritis, rheumatoid arthritis, fibromyalgia, pain and other signs and symptoms associated with psoriasis, pain and other signs and symptoms associated with cancer, emesis, urinary incontinence, hyperactive bladder and HIV neuropathy.

Additional relevant disorders may be selected from the group comprising gastro-esophageal reflux disease (GERD), irritable bowel syndrome (IBS), inflammatory bowel disease (IBD) and pancreatitis.

Other relevant disorders are related to respiratory diseases and may be selected from the group comprising asthma, cough, chronic obstructive lung disease, specifically chronic obstructive pulmonary disease (COPD) and emphysema, lung fibrosis and interstitial lung disease.

Yet other relevant disorders are obesity and obesity-related diseases or disorders, and migraine.

In one embodiment the obesity or obesity-related diseases or disorders is selected from the following: cardiovascular disease, hypertension, cancer and reproductive disorders.

The VR1 inhibitor(s) may be administrated by either an oral or inhaled route. The respiratory disease may be an acute and chronic illness and may be related to infection(s) and/or exposure to environmental pollution and/or irritants.

The compounds of the invention may also be used as antitoxin to treat (over-) exposure to VR1 activators like capsaicin, tear gas, acids or heat. Regarding heat, there is a potential use for VR1 antagonists in (sun-) burn induced pain, or inflammatory pain resulting from brun injuries.

The compounds may further be used for treatment of tolerance to VR1 activators.

One embodiment of the invention relates to the compounds of the invention as hereinbefore defined, for use as a medicament.

Another embodiment of the invention relates to the compounds of the invention as hereinbefore defined, for use as a medicament for treatment of VR1 mediated disorders.

A further embodiment of the invention relates to the compounds of the invention as hereinbefore defined, for use as a medicament for treatment of acute and chronic pain disorders.

Another embodiment of the invention relates to the compounds of the invention as hereinbefore defined for use as medicaments for treatment of acute and chronic nociceptive pain.

Yet another embodiment of the invention relates to the compounds of the invention as hereinbefore defined, for use as a medicament for treatment of acute and chronic neuropathic pain.

Yet a further embodiment of the invention relates to the compounds of the invention as hereinbefore defined, for use as a medicament for treatment of acute and chronic inflammatory pain.

One embodiment of the invention relates to the compounds of the invention as hereinbefore defined, for use as a medicament for treatment of low back pain, post-operative pain and visceral pains like chronic pelvic pain.

Another embodiment of the invention relates to the compounds and enatiomers of the invention as hereinbefore defined, for use as medicaments for treatment of cystitis, including interstitial cystitis and pain related thereto, ischeamic, sciatia, multiple sclerosis, arthritis, osteoarthritis, rheumatoid arthritis, fibromyalgia, pain and other signs and symptoms associated with psoriasis, pain and other signs and symptoms associated with cancer, emesis, urinary incontinence, hyperactive bladder and HIV neuropathy.

A further embodiment of the invention relates to the compounds of the invention as hereinbefore defined, for use as a medicament for treatment of gastro-esophageal reflux disease (GERD), irritable bowel syndrome (IBS), inflammatory bowel disease (IBD) and pancreatitis.

Yet a further embodiment of the invention relates to the compounds of the invention as hereinbefore defined, for use as medicaments for treatment of respiratory diseases selected from the group comprising asthma, cough, chronic obstructive pulmonary disease

(COPD), chronic obstructive lung disease and emphysema, lung fibrosis and interstitial lung disease.

One embodiment of the invention relates to the use of the compound of the invention as hereinbefore defined, in the manufacture of a medicament for treatment of VR1 mediated disorders and for treatment of acute and chronic pain disorders, acute and chronic neuropathic pain, acute and chronic nociceptive pain, and acute and chronic inflammatory pain, and respiratory diseases and any other disorder mentioned above.

Another embodiment of the invention relates to a method of treatment of VR1 mediated disorders and acute and chronic pain disorders, acute and chronic neuropathic pain, acute and chronic nociceptive pain, and acute and chronic inflammatory pain, and respiratory diseases, and any other disorder mentioned above, comprising administrering to a mammal, including man in need of such treatment, a therapeutically effective amount of a compound of the invention, as hereinbefore defined.

A further embodiment of the invention relates to a pharmaceutical composition comprising a compound of the invention as hereinbefore defined, for use in treatment of VR1 mediated disorders and for treatment of acute and chronic pain disorders, acute and chronic neuropathic pain and acute, acute and chronic nociceptive pain and chronic inflammatory pain, and respiratory diseases, and any other disorder mentioned above.

In the context of the present specification, the term "therapy" and "treatment" includes prevention and prophylaxis, unless there are specific indications to the contrary. The terms "treat", "therapeutic" and "therapeutically" should be construed accordingly.

In this specification, unless stated otherwise, the term "inhibitor" and "antagonist" mean a compound that by any means, partly or completely, blocks the transduction pathway leading to the production of a response by the ligand.

The term "disorder", unless stated otherwise, means any condition and disease associated with vanilloid receptor activity.

Non- Medical use

In addition to their use in therapeutic medicine, the compounds of the invention, or salts, solvates or solvated salts thereof, are also useful as pharmacological tools in the development and standardisation of *in vitro* and *in vivo* test systems for the evaluation of

the effects of inhibitors of VR1 related activity in laboratory animals such as cats, dogs, rabbits, monkeys, rats and mice, as part of the search for new therapeutics agents.

Examples

The invention will now be illustrated by the following non-limiting examples.

General methods

The invention will now be illustrated by the following Examples in which, generally :

(i) operations were carried out at ambient or room temperature, *i.e.* in the range 17 to 25°C and under an atmosphere of an inert gas such as argon unless otherwise stated;

(ii) evaporations were carried out by rotary evaporation *in vacuo* and work-up procedures were carried out after removal of residual solids by filtration;

(iii) The ^{1}H NMR spectra were recorded on Brucker at 400 MHz. The mass spectra were recorded utilising electrospray (LC-MS; LC:Waters 2790, column XTerra MS C_8 2.5 μm 2.1X30 mm, buffer gradient H_2O+0.1%TFA:CH_3CN+0.04%TFA, MS: micromass ZMD// ammonium acetate buffer) ionisation techniques;

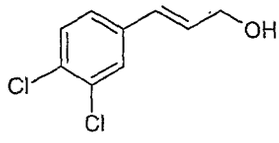
(iii) yields, where present, are not necessarily the maximum attainable;

(v) the following abbreviations have been used:-

alloc	allyloxycarbonyl
DCE	dichloroethane
DCM	dichloromethane
DMAP	dimethylaminopyridine
EDC	1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride
HATU	O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate
HPLC	high performance liquid chromatography
LC	liquid chromatography
MsCl	methanesulfonyl chloride
MS	mass spectometry
ret. time	retention time
TFA	trifluroacetic acid

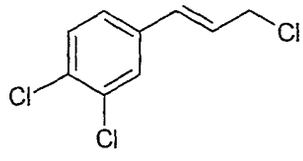
THF	tetrahydrofurane
DMF	dimethyformamide
TMEDA	tetramethylethylenediamine
EtOAc	ethyl acetate
BuLi	butyl lithium
TMEDA	tetramethylethylenediamine

INTERMEDIATE 1: (2*E*)-3-(3,4-dichlorophenyl)prop-2-en-1-ol



To a mixture of 3,4-dichlorocinnamic acid (2.00 g, 9.21 mmol) in toluene (46 mL) at 0 □C was added DIBAL-H (1.0 M solution in toluene, 24 mL, 23.96 mmol). The reaction gradually warmed up to room temperature and was stirred overnight. The reaction was then cooled to 0 □C and quenched with 5N HCl (8 mL). The reaction was diluted with EtOAc and washed with H_2O (2x). The aqueous layers were extracted with additional EtOAc (1x). The combined organic phases was dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified by silica gel column chromatography, eluting with 3:2 EtOAc:Hexanes, to give the title compound as a pale yellow solid (1.17 g, 63% yield). ^{1}H NMR (400MHz, $CDCl_3$) □ 4.34 (dd, J = 5.37, 1.66 Hz, 2H), 6.36 (dt, J = 15.87, 5.35 Hz, 1H), 6.54 (dt, J = 16.01, 1.46 Hz, 1H), 7.21 (dd, J = 8.30, 2.05 Hz, 1H), 7.38 (d, J = 8.40 Hz, 1H), 7.46 (d, J = 2.15 Hz, 1H).

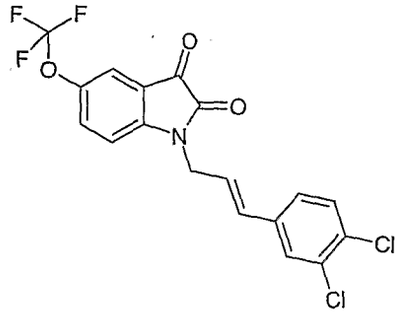
INTERMEDIATE 2: 1,2-dichloro-4-[(1*E*)-3-chloroprop-1-en-1-yl]benzene



A mixture of (2*E*)-3-(3,4-dichlorophenyl)prop-2-en-1-ol (530 mg, 2.61 mmol) in concentrated HCl (4 mL) was heated at 80 □C for 3 hours. The reaction was then cooled, diluted with ether and washed with H_2O (3x). The aqueous layers were extracted with additional ether (1x). The combined organic phases was dried over Na_2SO_4, filtered and concentrated *in vacuo*. Further purification of the residue was not necessary. The title com-

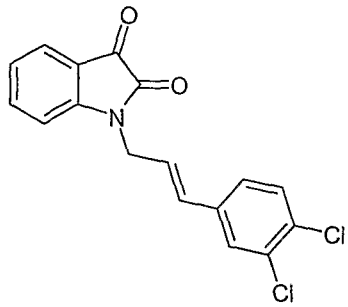
pound was obtained as a yellow oil (547 mg, 95% yield). ^{1}H NMR (400 MHz, $CDCl_3$) □ 4.22 (dd, J = 7.03, 1.37 Hz, 2H), 6.32 (dt, J = 15.67, 7.01 Hz, 1H), 6.57 (d, J = 15.62 Hz, 1H), 7.21 (dd, J = 8.40, 2.15 Hz, 1H), 7.40 (d, J = 8.20 Hz, 1H), 7.47 (d, J = 2.15 Hz, 1H).

INTERMEDIATE 3: 1-[(2*E*)-3-(3,4-dichlorophenyl)prop-2-en-1-yl]-5-(trifluoromethoxy)-1*H*-indole-2,3-dione



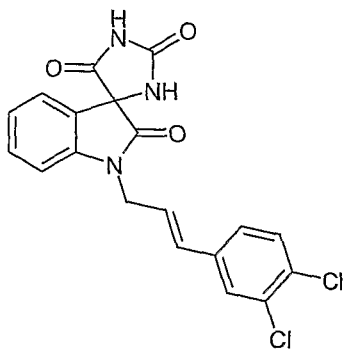
To a solution of 5-(trifluoromethoxy)isatin (197 mg, 0.85 mmol) in DMSO (2.0 mL) was added a solution of potassium hydroxide (48 mg, 0.85 mmol) in EtOH (1.0 mL). The reaction was stirred at room temperature for 15 minutes and then 1,2-dichloro-4-[(1*E*)-3-chloroprop-1-en-1-yl]benzene (208 mg, 0.94 mmol) was added. The reaction was stirred at room temperature overnight, poured into H_2O and filtered. The precipitate was rinsed with H_2O, dissolved in CH_2Cl_2 and washed with H_2O (2x). The aqueous layers were extracted with additional CH_2Cl_2 (1x). The combined organic phases was dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified by silica gel column chromatography, eluting with 1:3 EtOAc:Hexanes, to give the title compound as an orange solid (181 mg, 51% yield). ^{1}H NMR (400 MHz, $CDCl_3$) □ 4.55 (dd, J = 5.86, 1.56 Hz, 2H), 6.18 (dt, J = 15.96, 5.98 Hz, 1H), 6.59 (d, J = 15.82 Hz, 1H), 6.96 (d, J = 8.59 Hz, 1H), 7.18 (dd, J = 8.40, 1.95 Hz, 1H), 7.39 (d, J = 8.20 Hz, 1H), 7.43 - 7.47 (m, 1H), 7.44 (d, J = 1.95 Hz, 1H), 7.52 (d, J = 1.37 Hz, 1H).

INTERMEDIATE 4: 1-[(2*E*)-3-(3,4-dichlorophenyl)prop-2-en-1-yl]-1*H*-indole-2,3-dione



Using the same method as for 1-[(2*E*)-3-(3,4-dichlorophenyl)prop-2-en-1-yl]-5-(trifluoromethoxy)-1*H*-indole-2,3-dione and using isatin (200 mg, 1.36 mmol) and 1,2-dichloro-4-[(1*E*)-3-chloroprop-1-en-1-yl]benzene (150 mg, 0.36 mmol), except residue did not have to further purified after the work-up, afforded the title compound as an orange solid (341 mg, 76% yield). Purity (HPLC): > 99%; ^{1}H NMR (400 MHz, $CDCl_3$) □ 4.53 (dd, J = 5.86, 1.56 Hz, 2H), 6.20 (dt, J = 15.82, 5.86 Hz, 1H), 6.57 (d, J = 16.01 Hz, 1H), 6.92 (d, J = 8.01 Hz, 1H), 7.12-7.20 (m, 2H), 7.38 (d, J = 8.40 Hz, 1H), 7.43 (d, J = 2.15 Hz, 1H), 7.58 (dt, J = 7.81, 1.37 Hz, 1H), 7.65 (ddd, J = 7.42, 1.37, 0.59 Hz, 1H). Found: C, 60.72; H, 3.40; N, 4.06. $C_{17}H_{11}Cl_2NO_2 + 0.2\ H_2O$ has C, 60.81; H, 3.42; N, 4.17 %.

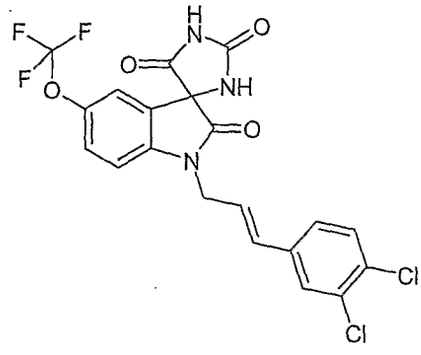
INTERMEDIATE 7: 1'-[(2*E*)-3-(3,4-dichlorophenyl)prop-2-en-1-yl]-2*H*,5*H*-spiro[imidazolidine-4,3'-indole]-2,2',5(1'*H*)-trione



A mixture of 1-[(2*E*)-3-(3,4-dichlorophenyl)prop-2-en-1-yl]-1*H*-indole-2,3-dione (200 mg, 0.60 mmol), potassium cyanide (47 mg, 0.72 mmol), and ammonium carbonate (555 mg, 5.78 mmol) in 1:1 MeOH:H_2O (10 mL) was heated at 100 □C for 3 hours. The reaction was then cooled, concentrated *in vacuo* to remove the MeOH and filtered. The residue was dissolved in EtOAc and washed with H_2O (1x). The layers were separated and the aqueous layer was extracted with additional EtOAc (2x). The combined organic phases

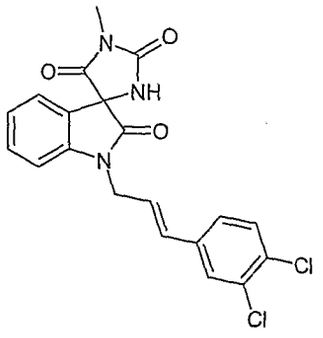
was dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified by silica gel column chromatography, eluting with 3:1 EtOAc:Hexanes, to give the title compound as a beige solid (189 mg, 78% yield). Purity (HPLC): > 99%; ^{1}H NMR (400 MHz, CD_3OD) □ 4.49 (ddd, J = 17.09, 5.08, 1.66 Hz, 1H), 4.61 (ddd, J = 17.09, 4.98, 1.76 Hz, 1H), 6.35 (dt, J = 16.01, 4.98 Hz, 1H), 6.58 (d, J = 16.01 Hz, 1H), 7.08 (d, J = 7.81 Hz, 1H), 7.17 (dt, J = 7.62, 0.98 Hz, 1H), 7.30 (dd, J = 8.59, 1.95 Hz, 1H), 7.35 - 7.38 (m, 1H), 7.39 - 7.44 (m, 2H), 7.52 (d, J = 1.95 Hz, 1H). Found: C, 56.64; H, 3.26; N, 10.27. $C_{19}H_{13}Cl_2N_3O_3$ has C, 56.74; H, 3.26; N, 10.45 %.

COMPOUND 3: 1-[(2*E*)-3-(3,4-dichlorophenyl)prop-2-en-1-yl]-5-(trifluoromethoxy)-1*H*-indole-2,3-dione



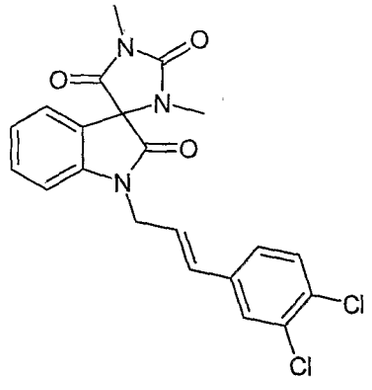
Using the same method as for 1'-[(2*E*)-3-(3,4-dichlorophenyl)prop-2-en-1-yl]-2*H*,5*H*-spiro[imidazolidine-4,3'-indole]-2,2',5(1'*H*)-trione and using 1-[(2*E*)-3-(3,4-dichlorophenyl)prop-2-en-1-yl]-5-(trifluoromethoxy)-1*H*-indole-2,3-dione (150 mg, 0.36 mmol), except residue was purified by silica gel column chromatography, eluting with 1:1 EtOAc:Hexanes, afforded the title compound as a pale yellow solid (63 mg, 36% yield). Purity (HPLC): 94% (215 nm), >98% (254nm); ^{1}H NMR (400 MHz, CD_3OD) □ 4.52 (ddd, J = 17.14, 5.13, 1.76 Hz, 1H), 4.64 (ddd, J = 16.99, 5.08, 1.76 Hz, 1H), 6.36 (dt, J = 16.01, 5.08 Hz, 1H), 6.61 (d, J = 16.01 Hz, 1H), 7.18 (d, J = 8.59 Hz, 1H), 7.32 (dd, J = 8.49, 1.85 Hz, 1H), 7.37 (ddd, J = 8.59, 2.44, 0.88 Hz, 1H), 7.41 - 7.45 (m, 2H), 7.55 (d, J = 1.95 Hz, 1H). Found: C, 50.39; H, 2.31; N, 8.35. $C_{20}H_{12}Cl_2F_3N_3O_4$ + 0.3 EtOAc has C, 50.14; H, 2.86; N, 8.27 %.

COMPOUND 4: 1'-[(2*E*)-3-(3,4-dichlorophenyl)prop-2-en-1-yl]-1-methyl-2*H*,5*H*-spiro[imidazolidine-4,3'-indole]-2,2',5(1'*H*)-trione



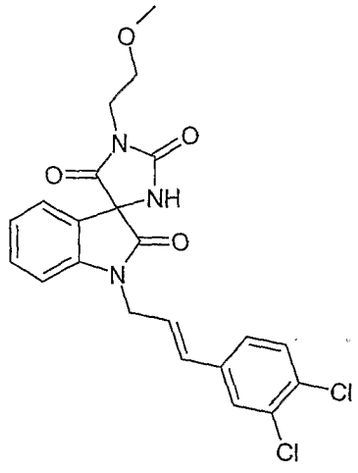
To a mixture of 1'-[(2*E*)-3-(3,4-dichlorophenyl)prop-2-en-1-yl]-2*H*,5*H*-spiro[imidazolidine-4,3'-indole]-2,2',5(1'*H*)-trione (50 mg, 0.12 mmol) and potassium carbonate (34 mg, 0.25 mmol) in DMF (5 mL) was added iodomethane (19.3 □L, 0.31 mmol). The reaction was stirred at room temperature overnight and concentrated *in vacuo* to provide a mixture of two alkylated compounds. The residue was purified by reverse phase HPLC (gradient 40-70% CH_3CN in H_2O containing 0.1% trifluoroacetic acid) to give the title compound (25 mg, 49% yield) as its TFA salt. This material was lyophilized from CH_3CN/H_2O to produce a colorless solid. Purity (HPLC): > 99%; ^{1}H NMR (400 MHz, CD_3OD) □ 3.07 (s, 3H), 4.50 (ddd, J = 17.09, 5.13, 1.71 Hz, 1H), 4.61 (ddd, J = 17.16, 5.00, 1.85 Hz, 1H), 6.35 (dt, J = 16.04, 5.06 Hz, 1H), 6.59 (dt, J = 15.84, 1.50 Hz, 1H), 7.10 (d, J = 7.91 Hz, 1H), 7.16 (dt, J = 7.62, 0.98 Hz, 1H), 7.31 (dd, J = 8.35, 2.10 Hz, 1H), 7.35 (ddd, J = 7.49, 1.24, 0.54 Hz, 1H), 7.42 (dt, J = 7.91, 1.27 Hz, 1H), 7.42 (d, J = 8.40 Hz, 1H), 7.53 (d, J = 2.05 Hz, 1H).

COMPOUND 5: 1'-[(2*E*)-3-(3,4-dichlorophenyl)prop-2-en-1-yl]-1,3-dimethyl-2*H*,5*H*-spiro[imidazolidine-4,3'-indole]-2,2',5(1'*H*)-trione



The second compound isolated from purification of the residue from the preparation of 1'-[(2*E*)-3-(3,4-dichlorophenyl)prop-2-en-1-yl]-1-methyl-2*H*,5*H*-spiro[imidazolidine-4,3'-indole]-2,2',5(1'*H*)-trione was the TFA salt of the title compound (17 mg, 32%). This material was lyophilized from CH_3CN/H_2O to produce a beige solid. Purity (HPLC): > 99%; ^{1}H NMR (400 MHz, CD_3OD) □ 2.75 (s, 3H), 3.09 (s, 3H), 4.48 (ddd, J = 17.09, 5.17, 1.56 Hz, 1H), 4.68 (ddd, J = 17.14, 4.93, 1.76 Hz, 1H), 6.37 (dt, J = 16.06, 5.05 Hz, 1H), 6.60 (d, J = 16.01 Hz, 1H), 7.15 (d, J = 8.01 Hz, 1H), 7.19 (dt, J = 7.62, 0.78 Hz, 1H), 7.31 (dd, J = 8.40, 1.95 Hz, 1H), 7.34 (d, J = 6.83 Hz, 1H), 7.41 - 7.44 (m, J = 8.40 Hz, 1H), 7.47 (dt, J = 7.81, 1.17 Hz, 1H), 7.54 (d, J = 1.95 Hz, 1H).

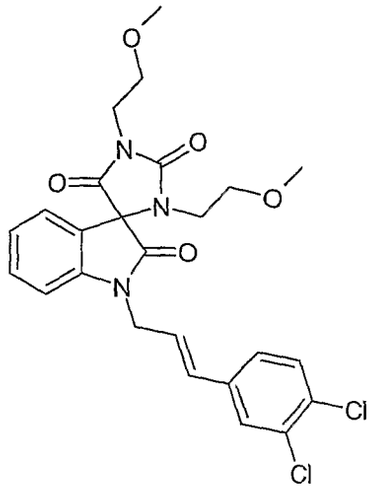
COMPOUND 6: 1'-[(2*E*)-3-(3,4-dichlorophenyl)prop-2-en-1-yl]-1-(2-methoxyethyl)-2*H*,5*H*-spiro[imidazolidine-4,3'-indole]-2,2',5(1'*H*)-trione



Using the same method as for 1'-[(2*E*)-3-(3,4-dichlorophenyl)prop-2-en-1-yl]-1-methyl-2*H*,5*H*-spiro[imidazolidine-4,3'-indole]-2,2',5(1'*H*)-trione and using 1'-[(2*E*)-3-(3,4-dichlorophenyl)prop-2-en-1-yl]-2*H*,5*H*-spiro[imidazolidine-4,3'-indole]-2,2',5(1'*H*)-trione (36 mg, 0.089 mmol), potassium carbonate (15 mg, 0.112 mmol) and 2-bromoethyl methyl ether (17 □L, 0.179 mmol) afforded a mixture of two alkylated compounds. The TFA salt of the title compound (10.1 mg, 25%) was obtained following purification of the residue by reverse phase HPLC (gradient 50-85% CH_3CN in H_2O containing 0.1% trifluoroacetic acid). This material was lyophilized from CH_3CN/H_2O to produce a pale yellow solid. Purity (HPLC): > 99%; ^{1}H NMR (400 MHz, CD_3OD) □ 3.36 (s, 3H), 3.57 - 3.67 (m, 2H), 3.70 - 3.82 (m, 2H), 4.46 - 4.65 (m, 2H), 6.36 (dt, J = 16.06, 5.05 Hz, 1H),

6.59 (d, J = 16.21 Hz, 1H), 7.10 (d, J = 7.81 Hz, 1H), 7.16 (dt, J = 7.62, 0.98 Hz, 1H), 7.29 - 7.33 (m, 2H), 7.40 - 7.45 (m, 2H), 7.53 (d, J = 1.95 Hz, 1H).

COMPOUND 7: 1'-[(2*E*)-3-(3,4-dichlorophenyl)prop-2-en-1-yl]-1,3-bis(2-methoxyethyl)-2*H*,5*H*-spiro[imidazolidine-4,3'-indole]-2,2',5(1'*H*)-trione



The second compound isolated from purification of the residue from the preparation of 1'-[(2*E*)-3-(3,4-dichlorophenyl)prop-2-en-1-yl]-1-(2-methoxyethyl)-2*H*,5*H*-spiro[imidazolidine-4,3'-indole]-2,2',5(1'*H*)-trione was the TFA salt of the title compound (9.9 mg, 21%). This material was lyophilized from CH_3CN/H_2O to produce a yellow hygroscopic solid. Purity (HPLC): 98% (215nm), 96% (254nm); ^{1}H NMR (400 MHz, CD_3OD) □ 2.92 (s, 3H), 3.26 - 3.38 (m, 2H), 3.34 (s, 3H), 3.56 - 3.84 (m, 6H), 4.45 (ddd, J = 17.18, 5.08, 1.56 Hz, 1H), 4.68 (ddd, J = 17.14, 4.83, 1.86 Hz, 1H), 6.37 (dt, J = 16.16, 4.91 Hz, 1H), 6.65 (d, J = 16.21 Hz, 1H), 7.10 (d, J = 8.01 Hz, 1H), 7.16 (dt, J = 7.52, 0.98 Hz, 1H), 7.24 - 7.28 (m, 1H), 7.31 (dd, J = 8.40, 2.15 Hz, 1H), 7.41 - 7.46 (m, 2H), 7.53 (d, J = 2.15 Hz, 1H).

General Procedure 1:

As illustrated in Scheme 2, stock solutions (0.375 M) of the alkyl halides (187.5 □mol/well) in DMF (500 □L/well) were prepared. Stock solutions (0.25 M) of the isatins (125 □mol/well) in DMF (500 □L/well) were also prepared. PS-TBD (~130 mg/well, 1.48 mmol/g) was dispensed into Robbins blocks equipped with filters followed by the isatin stock solutions (500 □L/well) and DMF (500 □L/well). The reactions were mixed for 1

hour at room temperature. The alkyl halide stock solutions (500 □L/well) were then added and the reactions were heated at 50 °C for 4 days, and then filtered into a 96-well plate. The Robbins blocks were rinsed with DMF. The filtrates were combined and concentrated *in vacuo*. The crude alkylated isatins were transferred to Robbins blocks equipped with filters using DMA (500 □L/well). Ammonium carbonate (~130 mg/well) was dispensed into the Robbins block, followed by H_2O (400 □L/well) and a solution of KCN in H_2O (100 □L/well, 3.75 M). The reactions were heated at 50 °C for 24 hours, and then filtered into a 96-well plate. The Robbins blocks were rinsed with DMA. The filtrates were combined and concentrated *in vacuo*. The residues were dissolved in EtOAc (700 □L/well) and washed with H_2O (500 □L/well). The organic layer was transferred into a new plate. The aqueous layer was extracted with more EtOAc (3 x 700 □L/well). The organic layers were combined and concentrated *in vacuo*. The products were purified by reverse phase HPLC to provide the corresponding hydantoins.

Example #	**Name (IUPAC)**	**Retention Time**	**MH+**
15	1'-(2-methylpropyl)-2H,5H-spiro[imidazolidine-4,3'-indole]-2,2',5(1'H)-trione	1.16	273.48
16	1'-(2-ethylbutyl)-2H,5H-spiro[imidazolidine-4,3'-indole]-2,2',5(1'H)-trione	1.41	301.45
18	1'-{[4-(methylsulfonyl)phenyl]methyl}-2H,5H-spiro[imidazolidine-4,3'-indole]-2,2',5(1'H)-trione	1.13	385.2
26	1'-(phenylmethyl)-2H,5H-spiro[imidazolidine-4,3'-indole]-2,2',5(1'H)-trione	1.32	307.39
30	5'-chloro-1'-(3-methylbutyl)-2H,5H-spiro[imidazolidine-4,3'-indole]-2,2',5(1'H)-trione	1.45	321.36
32	1'-[(2E)-2-butenyl]-5'-chloro-2H,5H-spiro[imidazolidine-4,3'-indole]-2,2',5(1'H)-trione	1.33	305.37
33	1'-[(2-bromophenyl)methyl]-5'-fluoro-2H,5H-spiro[imidazolidine-4,3'-indole]-2,2',5(1'H)-trione	1.57	403.04

Example #	Name (IUPAC)	Retention Time	MH+
34	5'-fluoro-1'-(2-methylpropyl)-2H,5H-spiro[imidazolidine-4,3'-indole]-2,2',5(1'H)-trione	1.22	291.41
35	5'-fluoro-1'-{[4-(1-methylethyl)phenyl]methyl}-2H,5H-spiro[imidazolidine-4,3'-indole]-2,2',5(1'H)-trione	1.6	367.26
36	5'-fluoro-1'-{[3-(methyloxy)phenyl]methyl}-2H,5H-spiro[imidazolidine-4,3'-indole]-2,2',5(1'H)-trione	1.38	355.26
38	5'-fluoro-1'-(4-methyl-3-pentenyl)-2H,5H-spiro[imidazolidine-4,3'-indole]-2,2',5(1'H)-trione	1.38	317.37
39	5'-fluoro-1'-{[2-(trifluoromethyl)phenyl]methyl}-2H,5H-spiro[imidazolidine-4,3'-indole]-2,2',5(1'H)-trione	1.52	393.16
40	1'-(2-ethylbutyl)-5'-fluoro-2H,5H-spiro[imidazolidine-4,3'-indole]-2,2',5(1'H)-trione	1.43	319.39
43	1'-(1,1'-biphenyl-2-ylmethyl)-5'-fluoro-2H,5H-spiro[imidazolidine-4,3'-indole]-2,2',5(1'H)-trione	1.65	401.18
44	5'-fluoro-1'-{[4-(methylsulfonyl)phenyl]methyl}-2H,5H-spiro[imidazolidine-4,3'-indole]-2,2',5(1'H)-trione	1.2	403.13
46	1'-{[2-chloro-5-(trifluoromethyl)phenyl]methyl}-5'-fluoro-2H,5H-spiro[imidazolidine-4,3'-indole]-2,2',5(1'H)-trione	1.6	427.05
50	5'-fluoro-1'-[(2,4,6-trimethylphenyl)methyl]-2H,5H-spiro[imidazolidine-4,3'-indole]-2,2',5(1'H)-trione	1.58	367.29
51	1'-[(2-chloro-6-fluorophenyl)methyl]-5'-fluoro-2H,5H-spiro[imidazolidine-4,3'-indole]-2,2',5(1'H)-trione	1.41	377.17
58	1'-[(2,3-dichlorophenyl)methyl]-5'-fluoro-2H,5H-spiro[imidazolidine-4,3'-indole]-2,2',5(1'H)-trione	1.58	393.11
60	5'-fluoro-1'-(3-methylbutyl)-2H,5H-spiro[imidazolidine-4,3'-indole]-2,2',5(1'H)-trione	1.37	305.41
64	5'-fluoro-1'-pentyl-2H,5H-spiro[imidazolidine-4,3'-indole]-2,2',5(1'H)-trione	1.37	305.42

Example #	Name (IUPAC)	Retention Time	MH+
67	5'-fluoro-1'-{[4-(1,2,3-thiadiazol-4-yl)phenyl]methyl}-2H,5H-spiro[imidazolidine-4,3'-indole]-2,2',5(1'H)-trione	1.41	409.13
68	5'-fluoro-1'-(phenylmethyl)-2H,5H-spiro[imidazolidine-4,3'-indole]-2,2',5(1'H)-trione	1.37	325.35
69	1'-[(2E)-2-butenyl]-5'-fluoro-2H,5H-spiro[imidazolidine-4,3'-indole]-2,2',5(1'H)-trione	1.22	289.43
71	5'-fluoro-1'-(2-propenyl)-2H,5H-spiro[imidazolidine-4,3'-indole]-2,2',5(1'H)-trione	1.05	275.45
72	5'-fluoro-1'-[(2E)-3-phenyl-2-propenyl]-2H,5H-spiro[imidazolidine-4,3'-indole]-2,2',5(1'H)-trione	1.5	351.3
74	5'-chloro-7'-methyl-1'-{[3-(methyloxy)phenyl]methyl}-2H,5H-spiro[imidazolidine-4,3'-indole]-2,2',5(1'H)-trione	1.55	385.19
76	5'-chloro-1'-{[2-fluoro-4-(trifluoromethyl)phenyl]methyl}-7'-methyl-2H,5H-spiro[imidazolidine-4,3'-indole]-2,2',5(1'H)-trione	1.7	441.03
77	5'-chloro-1'-{[4-fluoro-3-(trifluoromethyl)phenyl]methyl}-7'-methyl-2H,5H-spiro[imidazolidine-4,3'-indole]-2,2',5(1'H)-trione	1.66	441.03
78	5'-chloro-1'-[(2-chloro-6-fluorophenyl)methyl]-7'-methyl-2H,5H-spiro[imidazolidine-4,3'-indole]-2,2',5(1'H)-trione	1.58	407.08
79	5'-chloro-7'-methyl-1'-{[3-(trifluoromethyl)phenyl]methyl}-2H,5H-spiro[imidazolidine-4,3'-indole]-2,2',5(1'H)-trione	1.65	423.09
80	5'-chloro-7'-methyl-1'-{[4-(trifluoromethyl)phenyl]methyl}-2H,5H-spiro[imidazolidine-4,3'-indole]-2,2',5(1'H)-trione	1.66	423.09
83	5'-chloro-7'-methyl-1'-(3-methylbutyl)-2H,5H-spiro[imidazolidine-4,3'-indole]-2,2',5(1'H)-trione	1.53	335.32
86	5'-chloro-7'-methyl-1'-pentyl-2H,5H-spiro[imidazolidine-4,3'-indole]-2,2',5(1'H)-trione	1.55	335.33

Example #	Name (IUPAC)	Retention Time	MH+
89	5'-chloro-7'-methyl-1'-(phenylmethyl)-2H,5H-spiro[imidazolidine-4,3'-indole]-2,2',5(1'H)-trione	1.53	355.25
90	1'-[(2E)-2-butenyl]-5'-chloro-7'-methyl-2H,5H-spiro[imidazolidine-4,3'-indole]-2,2',5(1'H)-trione	1.43	319.33
92	5'-chloro-7'-methyl-1'-(2-propenyl)-2H,5H-spiro[imidazolidine-4,3'-indole]-2,2',5(1'H)-trione	1.32	305.35
94	5'-methyl-1'-(2-methylpropyl)-2H,5H-spiro[imidazolidine-4,3'-indole]-2,2',5(1'H)-trione	1.3	287.46
96	1'-[(2-chloro-6-fluorophenyl)methyl]-2H,5H-spiro[imidazolidine-4,3'-indole]-2,2',5(1'H)-trione	1.38	359.22
98	1'-(3-methylbutyl)-2H,5H-spiro[imidazolidine-4,3'-indole]-2,2',5(1'H)-trione	1.32	287.46
103	1'-[(2E)-2-butenyl]-2H,5H-spiro[imidazolidine-4,3'-indole]-2,2',5(1'H)-trione	1.15	271.47
104	1'-(2-propenyl)-2H,5H-spiro[imidazolidine-4,3'-indole]-2,2',5(1'H)-trione	0.97	257.49
106	1'-[(4-fluorophenyl)methyl]-5'-methyl-2H,5H-spiro[imidazolidine-4,3'-indole]-2,2',5(1'H)-trione	1.43	339.31
107	1'-[(2-bromophenyl)methyl]-5'-methyl-2H,5H-spiro[imidazolidine-4,3'-indole]-2,2',5(1'H)-trione	1.53	399.1
108	5'-methyl-1'-{[4-(1-methylethyl)phenyl]methyl}-2H,5H-spiro[imidazolidine-4,3'-indole]-2,2',5(1'H)-trione	1.63	363.32
109	5'-methyl-1'-{[3-(methyloxy)phenyl]methyl}-2H,5H-spiro[imidazolidine-4,3'-indole]-2,2',5(1'H)-trione	1.43	352.33
110	5'-methyl-1'-(4-methyl-3-pentenyl)-2H,5H-spiro[imidazolidine-4,3'-indole]-2,2',5(1'H)-trione	1.43	314.43
112	1'-{[2-fluoro-4-(trifluoromethyl)phenyl]methyl}-5'-methyl-2H,5H-spiro[imidazolidine-4,3'-indole]-2,2',5(1'H)-trione	1.6	407.16

Example #	Name (IUPAC)	Retention Time	MH+
113	5'-methyl-1'-({4-[(trifluoromethyl)oxy]phenyl}methyl)-2H,5H-spiro[imidazolidine-4,3'-indole]-2,2',5(1'H)-trione	1.6	405.16
114	1'-(1,1'-biphenyl-2-ylmethyl)-5'-methyl-2H,5H-spiro[imidazolidine-4,3'-indole]-2,2',5(1'H)-trione	1.68	398.24
116	1'-{[2-chloro-5-(trifluoromethyl)phenyl]methyl}-5'-methyl-2H,5H-spiro[imidazolidine-4,3'-indole]-2,2',5(1'H)-trione	1.63	423.09
119	1'-[(2-chloro-6-fluorophenyl)methyl]-5'-methyl-2H,5H-spiro[imidazolidine-4,3'-indole]-2,2',5(1'H)-trione	1.47	373.21
120	1'-[(4-chlorophenyl)methyl]-5'-methyl-2H,5H-spiro[imidazolidine-4,3'-indole]-2,2',5(1'H)-trione	1.52	355.27
121	1'-{[4-(1,1-dimethylethyl)phenyl]methyl}-5'-methyl-2H,5H-spiro[imidazolidine-4,3'-indole]-2,2',5(1'H)-trione	1.68	377.31
122	5'-methyl-1'-{[4-(trifluoromethyl)phenyl]methyl}-2H,5H-spiro[imidazolidine-4,3'-indole]-2,2',5(1'H)-trione	1.58	389.21
123	1'-[(2,4-dichlorophenyl)methyl]-5'-methyl-2H,5H-spiro[imidazolidine-4,3'-indole]-2,2',5(1'H)-trione	1.62	389.15
125	1'-[(2,3-dichlorophenyl)methyl]-5'-methyl-2H,5H-spiro[imidazolidine-4,3'-indole]-2,2',5(1'H)-trione	1.6	389.16
126	5'-methyl-1'-(3-methylbutyl)-2H,5H-spiro[imidazolidine-4,3'-indole]-2,2',5(1'H)-trione	1.41	301.45
128	5'-methyl-1'-pentyl-2H,5H-spiro[imidazolidine-4,3'-indole]-2,2',5(1'H)-trione	1.43	301.44
129	1'-[(2-iodophenyl)methyl]-5'-methyl-2H,5H-spiro[imidazolidine-4,3'-indole]-2,2',5(1'H)-trione	1.57	446.98
130	1'-[(4-ethenylphenyl)methyl]-5'-methyl-2H,5H-spiro[imidazolidine-4,3'-indole]-2,2',5(1'H)-trione	1.53	347.34
131	5'-methyl-1'-(phenylmethyl)-2H,5H-spiro[imidazolidine-4,3'-indole]-2,2',5(1'H)-trione	1.4	321.37

Example #	Name (IUPAC)	Retention Time	MH+
132	1'-[(2E)-2-butenyl]-5'-methyl-2H,5H-spiro[imidazolidine-4,3'-indole]-2,2',5(1'H)-trione	1.27	285.46
134	5'-methyl-1'-(2-propenyl)-2H,5H-spiro[imidazolidine-4,3'-indole]-2,2',5(1'H)-trione	1.16	271.47
135	5'-methyl-1'-[(2E)-3-phenyl-2-propenyl]-2H,5H-spiro[imidazolidine-4,3'-indole]-2,2',5(1'H)-trione	1.53	347.34
139	5'-methyl-1'-{[2-(trifluoromethyl)phenyl]methyl}-2H,5H-spiro[imidazolidine-4,3'-indole]-2,2',5(1'H)-trione	1.58	389.2
140	1'-(2-ethylbutyl)-5'-methyl-2H,5H-spiro[imidazolidine-4,3'-indole]-2,2',5(1'H)-trione	1.48	315.42
141	1'-{[4-fluoro-3-(trifluoromethyl)phenyl]methyl}-5'-methyl-2H,5H-spiro[imidazolidine-4,3'-indole]-2,2',5(1'H)-trione	1.57	407.16
142	5'-methyl-1'-{[4-(methylsulfonyl)phenyl]methyl}-2H,5H-spiro[imidazolidine-4,3'-indole]-2,2',5(1'H)-trione	1.25	399.18
145	5'-methyl-1'-[(2,4,6-trimethylphenyl)methyl]-2H,5H-spiro[imidazolidine-4,3'-indole]-2,2',5(1'H)-trione	1.62	363.34
148	5'-methyl-1'-{[3-(trifluoromethyl)phenyl]methyl}-2H,5H-spiro[imidazolidine-4,3'-indole]-2,2',5(1'H)-trione	1.55	389.22
149	5'-methyl-1'-({3-[(trifluoromethyl)oxy]phenyl}methyl)-2H,5H-spiro[imidazolidine-4,3'-indole]-2,2',5(1'H)-trione	1.58	405.18
158	1'-[(4-bromo-2-fluorophenyl)methyl]-5'-methyl-2H,5H-spiro[imidazolidine-4,3'-indole]-2,2',5(1'H)-trione	1.57	417.06
159	5'-methyl-1'-{[4-(1,2,3-thiadiazol-4-yl)phenyl]methyl}-2H,5H-spiro[imidazolidine-4,3'-indole]-2,2',5(1'H)-trione	1.45	405.17
162	5'-chloro-1'-(4-methyl-3-pentenyl)-2H,5H-spiro[imidazolidine-4,3'-indole]-2,2',5(1'H)-trione	1.48	333.32
169	5'-chloro-1'-(phenylmethyl)-2H,5H-spiro[imidazolidine-4,3'-indole]-2,2',5(1'H)-trione	1.45	341.29

Example #	Name (IUPAC)	Retention Time	MH+
172	5'-chloro-1'-pentyl-2H,5H-spiro[imidazolidine-4,3'-indole]-2,2',5(1'H)-trione	1.47	321.36
178	5'-fluoro-1'-{[2-fluoro-4-(trifluoromethyl)phenyl]methyl}-2H,5H-spiro[imidazolidine-4,3'-indole]-2,2',5(1'H)-trione	1.57	411.12
179	5'-fluoro-1'-{[4-fluoro-3-(trifluoromethyl)phenyl]methyl}-2H,5H-spiro[imidazolidine-4,3'-indole]-2,2',5(1'H)-trione	1.55	411.12
180	5'-chloro-7'-methyl-1'-(2-methylpropyl)-2H,5H-spiro[imidazolidine-4,3'-indole]-2,2',5(1'H)-trione	1.43	321.34
182	5'-chloro-7'-methyl-1'-(4-methyl-3-pentenyl)-2H,5H-spiro[imidazolidine-4,3'-indole]-2,2',5(1'H)-trione	1.57	347.3
183	5'-chloro-1'-(2-ethylbutyl)-7'-methyl-2H,5H-spiro[imidazolidine-4,3'-indole]-2,2',5(1'H)-trione	1.6	349.31
189	5'-chloro-7'-methyl-1'-[(2E)-3-phenyl-2-propenyl]-2H,5H-spiro[imidazolidine-4,3'-indole]-2,2',5(1'H)-trione	1.62	381.2

Intermediates

A further embodiment of the invention relates to compounds selected from the group consisting of

1-{[2-(3,4-dichlorophenyl)cyclopropyl]methyl}-1*H*-indole-2,3-dione, and

1-[3-(3,4-dichlorophenyl)prop-2-yn-1-yl]-1*H*-indole-2,3-dione,

which may be used as intermediates in the preparation of compounds suited for the treatment of VR1 mediated disorders, especially for use as intermediates for the preparation of compounds of formula I.

Pharmacology

1. hVR1 FLIPR (Fluorometric Image Plate Reader) screening assay

Transfected CHO cells, stably expessing hVR1 (15,000 cells/well) are seeded in 50 µL media in a black clear bottom 384 plate (Greiner) and grown in a humidified incubator (37°C, 2% CO_2), 24-30 hours prior to experiment.

Subsequently, the media is removed from the cell plate by inversion and 2 μM Fluo-4 is added using a multidrop (Labsystems). Following the 40 min dye incubation in the dark at 37°C and 2% CO_2, the extracellular dye present is washed away using an EM-BLA (Scatron), leaving the cells in 40 μL of assay buffer (1 X HBSS, 10 mM D-Glucose, 1 mM $CaCl_2$, 10 mM HEPES, 10 X 7.5% $NaHCO_3$ and 2.5 mM Probenecid).

FLIPR assay - IC_{50} determination protocol

For IC_{50} determinations the fluorescence is read using FLIPR filter 1 (em 520-545 nM). A cellular baseline recording is taken for 30 seconds, followed by a 20 μL addition of 10, titrated half-log concentrations of the test compound, yielding cellular concentration ranging from 3 μM to 0.1 nM. Data is collected every 2 seconds for a further 5 min prior to the addition of a VR1 agonist solution: either 50 nM solution of capsaicin or MES (2-[N-morpholino] ethanesulfonic acid) buffer (pH 5.2), by the FLIPR pipettor. The FLIPR continues to collect data for a further 4 min. Compounds having antagonistic properties against the hVR1 will inhibit the increase in intracellular calcium in response to the capsaicin addition. This consequently leading to a reduction in fluorescence signal and providing a reduced fluorescence reading, compared with no compound, buffer controls. Data is exported by the FLIPR program as a sum of fluorescence calculated under the curve upon the addition of capsaicin. Maximum inhibition, Hill slope and IC_{50} data for each compound are generated.

List of abbreviations

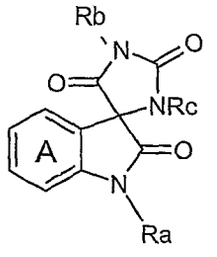
VR1	vanilloid receptor 1
IBS	irritable bowel syndrome
IBD	inflammatory bowel disease
GERD	gastro-esophageal reflux disease
HEPES	4-(2-Hydroxyethyl)piperazine-1-ethanesulfonic acid

Results

Typical IC_{50} values as measured in the assays described above are 10 μM or less. In one aspect of the invention the IC_{50} is below 5000 nM. In another aspect of the invention the IC_{50} is below 3000 nM

CLAIMS

1. Use of a compound of formula I



(I)

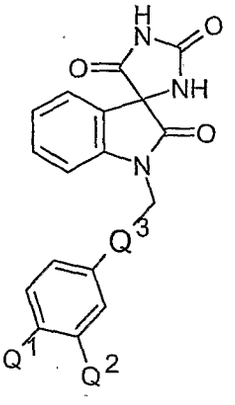
wherein:

Ra is a C_{1-12}alkyl radical, a phenyl, naphthylmethyl, cinnamyl radical or a benzyl radical optionally substituted by one or more groups selected from halogen, cyano, nitro, CF_3, OCF_3, trimethylsilyl, hydroxy, $-NR^6R^7$, SO_2R^7, R^6O-C_{1-6} alkyl, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{6-10}aryl and C_{5-10}heteroaryl;

Rb and Rc are independently selected from H, C_{1-10}alkyl, C_{2-10}alkenyl, C_{2-10}alkynyl, C_{3-10}cycloalkyl, C_{3-10}cycloalkyl-C_{1-6}alkyl, C_{4-8}cycloalkenyl-C_{1-6}alkyl, C_{3-6}heterocycloalkyl-C_{1-6}alkyl, C_{4-8}cycloalkenyl, C_{3-5}heteroaryl, C_{6-10}aryl and C_{3-6}heterocycloalkyl, C_{3-6}heteroaryl-C_{1-6}alkyl, C_{6-10}aryl-C_{1-6}alkyl and C_{1-6} alkyl-oxy-C_{1-5}alkyl,
optionally substituted by one or more groups selected from halogen, cyano, nitro, methoxy, ethoxy, methyl, ethyl, hydroxy and $-NR^6R^7$;

benzene ring A optionally substituted by one or more groups selected from H, halogen, C_{1-10}alkyl, haloalkyl, haloalkylO, C_{2-10}alkenyl, C_{2-10}alkynyl, C_{3-10}cycloalkyl, C_{3-10}cycloalkyl-C_{1-6}alkyl and C_{4-8}cycloalkenyl-C_{1-6}alkyl; and

R^6 and R^7 are independently selected from H, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, substituted or unsubstituted C_{6-10}aryl, substituted or unsubstituted C_{3-6}heteroaryl and a divalent C_{1-6}group that together with another divalent Ra, R^6 or R^7 forms a portion of a ring, or salts thereof, with the proviso that the compound does not have the formula III:



III

where Q^1 and Q^2 are independently halo or C_{1-3}haloalkyl and

Q^3 is ethenyl or ethynyl,

in the manufacturing of a medicament for the treatment of conditions associated with vanilloid receptor 1.

2. The use compounds according to claim 1, wherein;

Ra is a C_{1-6}alkyl radical, a phenyl or a benzyl radical optionally substituted by one or more groups selected from halogen, CF_3, methoxy, ethoxy, OCF_3, methyl, ethyl, *tert*-butyl, hydroxy, SO_2R^7, R^6O-C_{1-6}alkyl, C_{1-6}alkyl, C_{2-6}alkenyl, C_{6-10}aryl and C_{5-10}heteroaryl

Rb and Rc are independently selected from H, C_{1-10}alkyl and C_{1-6} alkyl-oxy-C_{1-5}alkyl;

benzene ring A optionally substituted by one or more groups selected from H, halogen, C_{1-10}alkyl, haloalkyl and haloalkylO; and

R^6 and R^7 are independently selected from H, C_{1-6}alkyl, substituted or unsubstituted C_{6-10}aryl and substituted or unsubstituted C_{3-6}heteroaryl.

3. Use of a compound selected from the group consisting

1'-(3,4-dichlorobenzyl)-1-pivaloyloxymethyl-spiro(imidazolidine- 4,3'-indoline]- 2,2',5-trione,

1'(3,4-dichlorobenzyl)-3-formyl- spiro(imidazolidine4,3'-indoline]-2,2',5-trione,

1'-(3,4-dichlorobenzyl)-1,3-d(ethoxycarbonyl)-spiro[imidazolidine-4,3'- indolinel-2,2'I5- - 36 trione,

3-ethoxycarbonyl-l'-(3,4-dichlorobenzyl)- spiro[imidazolidine-4,3'-indoline]-2,2',5trione,

3-benzoyl-l'-(3,4dichlorobenzyl)- spiro[imidazolidine-4,3'-indoline]2,2',5-trione,
l'-(3,4-dichlorobenzyl)3-phthalidyl-spiro(imidazolidine-4,3'- indoline]-2,2',5trione,
3- benzyloxy30 carbonyl-l'-(3,4-dichlorobenzyl)-spiro(imidazolidine4,3'- indoline]-2,2',5-trione,
3- benzyloxycarbonyl-l-ethoxycarbonyl-1'(3,4-dichlorobenzyl)- spiro[imidazolidine-4,3'-indoline]-2,2',5-trione,
l- ethoxycarbonyl-l'-(3,4-dichlorobenzylspiro[imidazolidine-4,3'-indolinel-2, 2',5-trione,
l-acetyl-3- benzyloxycarbonyl -l'-(3,4-dichlorobenzyl) -spiro £imidazolidine-4,3'- indolinel-2,2t,5-trione,
1-acetyl-l'-(3,4-dichlorobenzyl)-spirotimidazolidine-4, 3'indolinel-2,2',5-trione,
l'-(3,4-dichlorobenzyl)*3-ethoxyoxalyl- spiro[imidazolidine-4,3'-indoline]-2,2', 5-trione,
l'-(4-bromo-2- fluorobenzyl)-1(pivaloyloxymethyl)-spiro[imidazolidine-4,3'-indoline]15 2, 2',5-trione,
(+)-l'-(3,4- dichlorobenzyl)-1-(pivaloyloxymethyl)-spiro[imidazolidine-4,3'-indolinel-2,2',5trione, and
l'-(3,4- dichlorobenzyl)7'-fluoro-l-(pivaloyloxymethyl)-spirotimidazolidine-4, 3'indoline]-2,2',5-trione,
or salts thereof,
in the manufacturing of a medicament for the treatment of conditions associated with vanilloid receptor 1.

4. A compound selected from the group consisting of
1'-(2-methylpropyl)-2H,5H-spiro[imidazolidine-4,3'-indole]-2,2',5(1'H)-trione,
1'-(2-ethylbutyl)-2H,5H-spiro[imidazolidine-4,3'-indole]-2,2',5(1'H)-trione,
1'-{[4-(methylsulfonyl)phenyl]methyl}-2H,5H-spiro[imidazolidine-4,3'-indole]-2,2',5(1'H)-trione,
1'-(phenylmethyl)-2H,5H-spiro[imidazolidine-4,3'-indole]-2,2',5(1'H)-trione,
5'-chloro-1'-(3-methylbutyl)-2H,5H-spiro[imidazolidine-4,3'-indole]-2,2',5(1'H)-trione,
1'-[(2E)-2-butenyl]-5'-chloro-2H,5H-spiro[imidazolidine-4,3'-indole]-2,2',5(1'H)-trione,
1'-[(2-bromophenyl)methyl]-5'-fluoro-2H,5H-spiro[imidazolidine-4,3'-indole]-2,2',5(1'H)-trione,
5'-fluoro-1'-(2-methylpropyl)-2H,5H-spiro[imidazolidine-4,3'-indole]-2,2',5(1'H)-trione,

5'-fluoro-1'-{[4-(1-methylethyl)phenyl]methyl}-2H,5H-spiro[imidazolidine-4,3'-indole]-2,2',5(1'H)-trione,
5'-fluoro-1'-{[3-(methyloxy)phenyl]methyl}-2H,5H-spiro[imidazolidine-4,3'-indole]-2,2',5(1'H)-trione,
5'-fluoro-1'-(4-methyl-3-pentenyl)-2H,5H-spiro[imidazolidine-4,3'-indole]-2,2',5(1'H)-trione,
5'-fluoro-1'-{[2-(trifluoromethyl)phenyl]methyl}-2H,5H-spiro[imidazolidine-4,3'-indole]-2,2',5(1'H)-trione,
1'-(2-ethylbutyl)-5'-fluoro-2H,5H-spiro[imidazolidine-4,3'-indole]-2,2',5(1'H)-trione,
1'-(1,1'-biphenyl-2-ylmethyl)-5'-fluoro-2H,5H-spiro[imidazolidine-4,3'-indole]-2,2',5(1'H)-trione,
5'-fluoro-1'-{[4-(methylsulfonyl)phenyl]methyl}-2H,5H-spiro[imidazolidine-4,3'-indole]-2,2',5(1'H)-trione,
1'-{[2-chloro-5-(trifluoromethyl)phenyl]methyl}-5'-fluoro-2H,5H-spiro[imidazolidine-4,3'-indole]-2,2',5(1'H)-trione,
5'-fluoro-1'-[(2,4,6-trimethylphenyl)methyl]-2H,5H-spiro[imidazolidine-4,3'-indole]-2,2',5(1'H)-trione,
1'-[(2-chloro-6-fluorophenyl)methyl]-5'-fluoro-2H,5H-spiro[imidazolidine-4,3'-indole]-2,2',5(1'H)-trione,
1'-[(2,3-dichlorophenyl)methyl]-5'-fluoro-2H,5H-spiro[imidazolidine-4,3'-indole]-2,2',5(1'H)-trione,
5'-fluoro-1'-(3-methylbutyl)-2H,5H-spiro[imidazolidine-4,3'-indole]-2,2',5(1'H)-trione,
5'-fluoro-1'-pentyl-2H,5H-spiro[imidazolidine-4,3'-indole]-2,2',5(1'H)-trione,
5'-fluoro-1'-{[4-(1,2,3-thiadiazol-4-yl)phenyl]methyl}-2H,5H-spiro[imidazolidine-4,3'-indole]-2,2',5(1'H)-trione,
5'-fluoro-1'-(phenylmethyl)-2H,5H-spiro[imidazolidine-4,3'-indole]-2,2',5(1'H)-trione,
1'-[(2E)-2-butenyl]-5'-fluoro-2H,5H-spiro[imidazolidine-4,3'-indole]-2,2',5(1'H)-trione,
5'-fluoro-1'-(2-propenyl)-2H,5H-spiro[imidazolidine-4,3'-indole]-2,2',5(1'H)-trione,
5'-fluoro-1'-[(2E)-3-phenyl-2-propenyl]-2H,5H-spiro[imidazolidine-4,3'-indole]-2,2',5(1'H)-trione,
5'-chloro-7'-methyl-1'-{[3-(methyloxy)phenyl]methyl}-2H,5H-spiro[imidazolidine-4,3'-indole]-2,2',5(1'H)-trione,

5'-chloro-1'-{[2-fluoro-4-(trifluoromethyl)phenyl]methyl}-7'-methyl-2H,5H-spiro[imidazolidine-4,3'-indole]-2,2',5(1'H)-trione,
5'-chloro-1'-{[4-fluoro-3-(trifluoromethyl)phenyl]methyl}-7'-methyl-2H,5H-spiro[imidazolidine-4,3'-indole]-2,2',5(1'H)-trione,
5'-chloro-1'-[(2-chloro-6-fluorophenyl)methyl]-7'-methyl-2H,5H-spiro[imidazolidine-4,3'-indole]-2,2',5(1'H)-trione,
5'-chloro-7'-methyl-1'-{[3-(trifluoromethyl)phenyl]methyl}-2H,5H-spiro[imidazolidine-4,3'-indole]-2,2',5(1'H)-trione,
5'-chloro-7'-methyl-1'-{[4-(trifluoromethyl)phenyl]methyl}-2H,5H-spiro[imidazolidine-4,3'-indole]-2,2',5(1'H)-trione,
5'-chloro-7'-methyl-1'-(3-methylbutyl)-2H,5H-spiro[imidazolidine-4,3'-indole]-2,2',5(1'H)-trione,
5'-chloro-7'-methyl-1'-pentyl-2H,5H-spiro[imidazolidine-4,3'-indole]-2,2',5(1'H)-trione,
5'-chloro-7'-methyl-1'-(phenylmethyl)-2H,5H-spiro[imidazolidine-4,3'-indole]-2,2',5(1'H)-trione,
1'-[(2E)-2-butenyl]-5'-chloro-7'-methyl-2H,5H-spiro[imidazolidine-4,3'-indole]-2,2',5(1'H)-trione,
5'-chloro-7'-methyl-1'-(2-propenyl)-2H,5H-spiro[imidazolidine-4,3'-indole]-2,2',5(1'H)-trione,
5'-methyl-1'-(2-methylpropyl)-2H,5H-spiro[imidazolidine-4,3'-indole]-2,2',5(1'H)-trione,
1'-[(2-chloro-6-fluorophenyl)methyl]-2H,5H-spiro[imidazolidine-4,3'-indole]-2,2',5(1'H)-trione,
1'-(3-methylbutyl)-2H,5H-spiro[imidazolidine-4,3'-indole]-2,2',5(1'H)-trione,
1'-[(2E)-2-butenyl]-2H,5H-spiro[imidazolidine-4,3'-indole]-2,2',5(1'H)-trione,
1'-(2-propenyl)-2H,5H-spiro[imidazolidine-4,3'-indole]-2,2',5(1'H)-trione,
1'-[(4-fluorophenyl)methyl]-5'-methyl-2H,5H-spiro[imidazolidine-4,3'-indole]-2,2',5(1'H)-trione,
1'-[(2-bromophenyl)methyl]-5'-methyl-2H,5H-spiro[imidazolidine-4,3'-indole]-2,2',5(1'H)-trione,
5'-methyl-1'-{[4-(1-methylethyl)phenyl]methyl}-2H,5H-spiro[imidazolidine-4,3'-indole]-2,2',5(1'H)-trione,

5'-methyl-1'-{[3-(methyloxy)phenyl]methyl}-2H,5H-spiro[imidazolidine-4,3'-indole]-2,2',5(1'H)-trione,

5'-methyl-1'-(4-methyl-3-pentenyl)-2H,5H-spiro[imidazolidine-4,3'-indole]-2,2',5(1'H)-trione,

1'-{[2-fluoro-4-(trifluoromethyl)phenyl]methyl}-5'-methyl-2H,5H-spiro[imidazolidine-4,3'-indole]-2,2',5(1'H)-trione,

5'-methyl-1'-({4-[(trifluoromethyl)oxy]phenyl}methyl)-2H,5H-spiro[imidazolidine-4,3'-indole]-2,2',5(1'H)-trione,

1'-(1,1'-biphenyl-2-ylmethyl)-5'-methyl-2H,5H-spiro[imidazolidine-4,3'-indole]-2,2',5(1'H)-trione,

1'-{[2-chloro-5-(trifluoromethyl)phenyl]methyl}-5'-methyl-2H,5H-spiro[imidazolidine-4,3'-indole]-2,2',5(1'H)-trione,

1'-[(2-chloro-6-fluorophenyl)methyl]-5'-methyl-2H,5H-spiro[imidazolidine-4,3'-indole]-2,2',5(1'H)-trione,

1'-[(4-chlorophenyl)methyl]-5'-methyl-2H,5H-spiro[imidazolidine-4,3'-indole]-2,2',5(1'H)-trione,

1'-{[4-(1,1-dimethylethyl)phenyl]methyl}-5'-methyl-2H,5H-spiro[imidazolidine-4,3'-indole]-2,2',5(1'H)-trione,

5'-methyl-1'-{[4-(trifluoromethyl)phenyl]methyl}-2H,5H-spiro[imidazolidine-4,3'-indole]-2,2',5(1'H)-trione,

1'-[(2,4-dichlorophenyl)methyl]-5'-methyl-2H,5H-spiro[imidazolidine-4,3'-indole]-2,2',5(1'H)-trione,

1'-[(2,3-dichlorophenyl)methyl]-5'-methyl-2H,5H-spiro[imidazolidine-4,3'-indole]-2,2',5(1'H)-trione,

5'-methyl-1'-(3-methylbutyl)-2H,5H-spiro[imidazolidine-4,3'-indole]-2,2',5(1'H)-trione,

5'-methyl-1'-pentyl-2H,5H-spiro[imidazolidine-4,3'-indole]-2,2',5(1'H)-trione,

1'-[(2-iodophenyl)methyl]-5'-methyl-2H,5H-spiro[imidazolidine-4,3'-indole]-2,2',5(1'H)-trione,

1'-[(4-ethenylphenyl)methyl]-5'-methyl-2H,5H-spiro[imidazolidine-4,3'-indole]-2,2',5(1'H)-trione,

5'-methyl-1'-(phenylmethyl)-2H,5H-spiro[imidazolidine-4,3'-indole]-2,2',5(1'H)-trione,

1'-[(2E)-2-butenyl]-5'-methyl-2H,5H-spiro[imidazolidine-4,3'-indole]-2,2',5(1'H)-trione,

5'-methyl-1'-(2-propenyl)-2H,5H-spiro[imidazolidine-4,3'-indole]-2,2',5(1'H)-trione,
5'-methyl-1'-[(2E)-3-phenyl-2-propenyl]-2H,5H-spiro[imidazolidine-4,3'-indole]-2,2',5(1'H)-trione,
5'-methyl-1'-{[2-(trifluoromethyl)phenyl]methyl}-2H,5H-spiro[imidazolidine-4,3'-indole]-2,2',5(1'H)-trione,
1'-(2-ethylbutyl)-5'-methyl-2H,5H-spiro[imidazolidine-4,3'-indole]-2,2',5(1'H)-trione,
1'-{[4-fluoro-3-(trifluoromethyl)phenyl]methyl}-5'-methyl-2H,5H-spiro[imidazolidine-4,3'-indole]-2,2',5(1'H)-trione,
5'-methyl-1'-{[4-(methylsulfonyl)phenyl]methyl}-2H,5H-spiro[imidazolidine-4,3'-indole]-2,2',5(1'H)-trione,
5'-methyl-1'-[(2,4,6-trimethylphenyl)methyl]-2H,5H-spiro[imidazolidine-4,3'-indole]-2,2',5(1'H)-trione,
5'-methyl-1'-{[3-(trifluoromethyl)phenyl]methyl}-2H,5H-spiro[imidazolidine-4,3'-indole]-2,2',5(1'H)-trione,
5'-methyl-1'-({3-[(trifluoromethyl)oxy]phenyl}methyl)-2H,5H-spiro[imidazolidine-4,3'-indole]-2,2',5(1'H)-trione,
1'-[(4-bromo-2-fluorophenyl)methyl]-5'-methyl-2H,5H-spiro[imidazolidine-4,3'-indole]-2,2',5(1'H)-trione,
5'-methyl-1'-{[4-(1,2,3-thiadiazol-4-yl)phenyl]methyl}-2H,5H-spiro[imidazolidine-4,3'-indole]-2,2',5(1'H)-trione,
5'-chloro-1'-(4-methyl-3-pentenyl)-2H,5H-spiro[imidazolidine-4,3'-indole]-2,2',5(1'H)-trione,
5'-chloro-1'-(phenylmethyl)-2H,5H-spiro[imidazolidine-4,3'-indole]-2,2',5(1'H)-trione,
5'-chloro-1'-pentyl-2H,5H-spiro[imidazolidine-4,3'-indole]-2,2',5(1'H)-trione,
5'-fluoro-1'-{[2-fluoro-4-(trifluoromethyl)phenyl]methyl}-2H,5H-spiro[imidazolidine-4,3'-indole]-2,2',5(1'H)-trione,
5'-fluoro-1'-{[4-fluoro-3-(trifluoromethyl)phenyl]methyl}-2H,5H-spiro[imidazolidine-4,3'-indole]-2,2',5(1'H)-trione,
5'-chloro-7'-methyl-1'-(2-methylpropyl)-2H,5H-spiro[imidazolidine-4,3'-indole]-2,2',5(1'H)-trione,
5'-chloro-7'-methyl-1'-(4-methyl-3-pentenyl)-2H,5H-spiro[imidazolidine-4,3'-indole]-2,2',5(1'H)-trione,

5'-chloro-1'-(2-ethylbutyl)-7'-methyl-2H,5H-spiro[imidazolidine-4,3'-indole]-2,2',5(1'H)-trione, and
5'-chloro-7'-methyl-1'-[(2E)-3-phenyl-2-propenyl]-2H,5H-spiro[imidazolidine-4,3'-indole]-2,2',5(1'H)-trione,
or salts thereof.

5. The compound or salt thereof according to claim 4, for use as a medicament.

6. Use of a compound or salt thereof according to claim 4, in the manufacture of a medicament for the treatment of conditions associated with vanilloid receptor 1.

7. The use of a compound of formula I or salt thereof as defined in claim 1 or a compound or salt thereof according to claim 4, in the manufacture of a medicament for the treatment of acute and chronic pain disorders.

8. The use of a compound of formula I or salt thereof as defined in claim 1 or a compound or salt thereof according to claim 4, in the manufacture of a medicament for the treatment of acute and chronic neuropathic pain.

9. The use of a compound of formula I or salt thereof as defined in claim 1 or a compound or salt thereof according to claim 4, in the manufacture of a medicament for the treatment of acute and chronic inflammatory pain.

10. The use of a compound of formula I or salt thereof as defined in claim 1 or a compound or salt thereof according to claim 4 in the manufacture of a medicament for treatment of acute and chronic nociceptive pain.

11. The use of a compound of formula I or salt thereof as defined in claim 1 or a compound or salt thereof according to claim 4, in the manufacture of a medicament for treatment of low back pain, post-operative pain, visceral pains like chronic pelvic pain, cystitis, including interstitial cystitis and pain related thereto, ischeamic, sciatia, diabetic neuropathy, multiple sclerosis, arthritis, fibromyalgia, pain and other signs and symptoms

associated with psoriasis, pain and other signs and symptoms associated with cancer, emesis, urinary incontinence, hyperactive bladder, HIV neuropathy, gastro-esophageal reflux disease (GERD), irritable bowel syndrome (IBS), inflammatory bowel disease (IBD) and/or pancreatitis, including signs and/or symptoms related to said diseases.

12. The use of a compound of formula I or salt thereof as defined in claim 1 or a compound or salt thereof according to claim 4, in the manufacture of a medicament for the treatment of respiratory diseases.

13. A method of treatment of VR1 mediated disorders and for treatment of acute and chronic pain disorders, acute and chronic neuropathic pain, acute and chronic nociceptive pain, and acute and chronic inflammatory pain, and respiratory diseases, comprising administrering to a mammal, including man in need of such treatment, a therapeutically effective amount of a compound of formula I or salt thereof as defined in claim 1 or a compound or salt thereof according to claim 4.

14. A pharmaceutical composition comprising as active ingredient a therapeutically effective amount of a compound or salt thereof according to claim 4, in association with one or more pharmaceutically acceptable diluents, excipients and/or inert carriers.

15. The pharmaceutical composition according to claim 14 for use in treatment of VR1 mediated disorders and for treatment of acute and chronic pain disorders, acute and chronic neuropathic pain, acute and chronic nociceptive pain, and acute and chronic inflammatory pain, and respiratory diseases.

16. Compounds selected from the group consisiting of
1-{[2-(3,4-dichlorophenyl)cyclopropyl]methyl}-1*H*-indole-2,3-dione, and
1-[3-(3,4-dichlorophenyl)prop-2-yn-1-yl]-1*H*-indole-2,3-dione,

17. Use of compounds according to claim 16 as intermediates in the preparation of a compound according to any one of claims 1 to 4.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE2007/000106

A. CLASSIFICATION OF SUBJECT MATTER

IPC: see extra sheet
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)

IPC: C07D, A61K

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

SE,DK,FI,NO classes as above

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

EPO-INTERNAL, WPI DATA, PAJ, CHEM.ABS DATA

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	OTOMASU HIROTAKA ET AL "Spiro Heterocyclic Compounds I. Synthesis of Spiro[imidazolidine-4,3'-indoline]-2,2'5-triones", Chem. Pharm. Bull.1974, Vol. 23, No. 7, p. 1431-1435, compounds 7,8	4-5,14-15
A	WO 0105790 A1 (ASTRAZENECA AB), 25 January 2001 (25.01.2001), claim 1, abstract	1-17
A	WO 2004100865 A2 (ASTRAZENECA AB), 25 November 2004 (25.11.2004), page 2, line 19 - line 20, the claims	1-17

[X] Further documents are listed in the continuation of Box C. [X] 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 application or patent 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	Date of mailing of the international search report
29 May 2007	31 -05- 2007
Name and mailing address of the ISA/ Swedish Patent Office Box 5055, S-102 42 STOCKHOLM Facsimile No. +46 8 666 02 86	Authorized officer Solveig Gustavsson/ELY Telephone No. +46 8 782 25 00

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE2007/000106

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 2005049601 A1 (MERCK SHARP & DOHME LIMITED), 2 June 2005 (02.06.2005), abstract -- --------	1-17

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE2007/000106

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.: 13
because they relate to subject matter not required to be searched by this Authority, namely:

Claim 13 relates to a method of treatment of the human or animal body by surgery or by therapy /Rule 39.1(iv). Nevertheless, a search has been made for this claim, based on the alleged effects of the compounds.

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 all searchable claims.

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

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

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

Remark on Protest

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

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

☐ No protest accompanied the payment of additional search fees.

International patent classification (IPC)

C07D 487/10 (2006.01)
A61K 31/4188 (2006.01)
A61P 25/02 (2006.01)

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Use the application number as username.
The password is **KDCWHTSYEG**.

Paper copies can be ordered at a cost of 50 SEK per copy from PRV InterPat (telephone number 08-782 28 85).

Cited literature, if any, will be enclosed in paper form.

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INTERNATIONAL SEARCH REPORT
Information on patent family members

28/04/2007

International application No.
PCT/SE2007/000106

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