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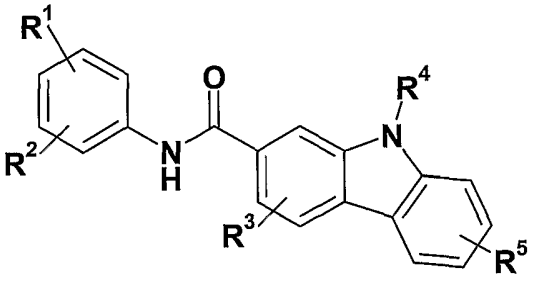
(54) Title: CARBAZOLE-2-CARBOXAMIDE DERIVATIVES HAVING VANILLOID RECEPTOR ANTAGONIST ACTIVITY



(I)

(57) Abstract: A compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, wherein R^1, R^2, R^3, R^4 and R^5 are as defined in the specification, a process for preparing such compounds, a pharmaceutical composition comprising such compounds and the use of such compounds and composition in medicine.

WO 2005/016922 A1

CARBAZOLE-2-CARBOXAMIDE DERIVATIVES HAVING VANILLOID RECEPTOR ANTAGONIST ACTIVITY

This invention relates to novel amide derivatives having pharmacological activity, processes for their preparation, to compositions containing them and to their use in medicine, especially in the treatment of various disorders.

Vanilloids are a class of natural and synthetic compounds that are characterised by the presence of a vanillyl (4-hydroxy 3-methoxybenzyl) group or a functionally equivalent group. Vanilloid Receptor (VR-1), whose function is modulated by such compounds, has been widely studied and is extensively reviewed by Szallasi and Blumberg (The American Society for Pharmacology and Experimental Therapeutics, 1999, Vol. 51, No. 2.).

A wide variety of Vanilloid compounds of different structures are known in the art, for example those disclosed in European Patent Application Numbers, EP 0 347 000 and EP 0 401 903, UK Patent Application Number GB 2226313 and International Patent Applications, Publication Numbers WO 92/09285, WO 02/100819 and WO 02/076946. Particularly notable examples of vanilloid compounds or vanilloid receptor modulators are capsaicin or trans 8-methyl-N-vanillyl-6-nonenamide which is isolated from the pepper plant, capsazepine (*Tetrahedron*, 53, 1997, 4791) and olvanil or - N-(4-hydroxy-3-methoxybenzyl)oleamide (*J. Med. Chem.*, 36, 1993, 2595).

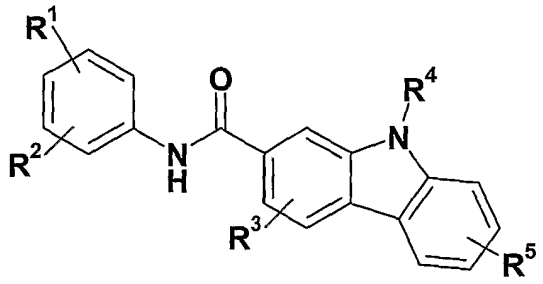
International Patent Application, Publication Number WO 02/08221 discloses diaryl piperazine and related compounds which bind with high selectivity and high affinity to vanilloid receptors, especially Type I Vanilloid receptors, also known as capsaicin or VR1 receptors. The compounds are said to be useful in the treatment of chronic and acute pain conditions, itch and urinary incontinence.

International Patent Applications, Publication Numbers WO 02/16317, WO 02/16318 and WO 02/16319 suggest that compounds having a high affinity for the vanilloid receptor are useful for treating stomach-duodenal ulcers.

International Patent Applications, Publication Numbers WO 02/072536, WO 02/090326, WO 03/022809, WO 03/053945, WO 03/068749 and WO

04/024710; and co-pending International Patent Application Numbers PCT/GB2004/000543, PCT/EP2004/002377, PCT/GB2004/000978 and PCT/EP2004/002376 also describe a variety of compounds having activity as vanilloid receptor antagonists.

According to a first aspect of the present invention, there is provided a compound of formula (I),



(I)

or a pharmaceutically acceptable salt or solvate thereof, wherein,

R^1 and R^2 may be the same or different and represent –H, alkyl, alkoxy, halo, -CF_3, cycloalkyl, cycloalkylalkyl, aryl, arylalkyl, aryloxyalkyl, -$(CH_2)_xOR^6$ or -$(CH_2)_xNR^6R^7$; or R^1 and R^2 together with the carbon atoms to which they are attached form a heteroaryl ring which may be optionally substituted by one or more alkyl, alkoxy, halo, -CF_3, -OH or -NO_2 groups;

R^3 and R^5, which may be the same or different, represent –H, halo, alkyl, alkoxy, cycloalkyl, aralkyl, aralkoxy, cycloalkylalkyl, cycloalkylalkoxy, -CN, -NO_2, -OH, -OCF_3, -CF_3, -NR^6R^7, -$S(O)_mR^8$, -$S(O)_2NR^6R^7$, -$OS(O)_2R^8$, -$OS(O)_2CF_3$, -$O(CH_2)_xNR^6R^7$, –$O(CH_2)_xOR^6$, -$C(O)CF_3$, -C(O)alkyl, -C(O)cycloalkyl, -C(O)aralkyl, -C(O)Ar, -$C(O)(CH_2)_xOR^8$, -$C(O)(CH_2)_xNR^6R^7$, -C(O)alkoxy, -$C(O)NR^6R^7$, -$(CH_2)_xC(O)$alkoxy, -$(CH_2)_xOC(O)R^8$, -$(CH_2)_xOR^8$, -$(CH_2)_xR^6R^7$, -$(CH_2)_xC(O)NR^6R^7$, -$(CH_2)_xN(R^6)C(O)R^8$, -$(CH_2)_xS(O)_2NR^6R^7$, -$(CH_2)_xN(R^6)S(O)_2R^8$, -ZAr, -$(CH_2)_xS(O)_2R^8$, -$(OCH_2)_xS(O)_2R^8$, -$N(R^6)S(O)_2R^8$, -$N(R^6)C(O)R^8$, or –$(CH_2)_xC(O)$alkyl;

R^4 represents –H, alkyl, –$(CH_2)_xOR^8$ or –$(CH_2)_xNR^6R^7$;

R^6 and R^7 may be the same or different and represent H or alkyl or R^6 and R^7 together with the atoms to which they are attached form a C_{3-6}azacycloalkane,

C_{3-6}(2-oxo)azacycloalkane ring or C_{5-8} polymethylene chain optionally interrupted by heteroatoms such as O or $-NR^8$;

R^8 represents -H, alkyl or aryl;

Ar represents aryl or heteroaryl;

x represents an integer 0, 1, 2, 3, 4, 5 or 6; and

Z represents a bond, O, S, NR^8 or CH_2.

Preferably, R^1 and R^2 may be the same or different and represent –H, alkyl such as methyl, alkoxy such as methoxy or $-CF_3$. Preferably, R^1 and R^2 together with the carbon atoms to which they are attached form a benzothiazole group (when taken together with the phenyl ring), which benzothiazole group may be optionally substituted by an alkyl group, such as methyl.

Preferably, R^3 and R^5 each represent -H.

Preferably, R^4 represents –H, $-(CH_2)_2OMe$ or $-(CH_2)_2$-NR^6R^7.

Preferably, x represents 0, 1, 2 or 3.

Preferably, R^6 represents hydrogen, methyl or ethyl.

Preferably, R^7 represents hydrogen, methyl or ethyl.

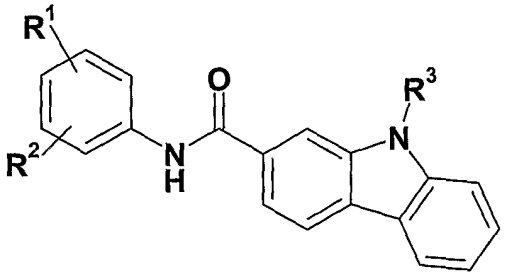
Examples of the C_{3-6} ring that R^6 and R^7 may independently represent, when taken together with the atoms to which they are attached, include pyrrolidine, morpholine and piperidine.

Preferably, R^8 represents methyl.

Preferably, Z represents a bond.

Preferably, Ar represents phenyl.

According to a further aspect of the present invention, there is provided a subset of compounds of formula (I), of formula (IA),



(IA)

or a pharmaceutically acceptable salt or solvate thereof, wherein,

R^1 and R^2 may be the same or different and represent –H, alkyl, alkoxy or $-CF_3$;

or R^1 and R^2 together with the carbon atoms to which they are attached form a benzothiazole group (when taken together with the phenyl ring), which benzothiazole group may be optionally substituted by one or more groups selected from alkyl, such as methyl, alkoxy, halo, $-CF_3$, -OH or $-NO_2$;

R^3 represents –H, alkyl, $-(CH_2)_xOR^6$ or $-(CH_2)_xNR^4R^5$;

R^4 and R^5 may be the same or different and represent H or alkyl or R^4 and R^5 together with the atoms to which they are attached form a C_{3-6}azacycloalkane, C_{3-6}(2-oxo)azacycloalkane ring or C_{5-8} polymethylene chain optionally interrupted by heteroatoms such as O or $-NR^6$;

R^6 represents -H, alkyl or aryl; and

x represents an integer 0, 1, 2, 3, 4, 5 or 6.

Preferred compounds according to this invention include Examples 1 - 9 or pharmaceutically acceptable salts or solvates thereof.

Particularly preferred compounds according to this invention include Examples 1 - 4 or pharmaceutically acceptable salts or solvates thereof.

Certain of the carbon atoms of formula (I) are chiral carbon atoms, and therefore compounds of formula (I) may exist as stereoisomers. The invention extends to all optical isomers such as stereoisomeric forms of the compounds of

formula (I) including enantiomers and mixtures thereof, such as racemates. The different stereoisomeric forms may be separated or resolved one from the other by conventional methods or any given isomer may be obtained by conventional stereospecific or asymmetric syntheses.

As indicated above, the compounds of formula (I) can form salts, especially pharmaceutically acceptable salts. Suitable pharmaceutically acceptable salts are those used conventionally in the art and include those described in *J. Pharm. Sci.*, 1977, **66**, 1-19, such as acid addition salts.

Suitable pharmaceutically acceptable salts include acid addition salts.

Suitable pharmaceutically acceptable acid addition salts include salts with inorganic acids such, for example, as hydrochloric acid, hydrobromic acid, orthophosphoric acid or sulphuric acid, or with organic acids such, for example as methanesulphonic acid, toluenesulphonic acid, acetic acid, propionic acid, lactic acid, citric acid, fumaric acid, malic acid, succinic acid, salicylic acid, maleic acid, glycerophosphoric acid or acetylsalicylic acid.

The salts and/or solvates of the compounds of the formula (I) which are not pharmaceutically acceptable may be useful as intermediates in the preparation of pharmaceutically acceptable salts and/or solvates of compounds of formula (I) or the compounds of the formula (I) themselves, and as such form another aspect of the present invention.

The compounds of formula (I) may be prepared in crystalline or non-crystalline form, and if crystalline, may be optionally hydrated or solvated. This invention includes in its scope stoichiometric hydrates as well as compounds containing variable amounts of water.

Suitable solvates include pharmaceutically acceptable solvates, such as hydrates.

Solvates include stoichiometric solvates and non-stoichiometric solvates.

As used herein the term “alkyl” as a group or part of a group refers to a straight or branched chain saturated aliphatic hydrocarbon radical containing 1 to 12 carbon atoms, suitably 1 to 6 carbon atoms. Such alkyl groups in particular include methyl ("Me"), ethyl ("Et"), n-propyl ("Pr^n"), *iso*-propyl ("Pr^i"), n-butyl ("Bu^n"), *sec*-butyl ("Bu^s"), *tert*-butyl ("Bu^t"), pentyl and hexyl. The term “cycloalkyl” as part of a group refers to a saturated alicyclic hydrocarbon radical

containing 3 to 12 carbon atoms, suitably 3 to 6 carbon atoms. Where appropriate, such alkyl groups may be substituted by one or more groups selected from halo (such as fluoro, chloro, bromo), -CN, -CF_3, -OH, –OCF_3, C_{2-6} alkenyl, C_{3-6} alkynyl, C_{1-6} alkoxy, aryl and di-C_{1-6} alkylamino. Alkyl is preferably unsubstituted.

As used herein, the term "alkoxy" as a group or part of a group refers to an alkyl ether radical, wherein the term "alkyl" is defined above. Such alkoxy groups in particular include methoxy, ethoxy, n-propoxy, *iso*-propoxy, n-butoxy, *iso*-butoxy, *sec*-butoxy and *tert*-butoxy. Where appropriate, such alkoxy groups may be substituted by one or more groups selected from halo (such as fluoro, chloro, bromo), -CN, -CF_3, -OH, –OCF_3, C_{1-6} alkyl, C_{2-6} alkenyl, C_{3-6} alkynyl, aryl and di-C_{1-6} alkylamino. Alkoxy is preferably unsubstituted.

As used herein, the term "aryl" as a group or part of a group refers to a carbocyclic aromatic radical ("Ar"). Suitably such aryl groups are 6 membered monocyclic groups or 8-10 membered fused bicyclic groups (including aromatic systems fused with non-aromatic systems), especially phenyl ("Ph"), biphenyl, indene and naphthyl, particularly phenyl.

Aryl and heteroaryl groups contained within moieties R^1 or Ar may optionally be substituted with one or more substituents selected from the list consisting of halo, hydroxy, carbonyl, alkoxy, alkyl, -CF^3, NR^6R^7 and -SO_2R^8.

The term "naphthyl" is used herein to denote, unless otherwise stated, both naphth-1-yl and naphth-2-yl groups.

As used herein, the term "heteroaryl" as a group or part of a group refers to a stable 5- 7-membered monocyclic or 7- to 10-membered bicyclic heterocyclic aromatic ring (including an aromatic ring system fused with a non-aromatic ring system) which consists of carbon atoms and from 1 to 4 heteroatoms independently selected from the group consisting of N, O and S. It is preferred that the total number of S and O atoms in the aromatic heterocycle is not more than 1. Examples of suitable heteroaryl groups include, but are not limited to, acridinyl, azocinyl, benzimidazolyl, benzofuranyl, benzothiofuranyl, benzothiophenyl, benzoxazolyl, benzthiazolyl, benztriazolyl, benztetrazolyl, benzisoxazolyl, benzisothiazolyl, benzimidazolyl, carbazolyl, carbolinyl, chromanyl, chromenyl, cinnolinyl, decahydroquinolinyl, 2H, 6H-1,5,2-dithiazinyl,

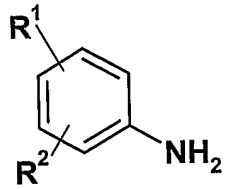
dihydrobenzofuranyl, furanyl, furazanyl, imidazolyl, 1H-indazolyl, indolinyl, indolyl, isobenzofuranyl, isochromanyl, isoindazolyl, isoindolyl, isoquinolinyl, isothiazolyl, isoxazolyl, naphthyridinyl, oxadiazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,2,5-oxadiazolyl, 1,3,4-oxadiazolyl, oxazolyl, pyrimidinyl, phthalazinyl, pteridinyl, purinyl, pyrazinyl, pyrazolyl, pyridooxazolyl, pyridoimidazolyl, pyridothiazolyl, pyridyl, pyrrolyl, quinazolinyl, quinolinyl, quinoxalinyl, tetrahydroisoquinolinyl, tetrahydroquinolinyl, 6H-1,2,5-thiadiazinyl, 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,2,5-thiadiazolyl, 1,3,4-thiadiazolyl, thiazolyl, thienyl, thienothiazolyl, thienooxazolyl, thienoimidazolyl, triazinyl, 1,2,3-triazolyl, 1,2,4-triazolyl, 1,2,5-triazolyl, 1,3,4-triazolyl and xanthenyl.

As used herein, the terms "heterocyclyl" and "heterocyclic" as a group or part of a group refer to stable heterocyclic non-aromatic single and fused rings containing one or more heteroatoms independently selected from nitrogen, oxygen and sulfur. A fused heterocyclyl ring system may include carbocyclic rings and need include only one heterocyclic ring. Examples of suitable heterocyclyl groups include, but are not limited to, piperazinyl, homopiperazinyl, piperidinyl, pyrrolidinyl and morpholinyl.

The term "halo" is used herein to describe, unless otherwise stated, a group selected from fluorine ("fluoro"), chlorine ("chloro"), bromine ("bromo") or iodine ("iodo").

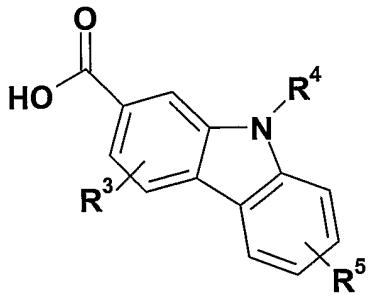
The present invention also provides a process for the preparation of a compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof, which process comprises:

(a) reacting a compound of formula (II),



(II)

wherein, R^1 and R^2 are as defined in relation to formula (I), with a compound of formula (III),



(III)

wherein, R^3, R^4 and R^5 are as defined in relation to formula (I) and thereafter, as necessary, carrying out one or more of the following reactions:

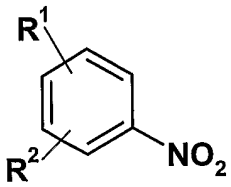
(i) converting one compound of formula (I) into another compound of formula (I);

(ii) removing any protecting group;

(iii) preparing a salt or a solvate of the compound so formed.

The reaction between a compound of formula (II) and a compound of formula (III) may be effected using conventional methods for the formation of an amide bond, such as those described in J March, *Advanced Organic Chemistry*, 4th edition, J Wiley & Sons, 1992, p. 419-421. Typically, the reaction may be carried out in a solvent such as DCM in the presence of a suitable diimide, such as 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride.

Compounds of formula (II) are either commercially available, or may be prepared by the reaction of a compound of formula (IV),



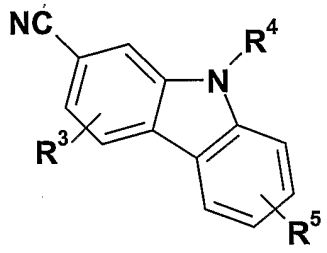
(IV)

wherein, R^1 and R^2 are as defined in relation to formula (I), with a suitable reducing agent.

The reaction of a compound of formula (IV) with a reducing agent may be effected by methods well known in the art, such as those described in J March, *Advanced Organic Chemistry*, 4th edition, J Wiley & Sons, 1992, p. 1216-1218. Suitable reducing agents include (a) iron or zinc metal in hydrochloric acid, or (b) hydrogen in the presence of a suitable catalyst, such as, 5% palladium on charcoal. Reduction using hydrogen may conveniently be performed in a solvent such as methanol or ethanol.

Compounds of formula (IV) are commercially available or may be prepared according to literature methods.

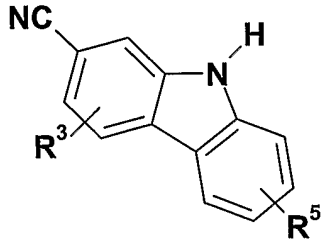
Compounds of formula (III) may be prepared by hydrolysis of a compound of formula (V),



(V)

wherein, R^3, R^4 and R^5 are as defined in relation to formula (I), in the presence of a suitable base. A suitable base is aqueous sodium hydroxide. A suitable hydrolysis agent is methanol.

Compounds of formula (V) may be prepared by reaction of a compound of formula (VI),

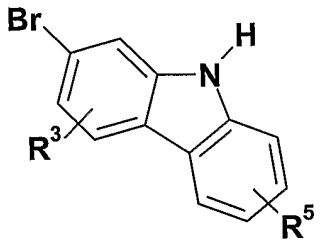


(VI)

wherein, R^3 and R^5 are as defined in relation to formula (I), with a suitable alkylating agent.

The reaction between a compound of formula (VI) with a suitable alkylating agent may be effected by methods well known in the art, such as those described in J March, *Advanced Organic Chemistry*, 4th edition, J Wiley & Sons, 1992, p411. A suitable alkylating reagent is an alkyl halide. Typically, the reaction is performed in the presence of a suitable base, such as, potassium carbonate or caesium carbonate, in a suitable solvent, such as, dimethylformamide.

Compounds of formula (VI) may be prepared from a compound of formula (VII),



(VII)

using methods similar to those described in D. Patrick *et al.*, Eur. J. Med. Chem. Chim.Ther., 1997, 32, 781; V.Percec *et al*, J. Polymer Sci., 2002, 40, 3509.

The above-mentioned conversions of a compound of formula (I) into another compound of formula (I) include any conversion, which may be effected using conventional procedures, but in particular the said conversions include any combination of:

(i) converting one group R^1 into another group R^1;

(ii) converting one group R^2 into another group R^2;

(iii) converting one group R^3 into another group R^3;

(iv) converting one group R^4 into another group R^4; and

(v) converting one group R^5 into another group R^5.

The above-mentioned conversions (i) – (v) may be performed using any appropriate method under conditions determined by the particular groups chosen.

It will be appreciated by those skilled in the art that it may be necessary to protect certain reactive substituents during some of the above procedures.

Standard protection and deprotection techniques, such as those described in Greene T.W. ' Protective groups in organic synthesis', New York, Wiley (1981), can be used. For example, primary amines can be protected as phthalimide, benzyl, benzyloxycarbonyl or trityl derivatives. Carboxylic acid groups can be protected as esters. Aldehyde or ketone groups can be protected as acetals, ketals, thioacetals or thioketals. Deprotection of such groups is achieved using conventional procedures known in the art.

Pharmaceutically acceptable salts may be prepared conventionally by reaction with the appropriate acid or acid derivative.

Compounds of formula (I) and their pharmaceutically acceptable salts and solvates thereof have Vanilloid receptor antagonist (VR1) activity and are believed to be of potential use for the treatment or prophylaxis of certain disorders, or treatment of the pain associated with them, such as: pain, chronic pain, neuropathic pain, postoperative pain, postrheumatoid arthritic pain, osteoarthritic pain, back pain, visceral pain, cancer pain, algesia, neuralgia, dental pain, headache, migraine, neuropathies, carpal tunnel syndrome, diabetic neuropathy, HIV-related neuropathy, post-herpetic neuralgia, fibromyalgia, neuritis, sciatica, nerve injury, ischaemia, neurodegeneration, stroke, post stroke pain, multiple sclerosis, respiratory diseases, asthma, cough, COPD, broncho constriction, inflammatory disorders, oesophagitis, heart burn, Barrett's metaplasia, dysphagia, gastroeosophageal relux disorder (GERD), stomach and duodenal ulcers, functional dyspepsia, irritable bowel syndrome, inflammatory bowel disease, colitis, Crohn's disease, pelvic hypersensitivity, pelvic pain, menstrual pain, renal colic, urinary incontinence, cystitis, burns, itch, psoriasis, pruritis, emesis (hereinafter referred to as the "Disorders of the Invention").

Accordingly, the invention also provides a compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof, for use as an active therapeutic substance, in particular, in the treatment and/or prophylaxis of the Disorders of the Invention.

In particular, the invention provides a compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof for use in the treatment or prophylaxis of pain.

The invention further provides a method for the treatment or prophylaxis of disorders in which antagonism of the Vanilloid (VR1) receptor is beneficial, in particular the Disorders of the Invention, in mammals including humans, which method comprises administering to a mammal in need thereof a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof.

The invention provides for the use of a compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof in the manufacture of a medicament for the treatment or prophylaxis of disorders in which antagonism of the Vanilloid (VR1) receptor is beneficial, particularly the Disorders of the Invention.

In order to use the compounds of the invention in therapy, they will normally be formulated into a pharmaceutical composition in accordance with standard pharmaceutical practice. Thus, the present invention also provides a pharmaceutical composition, which comprises a compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof and a pharmaceutically acceptable carrier or excipient therefor.

A pharmaceutical composition of the invention, which may be prepared by admixture, suitably at ambient temperature and atmospheric pressure, is usually adapted for oral, parenteral, rectal administration or intravesical administration to the bladder and, as such, may be in the form of tablets, capsules, oral liquid preparations, powders, granules, lozenges, reconstitutable powders, injectable or infusable solutions, suspensions or suppositories. Orally administrable compositions are generally preferred.

Tablets and capsules for oral administration may be in unit dose form, and may contain conventional excipients, such as binding agents, fillers, tabletting lubricants, disintegrants and acceptable wetting agents. The tablets may be coated according to methods well known in normal pharmaceutical practice.

Oral liquid preparations may be in the form of, for example, aqueous or oily suspension, solutions, emulsions, syrups or elixirs, or may be in the form of a dry product for reconstitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives such as suspending

agents, emulsifying agents, non-aqueous vehicles (which may include edible oils), preservatives, and, if desired, conventional flavourings or colourants.

For parenteral administration, fluid unit dosage forms are prepared utilising a compound of the invention or pharmaceutically acceptable salt thereof and a sterile vehicle. The compound, depending on the vehicle and concentration used, can be either suspended or dissolved in the vehicle. In preparing solutions, the compound can be dissolved for injection and filter sterilised before filling into a suitable vial or ampoule and sealing. Advantageously, adjuvants such as a local anaesthetic, preservatives and buffering agents are dissolved in the vehicle. To enhance the stability, the composition can be frozen after filling into the vial and the water removed under vacuum. Parenteral suspensions are prepared in substantially the same manner, except that the compound is suspended in the vehicle instead of being dissolved, and sterilization cannot be accomplished by filtration. The compound can be sterilised by exposure to ethylene oxide before suspension in a sterile vehicle. Advantageously, a surfactant or wetting agent is included in the composition to facilitate uniform distribution of the compound.

The composition may contain from 0.1% to 99% by weight, preferably from 10 to 60% by weight, of the active material, depending on the method of administration.

The dose of the compound used in the treatment of the aforementioned disorders will vary in the usual way with the seriousness of the disorders, the weight of the sufferer, and other similar factors. For systemic administration, dosage levels from 0.01 mg to 100 mg per kilogramme of body weight are useful in the treatment of pain. However, as a general guide suitable unit doses may be 0.05 to 1000 mg, more suitably 0.05 to 20, 20 to 250, or 0.1 to 500.0 mg, for example 0.2 to 5 and 0.1 to 250 mg; and such unit doses may be administered more than once a day, for example two or three a day, so that the total daily dosage is in the range of about 0.5 to 1000 mg; and such therapy may extend for a number of weeks or months.

No unacceptable toxicological effects are indicated with compounds of the invention when administered in accordance with the invention.

All publications, including but not limited to patents and patent applications, cited in this specification are herein incorporated by reference as if each individual publication were specifically and individually indicated to be incorporated by reference herein as though fully set forth.

The following Descriptions and Examples illustrate the preparation of the compounds of the invention.

Abbreviations

^{t}BuOH = *tert*-butanol, DCM = dichloromethane, DMF = dimethylformamide, EtOAc = ethyl acetate, MeOH = methanol, $MgSO_4$ = magnesium sulfate, $NaHCO_3$ = saturated aqueous sodium bicarbonate, HCl = hydrochloric acid, tlc = thin layer chromatography

Description 1

9-(2-Methoxyethyl)-9*H*-carbazole-2-carbonitrile (D1)

To a solution of 9*H*-carbazole-2-carbonitrile (166 mg) in DMF (2 ml) was added caesium carbonate (675mg) followed by 2-bromoethyl methyl ether (106 mg) and the reaction heated at 80°C for 24h. On cooling to room temperature the mixture was diluted with DCM, washed with $NaHCO_3$, water and brine. The organic phase was dried ($MgSO_4$) and concentrated *in vacuo* to give the *title compound* (187 mg), m/z (ES): MH^+ 251.

Description 2

9-(2-Methoxyethyl)-9*H*-carbazole-2-carboxylic acid (D2)

To a solution of D1 (187 mg) in MeOH (3 ml) was added 2M sodium hydroxide (2 ml) and the mixture heated at reflux until complete by tlc. On cooling, the solvent was removed *in vacuo*, the residue taken up in EtOAc and extracted into $NaHCO_3$ and the pH adjusted to 3 with 2M HCl. Extraction with EtOAc/ ^{t}BuOH (1:1) followed by drying ($MgSO_4$) and evaporation *in vacuo* gave the *title compound* (161 mg), m/z (ES): $(M-H)^-$ 268.

Description 3

9-[2-(4-Morpholino)ethyl]-9*H*-carbazole-2-carboxylic acid (D3)

The title compound was prepared using procedures outlined for D1 and D2, from 9*H*-carbazole-2-carbonitrile (166 mg) and 4-(2-chloroethyl) morpholine hydrochloride (209 mg) as a white solid (369 mg), m/z (ES): $(M-H)^-$ 323.

Description 4

9*H*-Carbazole-2-carboxylic acid (D4)

Prepared according to the method of G.Rodger, J.Het.Chem., 1970, 2, 239.

Description 5

9*H*-Carbazole-2-carbonitrile (D5)

Prepared using methods similar to those of V.Percec *et al.*, J.Polymer Sci., 2002, 40, 3509.

Example 1

***N*-(2-Methylbenzothiazol-5-yl)-9-[2-(methoxy)ethyl]-9*H*-carbazole-2-carboxamide (E1)**

D2 (50 mg), 5-amino-2-methylbenzothiazole dihydrochloride (37 mg), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide (36 mg) and 4-dimethylaminopyridine (4 mg) in DCM (2 ml) were stirred at room temperature for 24h. The reaction mixture was diluted with DCM, washed with saturated aqueous sodium bicarbonate, water, brine, and dried ($MgSO_4$); concentration *in vacuo* gave crude product. Purification by column chromatography eluting with 5% MeOH/DCM gave the *title compound* as a white solid (40mg), m/z (ES): MH^+ 416, $(M-H)^-$ 414

Example 2

***N*-(2-Methylbenzothiazol-5-yl)-9-[2-(4-morpholino)ethyl]-9*H*-carbazole-2-carboxamide (E2)**

Using a procedure similar to that of Example 1, the *title compound* was prepared from 5-amino-2-methylbenzothiazole dihydrochloride (31 mg) and D3 (50 mg) as a brown gum (31 mg), m/z (ES): MH^+ 471, $(M-H)^-$ 469.

Example 3

***N*-(3-Methoxyphenyl)-9-[2-(methoxy)ethyl]-9*H*-carbazole-2-carboxamide (E3)**

Using a procedure similar to that of Example 1, the *title compound* was prepared from *m*-anisidine (38 mg) and D2 (100 mg) as a white solid (32 mg), m/z (ES): MH^+ 375, $(M-H)^-$ 373.

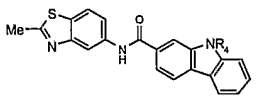
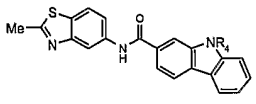
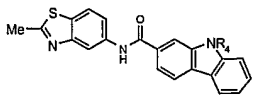
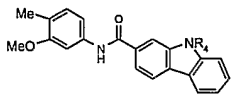
Example 4

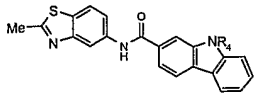
***N*-[4-Methyl-3-(trifluoromethyl)phenyl]-9-[2-(methoxy)ethyl]-9*H*-carbazole-2-carboxamide (E4)**

Using a procedure similar to that of Example 1, the *title compound* was prepared from 4-methyl-3-trifluoromethylaniline (43 mg) and D2 (80 mg) as a white solid (96 mg), m/z (ES): MH^+ 427, $(M-H)^-$ 425.

Examples 5-9 presented in Table 1 were prepared in accordance with the procedures described herein and similar to those of E1 and E2.

Table 1

Example No	Structure	R4	MH+ (observed)
5		-$(CH_2)_2NMe_2$	429
6		-$(CH_2)_2NEt_2$	457
7		-$(CH_2)_2$-N⟨ ⟩	455
8		-$(CH_2)_2OMe$	389

9		-H	358

Pharmacological Data

(a) In vitro assay

As referenced above, the compounds of the invention are vanilloid receptor (VR1) antagonists and hence have useful pharmaceutical properties. Vanilloid receptor (VR1) antagonist activity can be confirmed and demonstrated for any particular compound by use of conventional methods, for example those disclosed in standard reference texts such as D. Le Bars, M. Gozarin and S. W. Cadden, Pharmacological Reviews, 2001, 53(4), 597-652] or such other texts mentioned herein.

The screen used for the compounds of this invention was based upon a FLIPR based calcium assay, similar to that described by Smart et al. (British Journal of Pharmacology, 2000, 129, 227-230).

Transfected astrocytoma 1321N1 cells, stably expressing human VR1, were seeded into FLIPR plates at 25,000cells/well (96-well plate) and cultured overnight.

The cells were subsequently loaded in medium containing 4μM Fluo-3 AM (Molecular Probes) for 2 hours, at room temperature, in the dark. The plates were then washed 4 times with Tyrode containing 1.5mM calcium, without probenecid.

The cells were pre-incubated with compound or buffer control at room temperature for 30 minutes. Capsaicin (Sigma) was then added to the cells. Compounds having antagonist activity against the human VR1 were identified by detecting differences in fluorescence when measured after capsaicin addition, compared with no compound buffer controls. Thus, for example, in the buffer control capsaicin addition results in an increase in intracellular calcium concentration resulting in fluorescence. A compound having antagonist activity

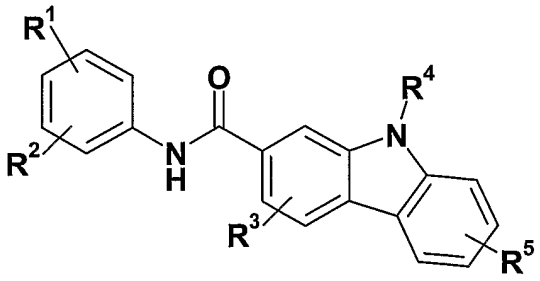
blocks the capsaicin binding to the receptor, there is no signalling and therefore no increase in intracellular calcium levels and consequently lower fluorescence. pKb values are generated from the IC_{50} values using the Cheng-Prusoff equation.

5

All compounds tested by the above methodology had pKb > 5, preferred compounds (Examples 1 - 4) having a pKb > 7.0.

Claims

1. A compound of formula (I),



(I)

or a pharmaceutically acceptable salt or solvate thereof, wherein,

R^1 and R^2 may be the same or different and represent –H, alkyl, alkoxy, halo, -CF_3, cycloalkyl, cycloalkylalkyl, aryl, arylalkyl, aryloxyalkyl, - $(CH_2)_xOR^6$ or - $(CH_2)_xNR^6R^7$; or R^1 and R^2 together with the carbon atoms to which they are attached form a heteroaryl ring which may be optionally substituted by one or more alkyl, alkoxy, halo, -CF_3, -OH and -NO_2 groups;

R^3 and R^5, which may be the same or different, represent –H, halo, alkyl, alkoxy, cycloalkyl, aralkyl, aralkoxy, cycloalkylalkyl, cycloalkylalkoxy, -CN, -NO_2, -OH, -OCF_3, -CF_3, -NR^6R^7, -$S(O)_mR^8$, -$S(O)_2NR^6R^7$, -$OS(O)_2R^8$, -$OS(O)_2CF_3$, -$O(CH_2)_xNR^6R^7$, –$O(CH_2)_xOR^6$, -$C(O)CF_3$, -C(O)alkyl, -C(O)cycloalkyl, -C(O)aralkyl, -C(O)Ar, -$C(O)(CH_2)_xOR^8$, -$C(O)(CH_2)_xNR^6R^7$, -C(O)alkoxy, -$C(O)NR^6R^7$, -$(CH_2)_xC(O)$alkoxy, -$(CH_2)_xOC(O)R^8$, -$(CH_2)_xOR^8$, -$(CH_2)_xR^6R^7$, -$(CH_2)_xC(O)NR^6R^7$, -$(CH_2)_xN(R^6)C(O)R^8$, -$(CH_2)_xS(O)_2NR^6R^7$, -$(CH_2)_xN(R^6)S(O)_2R^8$, -ZAr, -$(CH_2)_xS(O)_2R^8$, -$(OCH_2)_xS(O)_2R^8$, -$N(R^6)S(O)_2R^8$, -$N(R^6)C(O)R^8$, -$(CH_2)_xN(R^6)S(O)_2R^8$, -$(CH_2)_xN(R^6)C(O)R^8$ or –$(CH_2)_xC(O)$alkyl;

R^4 represents –$(CH_2)_xOR^8$ or –$(CH_2)_xNR^6R^7$;

R^6 and R^7 may be the same or different and represent -H or alkyl or R^6 and R^7 together with the nitrogen atom to which they are attached form a heterocyclic ring;

R^8 represents -H, alkyl or aryl;

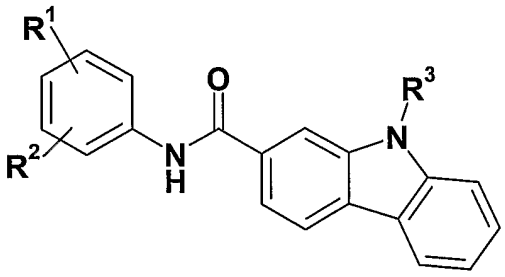
Ar represents aryl or heteroaryl;
m represents an integer 1 or 2;
x represents an integer 0, 1, 2, 3, 4, 5 or 6; and
Z represents a bond, O, S, NR^8 or CH_2.

2. A compound of formula (I), as claimed in claim 1, wherein R^1 and R^2 may be the same or different and represent –H, alkyl, alkoxy or $–CF_3$.

3. A compound of formula (I), as claimed in claim 1, wherein R^1 and R^2 together with the carbon atoms to which they are attached form a benzothiazole group (when taken together with the phenyl ring), which benzothiazole group may be optionally substituted by an alkyl group.

4. A compound of formula (I), as claimed in claim 1, wherein R^3 and R^5 represent -H.

5. A compound of formula (I), as claimed in claim 1, of formula (IA),



(IA)

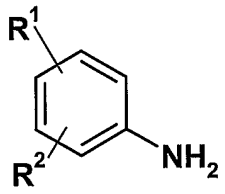
or a pharmaceutically acceptable salt or solvate thereof, wherein,
R^1 and R^2 may be the same or different and represent –H, alkyl, alkoxy or $-CF_3$;
or R^1 and R^2 together with the carbon atoms to which they are attached form a benzothiazole group (when taken together with the phenyl ring), which benzothiazole group may be optionally substituted by one or more groups selected from alkyl, such as methyl, alkoxy, halo, $-CF_3$, -OH or $-NO_2$;

R^3 represents –H, alkyl, $-(CH_2)_xOR^6$ or $-(CH_2)_xNR^4R^5$;
R^4 and R^5 may be the same or different and represent H or alkyl or R^4 and R^5 together with the atoms to which they are attached form a C_{3-6}azacycloalkane, C_{3-6}(2-oxo)azacycloalkane ring or C_{5-8} polymethylene chain optionally interrupted by heteroatoms such as O or $-NR^6$;
R^6 represents -H, alkyl or aryl; and
x represents an integer 0, 1, 2, 3, 4, 5 or 6.

6. A compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof, as claimed in claim 1, substantially as hereinbefore described with reference to any one of the Examples.

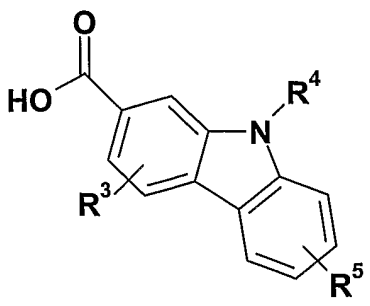
7. A process for the preparation of a compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof, as claimed in claim 1, which process comprises:

(a) reacting a compound of formula (II),



(II)

wherein, $R^1$and R^2 are as defined in relation to formula (I), with a compound of formula (III),



(III)

wherein, R^3, R^4 and R^5 are as defined in relation to formula (I) and thereafter, as necessary, carrying out one or more of the following reactions:

(i) converting one compound of formula (I) into another compound of formula (I);

(ii) removing any protecting group;

(iii) preparing a salt or a solvate of the compound so formed.

8. A pharmaceutical composition, which comprises a compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof, as claimed in claim 1, and a pharmaceutically acceptable carrier or excipient therefor.

9. A compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof, as claimed in claim 1, for use as an active therapeutic substance.

10. A method for the treatment or prophylaxis of disorders in which antagonism of the Vanilloid (VR1) receptor is beneficial, in particular the Disorders of the Invention, in mammals including humans, which method comprises administering to a mammal in need thereof a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof, as claimed in claim 1.

11. Use of a compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof, as claimed in claim 1, in the manufacture of a medicament for the treatment or prophylaxis of disorders in which antagonism of the Vanilloid (VR1) receptor is beneficial, particularly the Disorders of the Invention.

INTERNATIONAL SEARCH REPORT

Int[illegible]nal Application No
PCT/EP2004/009082

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D417/12 C07D417/14 C07D209/88

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 7 C07D

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

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

EPO-Internal, BEILSTEIN Data, WPI Data, PAJ

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 03/014064 A (BAYER AG ; FREITAG JOACHIM (DE); MEIER HEINRICH (DE); LOWINGER TIMOTHY) 20 February 2003 (2003-02-20) page 117; examples 3-17	1-11
A	WO 03/053945 A (RAMI HARSHAD KANTILAL ; THOMPSON MERVYN (GB); SMITHKLINE BEECHAM PLC () 3 July 2003 (2003-07-03) cited in the application the whole document	1-11
A	WO 03/022809 A (RAMI HARSHAD KANTILAL ; WYMAN PAUL ADRIAN (GB); THOMPSON MERVYN (GB);) 20 March 2003 (2003-03-20) cited in the application the whole document	1-11

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

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

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

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

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

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

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

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

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

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
28 October 2004	08/11/2004

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Zellner, A

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INTERNATIONAL SEARCH REPORT

Int ional Application No
PCT/EP2004/009082

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 03/059905 A (VALDENAIRE OLIVER ; GILLER THOMAS (CH); AXOVAN LTD (CH); HILPERT KURT) 24 July 2003 (2003-07-24) the whole document	1-11
E	WO 2004/072069 A (MITCHELL DARREN JASON ; RAMI HARSHAD KANTILAL (GB); TROUW LEONTINE SAS) 26 August 2004 (2004-08-26) the whole document	1-11
P,A	WO 03/068749 A (MITCHELL DARREN JASON ; RAMI HARSHAD KANTILAL (GB); GLAXO GROUP LTD (G) 21 August 2003 (2003-08-21) cited in the application the whole document	1-11

INTERNATIONAL SEARCH REPORT

ational application No.
PCT/EP2004/009082

Box 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. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claim 10 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

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

Box 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.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Inte ›nal Application No
PCT/EP2004/009082

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 03014064 A	20-02-2003	JP 2003055209 A	26-02-2003
		CA 2455754 A1	20-02-2003
		WO 03014064 A1	20-02-2003
		EP 1414788 A1	06-05-2004
WO 03053945 A	03-07-2003	WO 03053945 A2	03-07-2003
WO 03022809 A	20-03-2003	CA 2458632 A1	20-03-2003
		EP 1425277 A2	09-06-2004
		WO 03022809 A2	20-03-2003
WO 03059905 A	24-07-2003	CA 2471620 A1	24-07-2003
		WO 03059905 A1	24-07-2003
		EP 1463724 A1	06-10-2004
WO 2004072069 A	26-08-2004	WO 2004072069 A1	26-08-2004
WO 03068749 A	21-08-2003	WO 03068749 A1	21-08-2003