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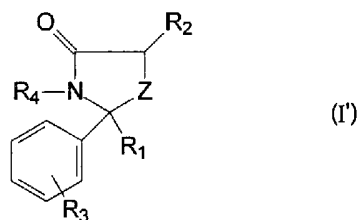
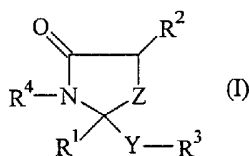
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(54) Title: 1,3-THIAZOLIN-4-ONES AS THERAPEUTIC COMPOUNDS IN THE TREATMENT OF PAIN



(57) Abstract: Compounds of formulae (I) and (I') channels wherein R₁, R₂ and R₃ are organic residues, Y is a linker and R₃ is aryl, heteroaryl, carbocyclyl or heterocyclyl are N-type calcium channel antagonists and are therefore useful in the treatment of pain.

1,3-THIAZOLIN-4-ONES AS THERAPEUTIC COMPOUNDS IN THE TREATMENT OF PAIN

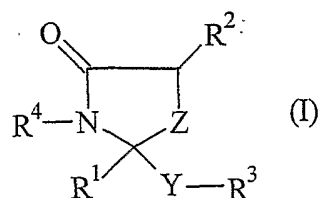
The present invention relates to specific thiazolidinone, oxazolidinone and imidazolone derivatives, which act as inhibitors of N-type calcium channels.

Mammalian ion channels are becoming increasingly well characterised, and this is especially true of calcium channels. Voltage-gated calcium channels are critical components for the functioning of the nervous system, and they signal a painful event. To date, 7 subtypes of these channels have been identified (L, N, T, O, P, Q and R), each expressed in various combinations by neuronal and non-neuronal cells (Perez-Reyes, E.; Schneider, T. *Drug Dev. Res.*, **1994**, *33*, 295-318). These channels are now recognised as valid targets for pain therapeutics and as neuroprotective agents (Cox, B.; Denyer, J.C. *Expert Opinion on Therapeutic Patents*, **1998**, *8*, 1237-1250).

WO 99/62891 discloses specific thiazolidinone and metathiazanone compounds as potassium channel inhibitors. The potassium channel inhibitors are contemplated for use in treating cardiac arrhythmias, cell proliferative disorders, disorders of the auditory system, central nervous system mediated motor dysfunction and disorders of pulmonary, vascular and visceral smooth muscle contractility.

EP-A-705816 relates to calcium antagonists. Some thiazolidinones are exemplified. A limited range of specific N-containing groups is present at the 3-position of the exemplified thiazolidinones.

It has now surprisingly been found that particular compounds of the general formula (I) set out below act as inhibitors of N-type calcium channels. Accordingly, the present invention provides the use, in the manufacture of a medicament for use in the treatment or prevention of a condition mediated by N-type calcium channels, of a compound of formula (I) or a pharmaceutically acceptable salt thereof,



wherein:

Z is -S-, -S(O)-, -SO₂-, -O- or -NR- wherein R is hydrogen, C₁-C₆ alkyl or -CO-(C₁-C₆ alkyl);

R¹ is hydrogen or C₁-C₆ alkyl;

R² is hydrogen, fluorine, C₁-C₆ alkyl, -(C₁-C₆ alkyl)-CO₂H or -(C₁-C₆ alkyl)-CO-NR₅R₆, wherein either (a) R₅ is hydrogen, aryl or -(C₁-C₆ alkyl)-aryl and R₆ is -L-R wherein L is a direct bond, a C₁-C₆ alkylene group, a C₂-C₆ alkenylene group or a C₂-C₆ alkynylene group and R is hydrogen, aryl, heteroaryl, carbocyclyl or heterocyclyl or (b) R₅ and R₆, together with the nitrogen atom to which they are attached, represent a moiety -Het₁-Het₂, wherein Het₁ is a heterocyclyl or heteroaryl group and Het₂ is hydrogen, aryl, heteroaryl, -CH(aryl)₂ or -CH(heteroaryl)₂;

Y is -(CR^Y₂)_q-, -(CR^Y₂)_m-X₄-(CR^Y₂)_n-, -(CR^Y₂)_m-A-(CR^Y₂)_m- or -(CR^Y₂)_m-A-(CR^Y₂)_p-X₃-(CR^Y₂)_m, wherein:

- p, q, m and n are each independently an integer of 0 to 4;
- A is aryl, heteroaryl, carbocyclyl or heterocyclyl;
- X₃ is -O-, -S-, -NR'-, -S(O)-, -SO₂-, -O-CO-, -S-CO-, -NR'-CO-, -CO-O-, -CO-S- or -CO-NR' wherein R' is hydrogen, C₁-C₆ alkyl, C₂-C₆ alkenyl or C₂-C₆ alkynyl;
- X₄ is -O-, -S-, -NR'-, -S(O)- or -SO₂- wherein R' is hydrogen, C₁-C₆ alkyl, C₂-C₆ alkenyl or C₂-C₆ alkynyl;
- each R^Y is the same or different and is hydrogen, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, aryl or heteroaryl;

R³ is hydrogen, aryl, heteroaryl, heterocyclyl or carbocyclyl; and

R₄ is methyl, -C₁-X₁-Ar₁ or -C₂-X₂-C₃, wherein:

- C₁ is a direct bond, a C₁-C₆ alkylene group, a C₂-C₆ alkenylene group or a C₂-C₆ alkynylene group;
- X₁ is a direct bond when C₁ is a direct bond and, when C₁ is a C₁-C₆ alkylene group, C₂-C₆ alkenylene group or C₂-C₆ alkynylene group, represents a direct bond or -O-, -S-, -NR'-, -SO-, -SO₂-, -CO-, -CO-S-, -CO-O-, -CO-NR'-, -S-CO-, -O-CO-, -NR'-CO-, -CO-O-R''-CO-O-, -CO-NR'-R''-CO-O-, -CO-O-R''-CO-NR'-, -CO-NR'-R''-CO-NR'-, -O-CO-NR'- or -NR'-CO-O-, wherein each R' is the same or different and represents hydrogen, phenyl, C₁-C₆ alkyl, C₂-C₆

- alkenyl or C₂-C₆ alkynyl and each R'' is the same or different and represents a C₁-C₆ alkylene group, a C₂-C₆ alkenylene group or a C₂-C₆ alkynylene group;
 - Ar₁ is heteroaryl, heterocyclyl, aryl, carbocyclyl, heteroaryl-R^a-, heterocyclyl-R^a-, aryl-R^a- or carbocyclyl-R^a-, wherein R^a is a C₁-C₆ alkylene group, a C₂-C₆ alkenylene group or a C₂-C₆ alkynylene group;
 - C₂ is a C₁-C₆ alkylene group, a C₂-C₆ alkenylene group or a C₂-C₆ alkynylene group;
 - X₂ is a direct bond or -O-, -S-, -NR'-, -SO-, -SO₂-, -CO-, -CO-S-, -CO-O-, -CO-NR'-, -S-CO-, -O-CO-, -NR'-CO-, -CO-O-R''-CO-O-, -CO-NR'-R''-CO-O-, -CO-O-R''-CO-NR'-, -CO-NR'-R''-CO-NR'-, -NR'-CO-O- or -O-CO-NR'-, wherein each R' is the same or different and represents hydrogen, phenyl, C₁-C₆ alkyl, C₂-C₆ alkenyl or C₂-C₆ alkynyl and each R'' is the same or different and represents a C₁-C₆ alkylene group, a C₂-C₆ alkenylene group or a C₂-C₆ alkynylene group; and
 - C₃ is a C₁-C₆ alkyl group, a C₂-C₆ alkenyl group or a C₂-C₆ alkynyl group,
- wherein:
- the alkyl, alkylene, alkenyl, alkenylene, alkynyl and alkynylene groups and moieties in the R¹ to R⁴ substituents are unsubstituted or carry 1, 2 or 3 unsubstituted substituents selected from aryl, hydroxy, C₁-C₆ alkoxy, C₁-C₆ alkylthio, -NH₂, -NH(C₁-C₆ alkyl), -N(C₁-C₆ alkyl)₂, halogen, cyano, nitro, -NHCO-(C₁-C₆ alkyl), -CO-NH-(C₁-C₆ alkyl), -CO-O-(C₁-C₆ alkyl) and -O-CO-(C₁-C₆ alkyl) substituents; and
 - the aryl, heteroaryl, carbocyclyl and heterocyclyl groups and moieties in the R¹ to R⁴ substituents are unsubstituted or carry 1, 2 or 3 substituents selected from halogen, C₁-C₆ alkyl, C₁-C₆ alkoxy, C₁-C₆ alkylthio, C₃-C₆ carbocyclyl, C₃-C₆ carbocycliloxy, C₃-C₆ carbocyclylthio, C₂-C₆ alkenyl, C₂-C₆ alkenyloxy, C₂-C₆ alkenylthio, C₂-C₆ alkynyl, C₂-C₆ alkynyloxy, C₂-C₆ alkynylthio, hydroxy, -NH₂, -NH(C₁-C₆ alkyl), -N(C₁-C₆ alkyl)₂, cyano, nitro, -NH-CO-(C₁-C₆ alkyl), -CO-NH-(C₁-C₆ alkyl), -CO-O-(C₁-C₆ alkyl) and -O-CO-(C₁-C₆ alkyl) substituents, said substituents being unsubstituted or substituted by 1, 2 or 3 further unsubstituted substituents selected from halogen, hydroxy, C₁-C₆ alkoxy, C₁-C₆ alkylthio, -NH₂, -NH(C₁-C₆ alkyl), -N(C₁-C₆ alkyl)₂, -NH-CO-(C₁-C₆ alkyl), -CO-NH-(C₁-C₆ alkyl) and -O-CO-(C₁-C₆ alkyl) substituents.

Typically, R_2 in the formula (I) is hydrogen, fluorine or C_1 - C_6 alkyl and R_4 in the formula (I) is $-C_1-X_1-Ar_1$ or $-C_2-X_2-C_3$ wherein C_1 , X_1 , Ar_1 , C_2 , X_2 and C_3 are as defined above.

As used herein, a C_1 - C_6 alkyl group or moiety is a linear or branched alkyl group or moiety containing from 1 to 6 carbon atoms, such as a C_1 - C_4 alkyl group or moiety. Examples of C_1 - C_4 alkyl groups are methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl and t-butyl.

Preferred substituents on an alkyl group or moiety in the formula (I) are hydroxy, halogen, C_1 - C_2 alkoxy, $-NH_2$, $-NH(C_1-C_2 \text{ alkyl})$ and $-N(C_1-C_2 \text{ alkyl})_2$, in particular fluorine and hydroxy. The substituents on an alkyl group are themselves unsubstituted.

As used herein, a C_1 - C_6 alkylene group is a linear or branched C_1 - C_6 alkylene group. Typically, it is a C_1 - C_4 alkylene group, for example a methylene, ethylene, n-propylene, i-propylene or n-butylene group.

Preferably, an alkylene group in the formula (I) is unsubstituted. When it is substituted, preferred substituents are hydroxy, halogen, C_1 - C_2 alkoxy, $-NH_2$, $-NH(C_1-C_2 \text{ alkyl})$ and $-N(C_1-C_2 \text{ alkyl})_2$, in particular fluorine and hydroxy. The substituents on an alkylene group are themselves unsubstituted.

As used herein, a C_2 - C_6 alkenyl group or moiety is a linear or branched alkenyl group or moiety containing from 2 to 6 carbon atoms, such as a C_2 - C_4 alkenyl group or moiety. Examples of C_2 - C_4 alkenyl groups are ethenyl, n-propenyl and n-butenyl. Typically an alkenyl group has only one double bond. This double bond is typically located at the α -position of the alkenyl group.

An alkenyl group or moiety in the formula (I) is preferably unsubstituted. When it is substituted, preferred substituents are hydroxy, halogen, C_1 - C_2 alkoxy, $-NH_2$, $-NH(C_1-C_2 \text{ alkyl})$ and $-N(C_1-C_2 \text{ alkyl})_2$, in particular fluorine and hydroxy. The substituents on an alkenyl group are themselves unsubstituted.

As used herein, a C_2 - C_6 alkenylene group is a linear or branched C_2 - C_6 alkenylene group. Typically, it is a C_2 - C_4 alkenylene group, for example an ethenylene, n-propenylene or n-butenylene group. Typically an alkenylene group has only one double bond. This double bond is typically located at the α -position of the alkenylene group.

An alkenylene group in the formula (I) is preferably unsubstituted. When it is substituted, preferred substituents are hydroxy, halogen, C₁-C₂ alkoxy, -NH₂, -NH(C₁-C₂ alkyl) and -N(C₁-C₂ alkyl)₂, in particular fluorine and hydroxy. The substituents on an alkenylene group are themselves unsubstituted.

As used herein, a C₂-C₆ alkynyl group or moiety is a linear or branched alkynyl group or moiety containing from 2 to 6 carbon atoms, such as a C₂-C₄ alkynyl group or moiety. Examples of C₂-C₄ alkynyl groups are ethynyl, propynyl and n-butynyl. Typically an alkynyl group has only one triple bond. This triple bond is typically located at the α -position of the alkynyl group.

An alkynyl group or moiety in the formula (I) is preferably unsubstituted. When it is substituted, preferred substituents are hydroxy, halogen, C₁-C₂ alkoxy, -NH₂, -NH(C₁-C₂ alkyl) and -N(C₁-C₂ alkyl)₂, in particular fluorine and hydroxy. The substituents on an alkynyl group are themselves unsubstituted.

As used herein, a C₂-C₆ alkynylene group is a linear or branched C₂-C₆ alkynylene group. Typically, it is a C₂-C₄ alkynylene group, for example an ethynylene, propynylene or n-butynylene group. Typically an alkynylene group has only one triple bond. This triple bond is typically located at the α -position of the alkynylene group.

An alkynylene group in the formula (I) is preferably unsubstituted. When it is substituted, preferred substituents are hydroxy, halogen, C₁-C₂ alkoxy, -NH₂, -NH(C₁-C₂ alkyl) and -N(C₁-C₂ alkyl)₂, in particular fluorine and hydroxy. The substituents on an alkynylene group are themselves unsubstituted.

As used herein, an aryl group is typically a C₆-C₁₀ aryl group such as phenyl or naphthyl. Phenyl is preferred. An aryl group in the formula (I) may be unsubstituted or substituted at any position. Preferred substituents include C₁-C₄ alkyl, C₁-C₄ alkoxy, C₁-C₄ alkylthio, C₅-C₆ carbocycloxy, C₂-C₄ alkenyloxy, halogen (for example fluorine), hydroxy, -NH₂, -NH(C₁-C₂ alkyl), -N(C₁-C₂ alkyl)₂ and -NH-CO-(C₁-C₂ alkyl).

Substituents on an aryl group in the formula (I) are unsubstituted or substituted by 1, 2 or 3 further substituents selected from halogen, hydroxy, C₁-C₆ alkoxy, C₁-C₆ alkylthio, -NH₂, -NH(C₁-C₆ alkyl), -N(C₁-C₆ alkyl)₂, -NH-CO-(C₁-C₆ alkyl), -CO-NH-(C₁-C₆ alkyl) and -O-CO-(C₁-C₆ alkyl). These further substituents are themselves unsubstituted. Preferably, the C₁-C₆ alkyl moieties present in the further substituents

are C₁-C₂ alkyl moieties. More preferably, substituents on an aryl group are unsubstituted or substituted with 1, 2 or 3 further substituents which are halo substituents.

References to an aryl group in the formula (I) include fused ring systems in which an aryl group is fused to a carbocyclyl, heterocyclyl or heteroaryl group. The carbocyclyl, heterocyclyl or heteroaryl group to which the aryl group is fused is typically monocyclic. Examples of such fused ring systems are a phenyl group fused to a pyridine ring to form a quinoline or isoquinoline group and a phenyl ring fused to a 5- or 6-membered heterocyclic ring containing 1, 2 or 3 heteroatoms selected from N, O and S; for example a phenyl ring fused to a 1,4-dioxanyl ring to form a 1,4-benzodioxanyl group, a phenyl ring fused to a 1,3-dioxolanyl ring to form a 1,3-benzodioxolyl group, and a phenyl ring fused to a tetrahydrofuran ring to form a 2,3-dihydrobenzofuran group.

As used herein, a heteroaryl group is typically a 5- to 10- membered aromatic ring, such as a 5- or 6- membered ring, containing at least one heteroatom, for example 1, 2 or 3 heteroatoms, selected from O, S and N. Examples include pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, furanyl, thienyl, imidazolyl, pyrazolidinyl, pyrrolyl, oxadiazolyl, isoxazolyl, thiadiazolyl, thiazolyl and pyrazolyl groups. Pyridyl, furanyl, thienyl, imidazolyl and pyrrolyl groups are preferred.

A heteroaryl group in the formula (I) may be unsubstituted or substituted at any position. Preferred substituents include C₁-C₄ alkyl, C₁-C₄ alkoxy, C₁-C₄ alkylthio, C₅-C₆ carbocycloxy, C₂-C₄ alkenyloxy, halogen (for example fluorine), hydroxy, -NH₂, -NH(C₁-C₂ alkyl), -N(C₁-C₂ alkyl)₂ and -NH-CO-(C₁-C₂ alkyl). Particularly preferred substituents include C₁-C₄ alkyl groups and halogen atoms.

Substituents on a heteroaryl group in the formula (I) are unsubstituted or substituted by 1, 2 or 3 further substituents selected from halogen, hydroxy, C₁-C₆ alkoxy, C₁-C₆ alkylthio, -NH₂, -NH(C₁-C₆ alkyl), -N(C₁-C₆ alkyl)₂, -NH-CO-(C₁-C₆ alkyl), -CO-NH-(C₁-C₆ alkyl) and -O-CO-(C₁-C₆ alkyl). These further substituents are themselves unsubstituted. Preferably, the C₁-C₆ alkyl moieties present in the further substituents are C₁-C₂ alkyl moieties. More preferably, substituents on a heteroaryl group are unsubstituted or substituted with 1, 2 or 3 further substituents which are halo substituents. Most preferably, substituents on a heteroaryl group are unsubstituted.

References in the formula (I) to a heteroaryl group include fused ring systems in which a heteroaryl group is fused to a said aryl group, to a further heteroaryl group or to a heterocyclyl group. The aryl, heteroaryl or heterocyclyl group to which the heteroaryl group is fused is typically monocyclic. Examples of such fused heteroaryl groups are heteroaryl groups fused to a phenyl ring including benzimidazolyl, benzofuranyl, quinolinyl and isoquinolinyl groups.

As used herein, a carbocyclyl group is a non-aromatic saturated or unsaturated hydrocarbon ring, typically having from 3 to 6 carbon atoms. Preferably it is a saturated hydrocarbon ring (i.e. a cycloalkyl group) having from 3 to 6 carbon atoms or an unsaturated ring having only one double bond. Examples include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexenyl and cyclohexyl. It is preferably cyclohexenyl, cyclohexyl or cyclopentyl.

A carbocyclyl group in the formula (I) may be unsubstituted or substituted at any position. Preferred substituents include C₁-C₄ alkyl, C₁-C₄ alkoxy, C₁-C₄ alkylthio, C₅-C₆ carbocycloxy, C₂-C₄ alkenyloxy, halogen (for example fluorine), hydroxy, -NH₂, -NH(C₁-C₂ alkyl), -N(C₁-C₂ alkyl)₂ and -NH-CO-(C₁-C₂ alkyl). Most preferably, a carbocyclyl group is unsubstituted.

Substituents on a carbocyclyl group in the formula (I) are unsubstituted or substituted by 1, 2 or 3 further substituents selected from halogen, hydroxy, C₁-C₆ alkoxy, C₁-C₆ alkylthio, -NH₂, -NH(C₁-C₆ alkyl), -N(C₁-C₆ alkyl)₂, -NH-CO-(C₁-C₆ alkyl), -CO-NH-(C₁-C₆ alkyl) and -O-CO-(C₁-C₆ alkyl). These further substituents are themselves unsubstituted. Preferably, the C₁-C₆ alkyl moieties present in the further substituents are C₁-C₂ alkyl moieties. More preferably, substituents on a carbocyclyl group are unsubstituted.

References in the formula (I) to a carbocyclyl group include fused ring systems in which a carbocyclyl group is fused to a phenyl ring. An example of such a fused ring system is 2,3-dihydro-1H-indenyl.

As used herein, a heterocyclyl group is typically a non-aromatic, saturated or unsaturated C₅-C₁₀ carbocyclic ring in which one or more, for example 1, 2 or 3, of the carbon atoms are replaced by a heteroatom selected from N, O and S. Saturated heterocyclyl groups are preferred. Examples of suitable heterocyclyl groups include piperidinyl, piperazinyl, morpholinyl, pyrrolidinyl, tetrahydrofuranyl, imidazolidinyl.

1,4 dioxanyl and 1,3 dioxolanyl. Tetrahydrofuranyl, 1,4-dioxanyl and 1,3-dioxolanyl are preferred, in particular 1,4-dioxanyl.

A heterocyclyl group in the formula (I) may be unsubstituted or substituted at any position. Preferred substituents include C₁-C₄ alkyl, C₁-C₄ alkoxy, C₁-C₄ alkylthio, C₅-C₆ carbocycloxy, C₂-C₄ alkenyloxy, halogen (for example fluorine), hydroxy, -NH₂, -NH(C₁-C₂ alkyl), -N(C₁-C₂ alkyl)₂ and -NH-CO-(C₁-C₂ alkyl). Most preferably, a heterocyclyl group is unsubstituted.

Substituents on a heterocyclyl group in the formula (I) are unsubstituted or substituted by 1, 2 or 3 further substituents selected from halogen, hydroxy, C₁-C₆ alkoxy, C₁-C₆ alkylthio, -NH₂, -NH(C₁-C₆ alkyl), -N(C₁-C₆ alkyl)₂, -NH-CO-(C₁-C₆ alkyl), -CO-NH-(C₁-C₆ alkyl) and -O-CO-(C₁-C₆ alkyl). These further substituents are themselves unsubstituted. Preferably, the C₁-C₆ alkyl moieties present in the further substituents are C₁-C₂ alkyl moieties. More preferably, substituents on a heterocyclyl group are unsubstituted.

References in the formula (I) to a heterocyclyl group include fused ring systems in which a heterocyclyl group is fused to a said aryl group, a said heteroaryl group or to a further heterocyclyl group. The aryl, heteroaryl or heterocyclyl group to which the heteroaryl group is fused is typically monocyclic. Preferred such fused ring systems are heterocyclyl groups fused to a phenyl ring. An example of such a fused heterocyclyl group is 1,4-benzodioxanyl.

As used herein a halogen is typically chlorine, fluorine, bromine or iodine and is preferably chlorine or fluorine. As used herein, an alkoxy, alkenyloxy, alkynyloxy or carbocycloxy group is typically a said alkyl, alkenyl, alkynyl or carbocyclyl group respectively, which is attached to an oxygen atom. An alkylthio, alkenylthio, alkynylthio or carbocyclylthio group is typically a said alkyl, alkenyl, alkynyl or carbocyclyl group respectively, which is attached to a thio group.

When Z is -NR-, R is typically -COCH₃ or -CO-CH₂-CH₃. Typically, Z is -S-, -S(O)- or -S(O)₂-. In a further embodiment, Z is typically -S- or -O-. Most preferably, Z is -S-.

Typically, R₁ is hydrogen or an unsubstituted C₁-C₄ alkyl group. Preferably, R₁ is hydrogen or -CH₃. More preferably, R₁ is hydrogen.

Typically, R_2 represents hydrogen, fluorine, C_1 - C_4 alkyl, $-(C_1$ - C_4 alkyl)- CO_2H or $-(C_1$ - C_4 alkyl)- $CONR_5R_6$, wherein either (a) R_5 is hydrogen, aryl or $-(C_1$ - C_2 alkyl)-aryl and R_6 is $-L-R$ wherein L is a direct bond or a C_1 - C_4 alkylene group and R is hydrogen, aryl, carbocyclyl, heterocyclyl or heteroaryl or (b) R_5 and R_6 , together with the nitrogen atom to which they are attached, represent a moiety $-Het_1-Het_2$, wherein Het_1 is a heterocyclyl group and Het_2 is hydrogen, aryl or $-CH(aryl)_2$.

More typically, R_2 represents hydrogen, an unsubstituted C_1 - C_4 alkyl group, $-(CH_2)_a-CO_2H$ or $-(CH_2)_b-CONR_5R_6$ wherein a and b are 1 or 2 and either (a) R_5 is hydrogen or an unsubstituted benzyl group and R_6 is $-L-R$ wherein L is a direct bond or an unsubstituted C_1 - C_4 alkylene group and R is hydrogen or a phenyl, cyclohexenyl, piperidyl, pyridyl or benzimidazolyl group which is unsubstituted or substituted by a halogen, hydroxy, $-OCH_3$ or $-OCH_2CH_3$ substituent, or (b) R_5 and R_6 , together with the N atom to which they are attached, represent a pyrrolidinyl, piperidinyl, homopiperidinyl or piperazinyl group which is unsubstituted or substituted by an unsubstituted $-CHPh_2$ group.

Preferably, R_2 is hydrogen or an unsubstituted C_1 - C_4 alkyl group. More preferably, R_2 is hydrogen.

Typically, each R^y is the same or different and is hydrogen, C_1 - C_6 alkyl, aryl or heteroaryl. Preferably, each R^y is the same or different and is hydrogen, a C_1 - C_4 alkyl or phenyl group. Preferably, each R^y is the same or different and is hydrogen, $-CH_3$, $-CH_2-CH_3$ or an unsubstituted phenyl group. Typically, when two or more R^y groups are present, no more than 2 of, preferably no more than 1 of, said R^y groups is aryl or heteroaryl.

Typically, each R^y is unsubstituted or substituted by 1, 2 or 3 substituents selected from C_1 - C_4 alkyl, C_1 - C_4 alkoxy, halogen, hydroxy, NH_2 , $NH(C_1$ - C_2 alkyl) or $N(C_1$ - C_2 alkyl) $_2$. Preferably, the substituents on R^y are selected from C_1 - C_2 alkyl, C_1 - C_2 alkoxy, halogen and hydroxy. Typically, the substituents on R^y are themselves unsubstituted. Preferably, R^y is unsubstituted.

Typically A is aryl, for example phenyl, or heteroaryl, for example pyridyl or pyrrolyl. Preferably, A is phenyl, pyridyl or pyrrolyl. The moiety A is typically unsubstituted or substituted with 1, 2 or 3 substituents. The substituents on A are typically selected from C_1 - C_4 alkyl, C_1 - C_4 alkoxy, halogen, hydroxy, NH_2 , $NH(C_1$ - C_2

alkyl) or $N(C_1-C_2 \text{ alkyl})_2$. Preferably, the substituents on A are selected from C_1-C_2 alkyl, C_1-C_2 alkoxy, halogen and hydroxy. Typically, the substituents on A are themselves unsubstituted.

In the group X_3 , R' is typically hydrogen or an unsubstituted C_1-C_6 alkyl group, preferably hydrogen or $-CH_3$, most preferably hydrogen. Typically, X_3 is $-O-$, $-S-$, $-SO-$, $-SO_2-$, $-O-CO-$, $-CO-O-$, $-NH-CO-$ or $-CO-NH-$. Preferably X_3 is $-O-$, $-S-$, $-SO-$, $-SO_2-$ or $-NH-CO-$, more preferably $-O-$, $-SO_2-$ or $-NH-CO-$. Typically, p is 0 or 1, preferably 0. Typically, q is 0, 1, 2 or 3, preferably 0 or 1. Typically, m is 0 or 1. Typically, n is 1 or 2, preferably 1.

In the group X_4 , R' is typically hydrogen or an unsubstituted C_1-C_6 alkyl group, preferably hydrogen or $-CH_3$, most preferably hydrogen. Typically, X_4 is $-O-$, $-S-$ or $-NR'$ wherein R' is as defined above. Preferably X_4 is $-O-$ or $-S-$. More preferably X_4 is $-O-$.

Y is preferably a direct bond or a group of formula $-(CR^y)_2-$, $-(CH_2)_mO(CH_2)_n-$, $-A-$ or $-A-X_3-(CH_2)_m-$, wherein R^y , A , X_3 , m and n are as defined above.

R^3 is typically hydrogen, aryl, heteroaryl or carbocyclyl. Preferably, when R^3 is aryl it is a phenyl group or a phenyl group fused to a heteroaryl or heterocyclyl group. Examples of such fused ring systems are phenyl groups fused to a 5- or 6-membered heterocyclyl ring having 1 or 2 heteroatoms selected from O, S and N. Preferred examples of such fused ring systems are 1,3-benzodioxolyl, 2,3-dihydrobenzofuran and 1,4-benzodioxanyl. Preferably, when R^3 is aryl it is phenyl, 1,3-benzodioxolyl, 2,3-dihydrobenzofuran or 1,4-benzodioxanyl. When R^3 is heteroaryl, it is preferably thienyl, furyl, pyrrolyl, pyridinyl or a heteroaryl ring fused to a phenyl ring, for example quinolinyl, isoquinolinyl or benzofuranyl. More preferably, when R^3 is heteroaryl, it is thienyl, furyl, quinolinyl or benzofuranyl. When R^3 is carbocyclyl it is preferably cyclopentyl or cyclohexyl, most preferably cyclopentyl.

More preferably, R^3 is hydrogen, phenyl, thienyl, furyl, quinolinyl, benzofuranyl, cyclopentyl, 1,4-benzodioxanyl, 1,3-benzodioxolyl or 2,3-dihydrobenzofuran.

Typically, R^3 is unsubstituted or substituted by 1, 2 or 3 substituents. The substituents are typically chosen from halogen, for example fluorine, chlorine or

bromine, hydroxy, C₁-C₆ alkyl, C₁-C₆ alkoxy, C₁-C₆ alkylthio, C₂-C₆ alkenyl, C₂-C₆ alkenyloxy, C₂-C₆ alkenylthio, C₂-C₆ alkynyl, C₂-C₆ alkynyloxy, C₂-C₆ alkynylthio, C₃-C₆ carbocyclyl, C₃-C₆ carbocyclyloxy, C₃-C₆ carbocyclylthio, -NH-CO-(C₁-C₆ alkyl), -CO-NH-(C₁-C₆ alkyl) and -NR'R'' wherein R' and R'' are each independently hydrogen or a C₁-C₆ alkyl group.

Preferred substituents on R³ are halogen, C₁-C₄ alkyl, C₁-C₄ alkoxy, C₁-C₄ alkylthio, C₂-C₄ alkenyl, C₂-C₄ alkenyloxy, C₃-C₆ carbocyclyl, C₃-C₆ carbocyclyloxy, -NH-CO-(C₁-C₂ alkyl) and -N(C₁-C₂ alkyl)₂. More preferred substituents on R³ are halogen, C₁-C₄ alkyl, C₁-C₄ alkoxy, C₁-C₄ alkylthio, C₂-C₄ alkenyloxy, C₃-C₆ carbocyclyloxy, -NH-CO-Me and -N(CH₃)₂.

Typically, the substituents on R³ are themselves unsubstituted or further substituted with 1, 2 or 3 further substituents selected from halogen, in particular fluorine, and hydroxy.

Typically, R⁴ is -CH₃ or is -C₁-X₁-Ar₁ or -C₂-X₂-C₃, wherein C₁, X₁, Ar₁, C₂, X₂ and C₃ are as defined above.

Typically, C₁ is a direct bond or a C₁-C₆ alkylene group, preferably a C₁-C₄ alkylene group. More preferably, C₁ is an unsubstituted C₁-C₄ alkylene group. Most preferably, C₁ is -CH₂-, -(CH₂)₂- or -(CH₂)₃-.

For the avoidance of doubt, the orientation of the group X₁ is such that the left hand side of the depicted moiety is attached to C₁ and the right hand side of the depicted moiety is attached to Ar₁. Thus, for example, when X₁ is -S-CO-, the moiety -C₁-X₁-Ar₁ is -C₁-S-CO-Ar₁.

Typically, each R' in the moiety X₁ is the same or different and is hydrogen, or an unsubstituted phenyl or C₁-C₆ alkyl group, preferably hydrogen, -CH₃ or -CH₂-CH₃. More preferably, each R' in the moiety X₁ is hydrogen. Typically, each R'' in the moiety X₁ is an unsubstituted C₁-C₆ alkylene group, preferably -CH₂- or -CH₂-CH₂-. More preferably, each R'' is -CH₂-.

Typically, X₁ is a direct bond or is -O-, -S-, -NR'-, -S-CO-, -O-CO-, -CO-O-, -CO-S-, -NR'-CO- or -CO-NR'-, wherein R' is as defined above. Preferably, X₁ is a direct bond or is -O-, -S-, -S-CO-, -O-CO- or -NH-CO-. More preferably, X₁ is a direct bond or is -O-, -S-, -S-CO- or -O-CO-.

Typically Ar₁ is heteroaryl, heterocyclyl, aryl, carbocyclyl, heteroaryl-(C₁-C₆ alkyl)-, heterocyclyl-(C₁-C₆ alkyl)-, aryl-(C₁-C₆ alkyl)- or carbocyclyl-(C₁-C₆ alkyl)-. When Ar₁ is a heteroaryl-(C₁-C₆ alkyl)-, aryl-(C₁-C₆ alkyl)-, heterocyclyl-(C₁-C₆ alkyl)- or carbocyclyl-(C₁-C₆ alkyl)- group, the alkyl moiety is typically an unsubstituted methylene or ethylene moiety.

Preferably, Ar₁ is heteroaryl, heterocyclyl, aryl, carbocyclyl, heteroaryl-(C₁-C₂ alkyl)- or aryl-(C₁-C₂ alkyl)-. More preferably Ar is heteroaryl, heterocyclyl, aryl, carbocyclyl or heteroaryl-(C₁-C₂ alkyl)-, most preferably heteroaryl, heterocyclyl, aryl or heteroaryl-(C₁-C₂ alkyl)-.

When Ar₁ is heteroaryl, it is preferably a pyridyl, thienyl or benzimidazolyl group, more preferably a thienyl or benzimidazolyl group. When Ar₁ is heteroaryl-(C₁-C₂ alkyl)-, it is preferably a thienyl-methyl-, pyridyl-methyl- or furanyl-methyl- group, more preferably a thienyl-methyl- or furanyl-methyl- group. When Ar₁ is heterocyclyl, it is preferably a morpholinyl, piperazinyl, piperadinyll or pyrrolidinyl group or a 5- or 6-membered heterocyclyl group fused to a phenyl ring, for example a 1,4-benzodioxanyl group or a 1,3-benzodioxolyl group. More preferably, when Ar₁ is heterocyclyl it is a 1,4-benzodioxanyl group. When Ar₁ is aryl, it is preferably a phenyl group or a phenyl group fused to a 5- or 6-membered heterocyclyl ring, for example a 1,3-benzodioxolyl group or a 1,4-benzodioxanyl group. More preferably, when Ar₁ is aryl it is a phenyl group or a 1,3-benzodioxolyl group. When Ar₁ is carbocyclyl, it is preferably cyclohexenyl or 1,2-dihydro-1H-indenyl.

Typically, the group Ar₁ is unsubstituted or carries one or more, for example 1, 2 or 3, substituents on the cyclic group. The substituents are typically selected from halogen, for example fluorine or chlorine, C₁-C₄ alkyl, hydroxy, C₁-C₄ alkoxy, -NR'R'' and -NH-CO-R' wherein R' and R'' are the same or different and are selected from hydrogen and unsubstituted C₁-C₄ alkyl. Preferred substituents are fluorine, hydroxy, methoxy, dimethylamino and -NH-CO-CH₃. Typically, the substituents on a group Ar₁ are themselves unsubstituted.

Preferably, Ar₁ is a pyridyl, thienyl, benzimidazolyl, furanyl-methyl-, 1,4-benzodioxanyl, phenyl or 1,3-benzodioxolyl group which is unsubstituted or carries, on the cyclic moiety, 1, 2 or 3 substituents selected from fluorine, hydroxy, -OCH₃, -N(CH₃)₂ and -NH-CO-CH₃.

Typically, C_2 is a C_1 - C_6 alkylene group, preferably an unsubstituted C_1 - C_4 alkylene group, more preferably an unsubstituted straight chain C_1 - C_4 alkylene group.

For the avoidance of doubt, the orientation of the group X_2 is such that the left hand side of the depicted moiety is attached to C_2 and the right hand side of the depicted moiety is attached to C_3 . Thus, for example, when X_2 is $-N-CO-O-$, the moiety $-C_2-X_2-C_3$ is $-C_2-N-CO-O-C_3$.

Typically, each R' in the moiety X_2 is the same or different and is hydrogen or an unsubstituted C_1 - C_6 alkyl or phenyl group, preferably hydrogen, $-CH_3$ or $-CH_2CH_3$. More preferably, each R' in the moiety X_2 is hydrogen. Typically, each R'' in the moiety X_2 is an unsubstituted C_1 - C_6 alkylene group, preferably $-CH_2-$ or $-CH_2-CH_2-$. More preferably, each R'' is $-CH_2-$.

Typically, X_2 is a direct bond or is $-O-$, $-S-$, $-NR'-$, $-CO-$, $-CO-S-$, $-CO-O-$, $-CO-NR'-$, $-S-CO-$, $-O-CO-$, $-NR'-CO-$, $-O-CO-NR'-$, $-NR'-CO-O-$, $-S-CO-$ or $-CO-S-$ wherein R' is as defined above. Preferably, X_2 is a direct bond or is $-O-$, $-S-$, $-CO-O-$, $-O-CO-$, $-S-CO-$, $-CO-S-$ or $-NH-CO-O-$. Most preferably, X_2 is a direct bond or is $-O-$, $-S-$, $-CO-O-$ or $-NH-CO-O-$.

Typically, C_3 is a C_1 - C_6 alkyl group, preferably a C_1 - C_4 alkyl group. C_3 is typically unsubstituted or substituted by one or more, for example 1, 2 or 3, substituents selected from hydroxy, $-NH_2$, $-NH(C_1-C_2 \text{ alkyl})$, $-N(C_1-C_2 \text{ alkyl})_2$ and halogen. Preferably, C_3 is unsubstituted or carries, on a primary carbon atom (i.e. a carbon atom at the end of a chain), either (a) one hydroxy or (b) 1, 2 or 3 halo substituents, which are preferably fluoro substituents. The substituents on C_3 are typically themselves unsubstituted.

Preferred compounds of formula (I) and pharmaceutically acceptable salts thereof are those in which:

Z is $-S-$, $-S(O)-$ or $-S(O)_2-$;

R_1 is hydrogen or an unsubstituted C_1 - C_4 alkyl group;

R_2 is hydrogen, an unsubstituted C_1 - C_4 alkyl group, $-(CH_2)_a-CO_2H$ or $-(CH_2)_b-$

$CONR_5R_6$ wherein a and b are 1 or 2 and either (a) R_5 is hydrogen or an unsubstituted benzyl group and R_6 is $-L-R$ wherein L is a direct bond or an unsubstituted C_1 - C_4 alkylene group and R is hydrogen or a phenyl, cyclohexenyl, piperidyl, pyridyl or benzimidazolyl group which is unsubstituted or substituted by a halogen, hydroxy,

-OCH₃ or -OCH₂CH₃ substituent, or (b) R₅ and R₆, together with the N atom to which they are attached, represent a pyrrolidiny, piperidiny, homopiperidiny or piperaziny group which is unsubstituted or substituted by an unsubstituted -CHPh₂ group;

Y is $-(CR^y_2)_q-$, $-(CR^y_2)_m-X_4-(CR^y_2)_n-$, $-(CR^y_2)_m-A-(CR^y_2)_m-$ or $-(CR^y_2)_m-A-(CR^y_2)_p-X_3-(CR^y_2)_m$, wherein

- each R^y is the same or different and is hydrogen or an unsubstituted C₁-C₄ alkyl or phenyl group;
- A is an aryl or heteroaryl group which is unsubstituted or substituted with 1, 2 or 3 substituents selected from unsubstituted C₁-C₄ alkyl, C₁-C₄ alkoxy, halogen, hydroxy, NH₂, NH(C₁-C₂ alkyl) and N(C₁-C₂ alkyl)₂ groups;
- X₃ is -O-, -S-, -SO-, -SO₂-, -O-CO-, -CO-O-, -NH-CO- or -CO-NH-;
- X₄ is -O-, -S- or -NR'- wherein R' is hydrogen or -CH₃;
- p is 0 or 1; q is 0, 1, 2 or 3; m is 0 or 1 and n is 1 or 2;

R₃ is hydrogen or an aryl, heteroaryl or carbocyclyl group which is unsubstituted or substituted by 1, 2 or 3 substituents selected from halogen, hydroxy, C₁-C₆ alkyl, C₁-C₆ alkoxy, C₁-C₆ alkylthio, C₂-C₆ alkenyl, C₂-C₆ alkenyloxy, C₂-C₆ alkenylthio, C₂-C₆ alkynyl, C₂-C₆ alkynyloxy, C₂-C₆ alkynylthio, C₃-C₆ carbocyclyl, C₃-C₆ carbocycliloxy, C₃-C₆ carbocyclylthio, -NH-CO-(C₁-C₆ alkyl), -CO-NH-(C₁-C₆ alkyl) and -NR'R'' wherein R' and R'' are each independently hydrogen or a C₁-C₆ alkyl group, the substituents on R₃ being themselves unsubstituted or further substituted with 1, 2 or 3 further substituents selected from halogen and hydroxy;

R₄ is -CH₃, -C₁-X₁-Ar₁ or -C₂-X₂-C₃, wherein:

- C₁ is an unsubstituted C₁-C₄ alkylene group;
- X₁ is a direct bond or is -O-, -S-, -NR'-, -S-CO-, -O-CO-, -CO-O-, CO-S-, -NR'-CO- or -CO-NR'-, wherein R' is hydrogen or an unsubstituted phenyl or C₁-C₆ alkyl group;
- Ar₁ is a heteroaryl, heterocyclyl, aryl, carbocyclyl or heteroaryl-(C₁-C₂ alkyl)- group which is unsubstituted or carries, on the cyclic moiety, 1, 2 or 3 unsubstituted groups selected from halogen, C₁-C₄ alkyl, hydroxy, C₁-C₄ alkoxy, -NR'R'' or -NH-CO-R' wherein R' and R'' are the same or different and are selected from hydrogen and C₁-C₄ alkyl;

- C₂ is an unsubstituted C₁-C₄ alkylene group;
- X₂ is a direct bond or is -O-, -S-, -NR'-, -CO-, -CO-S-, -CO-O-, -CO-NR'-, -S-CO-, -O-CO-, -NR'-CO-, -O-CO-NR'-, -NR'-CO-O-, -S-CO- or -CO-S- wherein R' is hydrogen, -CH₃ or -CH₂-CH₃; and
- C₃ is a C₁-C₄ alkyl group which is unsubstituted or substituted with 1, 2 or 3 unsubstituted groups selected from hydroxy, -NH₂, -NH(C₁-C₂ alkyl), -N(C₁-C₂ alkyl)₂ and halogen.

Further preferred compounds of formula (I) and pharmaceutically acceptable salts thereof are those in which:

Z is -S- or -O-;

R₁ is hydrogen or an unsubstituted C₁-C₄ alkyl group;

R₂ is hydrogen or an unsubstituted C₁-C₆ alkyl group;

Y is -(CR^Y₂)_q-, -(CR^Y₂)_m-X₄-(CR^Y₂)_n-, -(CR^Y₂)_m-A-(CR^Y₂)_m- or -(CR^Y₂)_m-A-(CR^Y₂)_p-X₃-(CR^Y₂)_m, wherein

- each R^Y is the same or different and is hydrogen or an unsubstituted C₁-C₄ alkyl or phenyl group;
- A is an aryl or heteroaryl group which is unsubstituted or substituted with 1, 2 or 3 substituents selected from unsubstituted C₁-C₄ alkyl, C₁-C₄ alkoxy, halogen, hydroxy, NH₂, NH(C₁-C₂ alkyl) and N(C₁-C₂ alkyl)₂ groups;
- X₃ is -O-, -S-, -SO-, -SO₂-, -O-CO-, -CO-O-, -NH-CO- or -CO-NH-;
- X₄ is -O-, -S- or -NR'- wherein R' is hydrogen or -CH₃;
- p is 0 or 1; q is 0, 1, 2 or 3; m is 0 or 1 and n is 1 or 2;

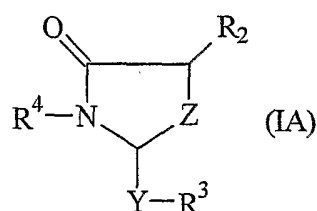
R₃ is hydrogen or an aryl, heteroaryl or carbocyclyl group which is unsubstituted or substituted by 1, 2 or 3 substituents selected from halogen, hydroxy, C₁-C₆ alkyl, C₁-C₆ alkoxy, C₁-C₆ alkylthio, C₂-C₆ alkenyl, C₂-C₆ alkenyloxy, C₂-C₆ alkenylthio, C₂-C₆ alkynyl, C₂-C₆ alkynyloxy, C₂-C₆ alkynylthio, C₃-C₆ carbocyclyl, C₃-C₆ carbocycliloxy, C₃-C₆ carbocyclylthio, -NH-CO-(C₁-C₆ alkyl), -CO-NH-(C₁-C₆ alkyl) and -NR'R'' wherein R' and R'' are each independently hydrogen or a C₁-C₆ alkyl group, the substituents on R₃ being themselves unsubstituted or further substituted with 1, 2 or 3 further substituents selected from halogen and hydroxy;

R₄ is -C₁-X₁-Ar₁ or -C₂-X₂-C₃, wherein:

- C₁ is an unsubstituted C₁-C₄ alkylene group;

- X_1 is a direct bond or is -O-, -S-, -NR'-, -S-CO-, -O-CO-, -CO-O-, CO-S-, -NR'-CO- or -CO-NR'-, wherein R' is hydrogen or an unsubstituted phenyl or C₁-C₆ alkyl group;
- Ar₁ is a heteroaryl, heterocyclyl, aryl or heteroaryl-(C₁-C₂ alkyl)- group which is unsubstituted or carries, on the cyclic moiety, 1, 2 or 3 unsubstituted groups selected from halogen, C₁-C₄ alkyl, hydroxy, C₁-C₄ alkoxy, -NR'R'' or -NH-CO-R' wherein R' and R'' are the same or different and are selected from hydrogen and C₁-C₄ alkyl;
- C₂ is an unsubstituted C₁-C₄ alkylene group;
- X_2 is a direct bond or is -O-, -S-, -NR'-, -CO-, -CO-S-, -CO-O-, -CO-NR'-, -S-CO-, -O-CO-, -NR'-CO-, -O-CO-NR'-, -NR'-CO-O-, -S-CO- or -CO-S- wherein R' is hydrogen, -CH₃ or -CH₂-CH₃; and
- C₃ is a C₁-C₄ alkyl group which is unsubstituted or substituted with 1, 2 or 3 unsubstituted groups selected from hydroxy, -NH₂, -NH(C₁-C₂ alkyl), -N(C₁-C₂ alkyl)₂ and halogen.

Further preferred compounds of formula (I) are those of formula (IA) and pharmaceutically acceptable salts thereof:



wherein:

Z is -S-, -S(O)- or -S(O)₂-;

R₂ represents hydrogen, an unsubstituted C₁-C₄ alkyl group, -(CH₂)_a-CO₂H or -(CH₂)_b-CONR₅R₆ wherein a and b are 1 or 2 and either (a) R₅ is hydrogen or an unsubstituted benzyl group and R₆ is -L-R wherein L is a direct bond or an unsubstituted C₁-C₄ alkylene group and R is hydrogen or a phenyl, cyclohexenyl, piperidyl, pyridyl or benzimidazolyl group which is unsubstituted or substituted by a halogen, hydroxy,

-OCH₃ or -OCH₂CH₃ substituent, or (b) R₅ and R₆, together with the N atom to which they are attached, represent a pyrrolidinyl, piperidinyl, homopiperidinyl or piperazinyl group which is unsubstituted or substituted by an unsubstituted -CHPh₂ group;

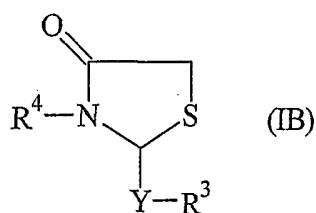
Y is a direct bond or a group of formula -(CR^y)₂-, -(CH₂)_mO(CH₂)-, -A- or -A-X₃-(CH₂)_m, wherein R^y is hydrogen, -CH₃, -CH₂-CH₃ or an unsubstituted phenyl group, wherein no more than one R^y group is phenyl; A is a phenyl, pyridyl or pyrrolyl group, which is unsubstituted or substituted with 1, 2 or 3 substituents selected from -CH₃, -CH₂-CH₃, -OCH₃, -OCH₂-CH₃, halogen and hydroxy; X₃ is -O-, -SO₂- or -NH-CO-; and m is 0 or 1;

R³ is hydrogen or a phenyl, thienyl, furyl, quinolinyl, benzofuranyl, cyclopentyl, 1,4-benzodioxanyl, 1,3-benzodioxolyl or 2,3-dihydrobenzofuran group which is unsubstituted or substituted with 1, 2 or 3 substituents selected from halogen, C₁-C₄ alkyl, C₁-C₄ alkoxy, C₁-C₄ alkylthio, C₂-C₄ alkenyloxy, C₃-C₆ carbocycloxy, -NH-CO-Me and -N(CH₃)₂, the substituents on R³ being themselves unsubstituted or further substituted with 1, 2 or 3 further substituents selected from halogen and hydroxy;

R₄ is an unsubstituted methyl group or is -C₁-X₁-Ar₁ or -C₂-X₂-C₃, wherein:

- C₁ is -(CH₂)-, -(CH₂)₂- or -(CH₂)₃-;
- X₁ is a direct bond or is -O-, -S-, -S-CO- or -O-CO-;
- Ar₁ is a phenyl, pyridyl, thienyl, benzimidazolyl, furanyl-methyl-, cyclohexenyl, quinolinyl, 2,3-dihydro-1H-indenyl, 1,3-benzodioxolyl, 1,3-benzodioxanyl or 1,4-benzodioxanyl group, which is unsubstituted or carries, on the cyclic moiety, 1, 2 or 3 substituents selected from fluorine, hydroxy, -OCH₃, -N(CH₃)₂ and -NH-CO-CH₃;
- C₂ is a straight chain unsubstituted C₁-C₄ alkylene group;
- X₂ is a direct bond or is -O-, -S-, -CO-O- or -NH-CO-O-; and
- C₃ is C₁-C₄ alkyl group which is unsubstituted or substituted on a primary carbon atom with either (a) one hydroxy or (b) 1, 2 or 3 halo substituents.

Further preferred compounds of formula (I) are those of formula (IB) and pharmaceutically acceptable salts thereof.



wherein:

Y is a direct bond or a group of formula $-(CR^y)_2-$, $-(CH_2)_mO(CH_2)-$, $-A-$ or $-A-X_3-$ $(CH_2)_m$, wherein R^y is hydrogen, $-CH_3$, $-CH_2-CH_3$ or an unsubstituted phenyl group, wherein no more than one R^y group is phenyl; A is a phenyl, pyridyl or pyrrolyl group, which is unsubstituted or substituted with 1, 2 or 3 substituents selected from $-CH_3$, $-CH_2-CH_3$, $-OCH_3$, $-OCH_2-CH_3$, halogen and hydroxy; X_3 is $-O-$, $-SO_2-$ or $-NH-CO-$; and m is 0 or 1;

R^3 is hydrogen or a phenyl, thienyl, furyl, quinolinyl, benzofuranyl, cyclopentyl, 1,4-benzodioxanyl, 1,3-benzodioxolyl or 2,3-dihydrobenzofuran group which is unsubstituted or substituted with 1, 2 or 3 substituents selected from halogen, C_1 - C_4 alkyl, C_1 - C_4 alkoxy, C_1 - C_4 alkylthio, C_2 - C_4 alkenyloxy, C_3 - C_6 carbocycloxyloxy, $-NH-CO-Me$ and $-N(CH_3)_2$, the substituents on R^3 being themselves unsubstituted or further substituted with 1, 2 or 3 further substituents selected from halogen and hydroxy;

R_4 is $-C_1-X_1-Ar_1$ or $-C_2-X_2-C_3$, wherein:

- C_1 is $-(CH_2)-$, $-(CH_2)_2-$ or $-(CH_2)_3-$;
- X_1 is a direct bond or is $-O-$, $-S-$, $-S-CO-$ or $-O-CO-$;
- Ar_1 is a phenyl, pyridyl, thienyl, benzimidazolyl, furanyl-methyl-, 1,3-benzodioxolyl or 1,4-benzodioxanyl group, which is unsubstituted or carries, on the cyclic moiety, 1, 2 or 3 substituents selected from fluorine, hydroxy, $-OCH_3$, $-N(CH_3)_2$ and $-NH-CO-CH_3$;
- C_2 is a straight chain unsubstituted C_1 - C_4 alkylene group;
- X_2 is a direct bond or is $-O-$, $-S-$, $-CO-O-$ or $-NH-CO-O-$; and
- C_3 is C_1 - C_4 alkyl group which is unsubstituted or substituted on a primary carbon atom with either (a) one hydroxy or (b) 1, 2 or 3 halo substituents.

Particularly preferred compounds of formulae (I), (IA) and (IB) are those which are more active as N-type calcium channel inhibitors than as L-type calcium channel inhibitors (i.e. which are selective N-type calcium channel antagonists). Typically such compounds have a lower IC_{50} for inhibition of N-type calcium channels expressed by IMR32 cells than for inhibition of L-type calcium channels expressed by IMR32 cells under the same conditions. They may therefore involve fewer side effects than non-selective N-type calcium channel antagonists.

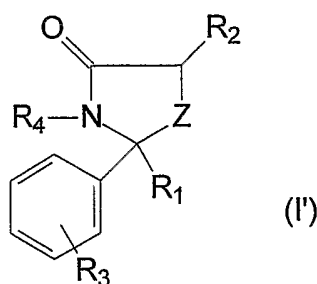
Typically, in the compounds of the formula (I), $-YR_3$ is other than a substituted or unsubstituted naphthalenyl, phenoxyphenyl, phenoxythiophenyl, benzyloxyphenyl, benzylthiophenyl, -furan-2-yl-phenyl or carbazolyl group. More typically, Y in the formula (I) is other than a direct bond or a phenoxy, benzyloxy, benzylthio or furanyl group. Preferably, in this embodiment, Y in the formula (I) is other than aryl, heteroaryl or $-(CH_2)_m-A-X_3$ - wherein m is 0 or 1, A is aryl or heteroaryl and X_3 is -O- or -S-.

Further, R_4 is typically other than (a) $-Y-NR_3R_4$, wherein Y is alkylene and R_3 and R_4 are the same or different and are selected from hydrogen, alkyl or aryl or R_3 and R_4 together form an alkylene chain having 4 to 5 carbon atoms optionally interrupted by a nitrogen or oxygen, (b) pyridylalkyl and (c) piperidin-4-yl-alkyl, optionally substituted by alkyl, aryl or aralkyl. Preferably, in this embodiment, X_2 is other than $-NR'$ -, C_3 is a C_1 - C_4 alkyl group which is unsubstituted or is substituted on a primary carbon atom with either (a) one hydroxy or (b) 1, 2 or 3 halo substituents and Ar_1 is other than a pyridyl or piperidyl group, preferably other than a 6-membered heteroaryl or heterocyclyl group.

In one embodiment of the invention, when Y is a group of formula -A- wherein A is an unsubstituted pyridyl or an unsubstituted thienyl group, R^3 is other than is a phenyl, thienyl, pyridyl or 1,3-benzodioxolyl group which is unsubstituted or substituted with 1, 2 or 3 substituents selected from halogen, hydroxy, cyano, C_1 - C_4 alkyl, C_1 - C_4 alkoxy, C_1 - C_4 alkylthio, C_2 - C_4 alkenyl, $-NR'R''$ wherein R' and R'' are each independently hydrogen or a C_1 - C_4 alkyl group, and $-Si(R''')_3$ wherein each R''' is independently a C_1 - C_4 alkyl group. Preferably, in this embodiment, when Y is a group of formula -A- wherein A is a heteroaryl group, R^3 is other than an aryl, heteroaryl or

carbocyclyl group. More preferably, in this embodiment, either Y is a group of formula $-(CR^Y_2)_q-$ wherein R^Y and q are as defined above, or R^3 is hydrogen.

The present invention also provides the use, in the manufacture of a medicament for use in the treatment or prevention of a condition mediated by N-type calcium channels, of a compound of formula (I') or a pharmaceutically acceptable salt thereof,



wherein:

Z is -S-, -S(O)-, -SO₂-, -O- or -NR- wherein R is hydrogen, C₁-C₆ alkyl or -CO-(C₁-C₆ alkyl);

R₁ is hydrogen or C₁-C₆ alkyl;

R² is hydrogen, fluorine, C₁-C₆ alkyl, -(C₁-C₆ alkyl)-CO₂H or -(C₁-C₆ alkyl)-CO-NR₅R₆, wherein either (a) R₅ is hydrogen, aryl or -(C₁-C₆ alkyl)-aryl and R₆ is -L-R wherein L is a direct bond, a C₁-C₆ alkylene group, a C₂-C₆ alkenylene group or a C₂-C₆ alkynylene group and R is hydrogen, aryl, heteroaryl, carbocyclyl or heterocyclyl or (b) R₅ and R₆, together with the nitrogen atom to which they are attached, represent a moiety -Het₁-Het₂, wherein Het₁ is a heterocyclyl or heteroaryl group and Het₂ is hydrogen, aryl, heteroaryl, -CH(aryl)₂ or -CH(heteroaryl)₂;

R₃ is -SCQ₃ or -OCQ₃ wherein Q is halogen; and

R₄ is methyl, -C₁-X₁-Ar₁ or -C₂-X₂-C₃, wherein

- C₁ is a direct bond, a C₁-C₆ alkylene group, a C₂-C₆ alkenylene group or a C₂-C₆ alkynylene group;
- X₁ is a direct bond when C₁ is a direct bond and, when C₁ is a C₁-C₆ alkylene group, C₂-C₆ alkenylene group or C₂-C₆ alkynylene group, represents a direct bond or -O-, -S-, -NR'-, -SO-, -SO₂-, -CO-, -CO-S-, -CO-O-, -CO-NR'-, -S-CO-, -O-CO-, -NR'-CO-, -CO-O-R''-CO-O-, -CO-NR'-R''-CO-O-, -CO-O-R''-CO-

- NR'-, -CO-NR'-R''-CO-NR'-, -OCO-NR'- or -NR'-CO-O- wherein each R' is the same or different and represents hydrogen, phenyl, C₁-C₆ alkyl, C₂-C₆ alkenyl or C₂-C₆ alkynyl and each R'' is the same or different and represents a C₁-C₆ alkylene group, a C₂-C₆ alkenylene group or a C₂-C₆ alkynylene group;
- Ar₁ is heteroaryl, heterocyclyl, aryl, carbocyclyl, heteroaryl-Y-, heterocyclyl-Y-, aryl-Y- or carbocyclyl-Y-, wherein each Y is the same or different and represents a C₁-C₆ alkylene, C₂-C₆ alkenylene or C₂-C₆ alkynylene group;
 - C₂ is a C₁-C₆ alkylene group, a C₂-C₆ alkenylene group or a C₂-C₆ alkynylene group;
 - X₂ is a direct bond or -O-, -S-, -NR'-, -SO-, -SO₂-, -CO-, -CO-S-, -CO-O-, -CO-NR'-, -S-CO-, -O-CO-, -NR'-CO-, -CO-O-R''-CO-O-, -CO-NR'-R''-CO-O-, -CO-O-R''-CO-NR'-, -CO-NR'-R''-CO-NR'-, -OCO-NR'- or -NR'-CO-O- wherein each R' is the same or different and represents hydrogen, phenyl, C₁-C₆ alkyl, C₂-C₆ alkenyl or C₂-C₆ alkynyl and each R'' is the same or different and represents a C₁-C₆ alkylene group, a C₂-C₆ alkenylene group or a C₂-C₆ alkynylene group; and
 - C₃ is a C₁-C₆ alkyl group, a C₂-C₆ alkenyl group or a C₂-C₆ alkynyl group.

wherein:

- the alkyl, alkylene, alkenyl, alkenylene, alkynyl and alkynylene groups and moieties in the R₁ to R₄ substituents are unsubstituted or carry 1, 2 or 3 unsubstituted substituents selected from aryl, for example phenyl, hydroxy, C₁-C₆ alkoxy, C₁-C₆ alkylthio, -NH₂, -NH(C₁-C₆ alkyl), -N(C₁-C₆ alkyl)₂, halogen, cyano, nitro, -NHCO-(C₁-C₆ alkyl), -CO-NH-(C₁-C₆ alkyl), -CO-O-(C₁-C₆ alkyl) and -O-CO-(C₁-C₆ alkyl);
- the aryl and heteroaryl groups and moieties in the R₁ to R₄ substituents are unsubstituted or carry 1, 2 or 3 substituents selected from halogen, C₁-C₆ alkyl, C₁-C₆ alkoxy, C₁-C₆ alkylthio, hydroxy, C₁-C₄ alkylenedioxy -NH₂, -NH(C₁-C₆ alkyl), -N(C₁-C₆ alkyl)₂, cyano, nitro, -NH-CO-(C₁-C₆ alkyl), -CO-NH-(C₁-C₆ alkyl), -CO-O-(C₁-C₆ alkyl) and -O-CO-(C₁-C₆ alkyl) substituents, said substituents being unsubstituted or substituted by 1, 2 or 3 further unsubstituted substituents selected from halogen, hydroxy, C₁-C₆ alkoxy, C₁-C₆ alkylthio, -NH₂, -NH(C₁-C₆ alkyl), -N(C₁-C₆ alkyl)₂, -NH-CO-(C₁-C₆ alkyl), -CO-NH-(C₁-C₆ alkyl) and -O-CO-(C₁-C₆ alkyl); and

- the carbocyclyl and heterocyclyl groups and moieties in the R_1 to R_4 substituents are unsubstituted or carry 1, 2 or 3 substituents selected from halogen, C_1 - C_6 alkyl, C_1 - C_6 alkoxy, C_1 - C_6 alkylthio, hydroxy, C_1 - C_4 alkylenedioxy, $-NH_2$, $-NH(C_1-C_6 \text{ alkyl})$, $-N(C_1-C_6 \text{ alkyl})_2$, cyano, nitro, oxo, $-NH-CO-(C_1-C_6 \text{ alkyl})$, $-CO-NH-(C_1-C_6 \text{ alkyl})$, $-CO-O-(C_1-C_6 \text{ alkyl})$ and $-O-CO-(C_1-C_6 \text{ alkyl})$ substituents, said substituents being unsubstituted or substituted by 1, 2 or 3 further unsubstituted substituents selected from halogen, hydroxy, C_1 - C_6 alkoxy, C_1 - C_6 alkylthio, $-NH_2$, $-NH(C_1-C_6 \text{ alkyl})$, $-N(C_1-C_6 \text{ alkyl})_2$, $-NH-CO-(C_1-C_6 \text{ alkyl})$, $-CO-NH-(C_1-C_6 \text{ alkyl})$ and $-O-CO-(C_1-C_6 \text{ alkyl})$.

Typically, in the formula (I'), R_2 is hydrogen, fluorine or C_1 - C_6 alkyl and R_4 is $-C_1-X_1-Ar_1$ or $-C_2-X_2-C_3$ wherein C_1 , X_1 , Ar_1 , C_2 , X_2 and C_3 are as defined above.

Preferred substituents on an alkyl group or moiety in the formula (I') are phenyl, hydroxy, halogen, C_1 - C_2 alkoxy, $-NH_2$, $-NH(C_1-C_2 \text{ alkyl})$, $-N(C_1-C_2 \text{ alkyl})_2$ and $-NHCO-(C_1-C_2 \text{ alkyl})$. The substituents on an alkyl group or moiety are themselves unsubstituted.

Preferred substituents on an alkenyl group or moiety in the formula (I') are phenyl, hydroxy, halogen, C_1 - C_2 alkoxy, $-NH_2$, $-NH(C_1-C_2 \text{ alkyl})$, $-N(C_1-C_2 \text{ alkyl})_2$ and $-NHCO-(C_1-C_2 \text{ alkyl})$. The substituents on an alkenyl group or moiety are themselves unsubstituted.

Preferred substituents on an alkynyl group or moiety in the formula (I') are phenyl, hydroxy, halogen, C_1 - C_2 alkoxy, $-NH_2$, $-NH(C_1-C_2 \text{ alkyl})$, $-N(C_1-C_2 \text{ alkyl})_2$ and $-NHCO-(C_1-C_2 \text{ alkyl})$. The substituents on an alkynyl group or moiety are themselves unsubstituted.

A C_1 - C_6 alkylene group in the formula (I') is typically a C_1 - C_5 alkylene group, for example a methylene, ethylene, propylene, n-butylene, or n-pentylene group, or the branched pentylene group $-CH_2-CH_2-CH_2-CH(CH_3)-$.

Preferred substituents on an alkylene group in the formula (I') are phenyl, hydroxy, halogen, C_1 - C_2 alkoxy, $-NH_2$, $-NH(C_1-C_2 \text{ alkyl})$, $-N(C_1-C_2 \text{ alkyl})_2$ and $-NHCO-(C_1-C_2 \text{ alkyl})$. The substituents on an alkylene group are typically themselves unsubstituted.

Preferred substituents on an alkenylene group in the formula (I') are phenyl, hydroxy, halogen, C₁-C₂ alkoxy, -NH₂, -NH(C₁-C₂ alkyl), -N(C₁-C₂ alkyl)₂ and -NHCO-(C₁-C₂ alkyl). The substituents on an alkenylene group are themselves unsubstituted.

A C₂-C₆ alkynylene group in the formula (I') is typically a C₂-C₅ alkynylene group, for example a ethynylene, propynylene, n-butynylene or n-pentynylene group. Typically, an alkynylene group has only one triple bond.

Preferred substituents on an alkynylene group in the formula (I') are phenyl, hydroxy, halogen, C₁-C₂ alkoxy, -NH₂, -NH(C₁-C₂ alkyl), -N(C₁-C₂ alkyl)₂ and -NHCO-(C₁-C₂ alkyl). The substituents on an alkynylene group are typically themselves unsubstituted.

An aryl group in the formula (I') may be unsubstituted or substituted at any position. Preferred substituents include C₁-C₄ alkyl, C₁-C₄ alkoxy, C₁-C₄ alkylthio, halogen (for example fluorine), hydroxy, methylenedioxy, -NH₂, -NH(C₁-C₂ alkyl), -N(C₁-C₂ alkyl)₂, -NH-CO-(C₁-C₂ alkyl) and -O-CO-(C₁-C₂ alkyl).

Substituents on an aryl group in the formula (I') are unsubstituted or substituted by 1, 2 or 3 further substituents selected from halogen, hydroxy, C₁-C₆ alkoxy, C₁-C₆ alkylthio, -NH₂, -NH(C₁-C₆ alkyl), -N(C₁-C₆ alkyl)₂, -NH-CO-(C₁-C₆ alkyl), -CO-NH-(C₁-C₆ alkyl) and -O-CO-(C₁-C₆ alkyl). These further substituents are themselves unsubstituted. Preferably, the C₁-C₆ alkyl moieties present in the further substituents are C₁-C₂ alkyl moieties. More preferably, substituents on an aryl group are unsubstituted or substituted either (a) with one further substituent selected from C₁-C₂ alkoxy, -NH-(C₁-C₂ alkyl) and -N(C₁-C₂ alkyl)₂ or (b) with 1, 2 or 3 further substituents which are halo substituents.

References to an aryl group in the formula (I') include fused ring systems in which an aryl group is fused to a carbocyclic, heterocyclic or heteroaryl group. The carbocyclic, heterocyclic or heteroaryl group to which the aryl group is fused is typically monocyclic. An example of such a fused ring system is a phenyl group fused to a pyridine ring to form a quinoline group or a phenyl ring fused to a cyclopentane group to form a 2,3-dihydro-1H-indenyl group.

A heteroaryl group in the formula (I') may be unsubstituted or substituted at any position. Preferred substituents include C₁-C₄ alkyl, C₁-C₄ alkoxy, C₁-C₄ alkylthio, halogen (for example fluorine), hydroxy, methylenedioxy, -NH₂, -NH(C₁-C₂ alkyl), -N(C₁-C₂ alkyl)₂, -NH-CO-(C₁-C₂ alkyl) and -O-CO-(C₁-C₂ alkyl). Particularly preferred substituents include C₁-C₄ alkyl and C₁-C₄ alkoxy groups.

Substituents on an heteroaryl group are unsubstituted or substituted by 1, 2 or 3 further substituents selected from halogen, hydroxy, C₁-C₆ alkoxy, C₁-C₆ alkylthio, -NH₂, -NH(C₁-C₆ alkyl), -N(C₁-C₆ alkyl)₂, -NH-CO-(C₁-C₆ alkyl), -CO-NH-(C₁-C₆ alkyl) and -O-CO-(C₁-C₆ alkyl). These further substituents are typically themselves unsubstituted. Preferably, the C₁-C₆ alkyl moieties present in the further substituents are C₁-C₂ alkyl moieties. More preferably, substituents on an heteroaryl group are unsubstituted or substituted either (a) with one further substituent selected from C₁-C₂ alkoxy, -NH-(C₁-C₂ alkyl) and -N(C₁-C₂ alkyl)₂ or (b) with 1, 2 or 3 further substituents which are halo substituents.

References in the formula (I') to a heteroaryl group include fused ring systems in which a heteroaryl group is fused to a said aryl group, to a further heteroaryl group or to a heterocyclic group. The aryl, heteroaryl or heterocyclic group to which the heteroaryl group is fused is typically monocyclic. An example of such a fused heteroaryl group is a benzimidazolyl group.

A carbocyclyl group in the formula (I') may be unsubstituted or substituted at any position. Preferred substituents include C₁-C₄ alkyl, C₁-C₄ alkoxy, C₁-C₄ alkylthio, halogen (for example fluorine), hydroxy, methylenedioxy, -NH₂, -NH(C₁-C₂ alkyl), -N(C₁-C₂ alkyl)₂, oxo, -NH-CO-(C₁-C₂ alkyl) and -O-CO-(C₁-C₂ alkyl).

Substituents on an carbocyclyl group are unsubstituted or substituted by 1, 2 or 3 further substituents selected from halogen, hydroxy, C₁-C₆ alkoxy, C₁-C₆ alkylthio, -NH₂, -NH(C₁-C₆ alkyl), -N(C₁-C₆ alkyl)₂, -NH-CO-(C₁-C₆ alkyl), -CO-NH-(C₁-C₆ alkyl) and -O-CO-(C₁-C₆ alkyl). These further substituents are themselves unsubstituted. Preferably, the C₁-C₆ alkyl moieties present in the further substituents are C₁-C₂ alkyl moieties. More preferably, substituents on a carbocyclyl group are unsubstituted or substituted either (a) with one further substituent selected from C₁-C₂

alkoxy, $\text{-NH-(C}_1\text{-C}_2\text{ alkyl)}$ and $\text{-N(C}_1\text{-C}_2\text{ alkyl)}_2$ or (b) with 1, 2 or 3 further substituents which are halo substituents.

References in the formula (I') to a carbocyclyl group include fused ring systems in which a carbocyclyl group is fused to a phenyl ring. An example of such a fused ring system is 2,3-dihydro-1H-indenyl.

A heterocyclyl group in the formula (I') may be unsubstituted or substituted at any position. Preferred substituents include $\text{C}_1\text{-C}_4$ alkyl, $\text{C}_1\text{-C}_4$ alkoxy, $\text{C}_1\text{-C}_4$ alkylthio, halogen (for example fluorine), hydroxy, methylenedioxy, -NH_2 , $\text{-NH(C}_1\text{-C}_2\text{ alkyl)}$, $\text{-N(C}_1\text{-C}_2\text{ alkyl)}_2$, oxo, $\text{-NH-CO-(C}_1\text{-C}_2\text{ alkyl)}$ and $\text{-O-CO-(C}_1\text{-C}_2\text{ alkyl)}$. Particularly preferred substituents are oxo and $\text{C}_1\text{-C}_4$ alkyl substituents.

Substituents on an heterocyclyl group are unsubstituted or substituted by 1, 2 or 3 further substituents selected from halogen, hydroxy, $\text{C}_1\text{-C}_6$ alkoxy, $\text{C}_1\text{-C}_6$ alkylthio, -NH_2 , $\text{-NH(C}_1\text{-C}_6\text{ alkyl)}$, $\text{-N(C}_1\text{-C}_6\text{ alkyl)}_2$, $\text{-NH-CO-(C}_1\text{-C}_6\text{ alkyl)}$, $\text{-CO-NH-(C}_1\text{-C}_6\text{ alkyl)}$ and $\text{-O-CO-(C}_1\text{-C}_6\text{ alkyl)}$. These further substituents are themselves unsubstituted. Preferably, the $\text{C}_1\text{-C}_6$ alkyl moieties present in the further substituents are $\text{C}_1\text{-C}_2$ alkyl moieties. More preferably, substituents on a heterocyclyl group are unsubstituted or substituted either (a) with one further substituent selected from $\text{C}_1\text{-C}_2$ alkoxy, $\text{-NH-(C}_1\text{-C}_2\text{ alkyl)}$ and $\text{-N(C}_1\text{-C}_2\text{ alkyl)}_2$ or (b) with 1, 2 or 3 further substituents which are halo substituents.

When Z in the formula (I') is -NR- , R is typically -COCH_3 or $\text{-CO-CH}_2\text{-CH}_3$. Typically, Z is -S- , -S(O)- or $\text{-S(O)}_2\text{-}$. In a further embodiment, Z is -S- or -O- . Most preferably, Z is -S- .

Typically, R_1 in the formula (I') is hydrogen or an unsubstituted $\text{C}_1\text{-C}_4$ alkyl group. Preferably, R_1 is hydrogen or methyl. More preferably, R_1 is hydrogen.

Typically, R_2 in the formula (I') represents hydrogen, fluorine, $\text{C}_1\text{-C}_4$ alkyl, $\text{-(C}_1\text{-C}_4\text{ alkyl)-CO}_2\text{H}$ or $\text{-(C}_1\text{-C}_4\text{ alkyl)-CONR}_5\text{R}_6$, wherein either (a) R_5 is hydrogen, aryl or $\text{-(C}_1\text{-C}_2\text{ alkyl)-aryl}$ and R_6 is -L-R wherein L is a direct bond or a $\text{C}_1\text{-C}_4$ alkylene group and R is hydrogen, aryl, carbocyclyl, heterocyclyl or heteroaryl or (b) R_5 and R_6 , together with the nitrogen atom to which they are attached, represent a moiety $\text{-Het}_1\text{-Het}_2$, wherein Het_1 is a heterocyclyl group and Het_2 is hydrogen, aryl or -CH(aryl)_2 .

More typically, R_2 represents hydrogen, an unsubstituted $\text{C}_1\text{-C}_4$ alkyl group,

$-(CH_2)_a-CO_2H$ or $-(CH_2)_b-CONR_5R_6$ wherein a and b are 1 or 2 and either (a) R_5 is hydrogen or an unsubstituted benzyl group and R_6 is $-L-R$ wherein L is a direct bond or an unsubstituted C_1-C_4 alkylene group and R is hydrogen or a phenyl, cyclohexenyl, piperidyl, pyridyl or benzimidazolyl group which is unsubstituted or substituted by a halogen, hydroxy, $-OCH_3$ or $-OCH_2CH_3$ substituent, or (b) R_5 and R_6 , together with the N atom to which they are attached, represent a pyrrolidinyl, piperidinyl, homopiperidinyl or piperazinyl group which is unsubstituted or substituted by an unsubstituted $-CHPh_2$ group.

Preferably, R_2 is hydrogen or an unsubstituted C_1-C_4 alkyl group. More preferably, R_2 is hydrogen or methyl. Most preferably, R_2 is hydrogen.

Typically, the R_3 group in the formula (I') is present at the 3-position of the phenyl ring to which it is attached. R_3 is typically $-SCQ_3$ or $-OCQ_3$ wherein Q is fluorine or chlorine. Preferably, R_3 is $-SCF_3$ or $-OCF_3$. More preferably, R_3 is $-OCF_3$.

Typically, R_4 in the formula (I') is $-CH_3$ or is $-C_1-X_1-Ar_1$ or $-C_2-X_2-C_3$, wherein C_1 , X_1 , Ar_1 , C_2 , X_2 and C_3 are as defined above.

Typically, C_1 in the formula (I') is a direct bond or a C_1-C_6 alkylene group. More typically, C_1 is a direct bond or a C_1-C_4 alkylene group which is unsubstituted when X_1 is other than a direct bond and, when X_1 is a direct bond, is unsubstituted or substituted at the carbon atom α to the moiety Ar_1 by one substituent selected from those set out above as examples of suitable alkylene substituents. Preferably the substituent α to the moiety X_1 is a phenyl group.

For the avoidance of doubt, the orientation of the group X_1 in the formula (I') is such that the left hand side of the depicted moiety is attached to C_1 and the right hand side of the depicted moiety is attached to Ar_1 . Thus, for example, when X_1 is $-CO-NH-CH_2-CO-O-$, the moiety $-C_1-X_1-Ar_1$ is $-C_1-CO-NH-CH_2-CO-O-Ar_1$.

Typically, each R' in the moiety X_1 is the same or different and is hydrogen, or an unsubstituted phenyl or C_1-C_6 alkyl group. More typically, each R' in the moiety X_1 is the same or different and is hydrogen, methyl or ethyl. Preferably, each R' in the moiety X_1 is hydrogen. Typically, each R'' in the moiety X_1 is the same or different and is an unsubstituted C_1-C_6 alkylene group. More typically, each R'' in the moiety X_1 is methylene or ethylene. Preferably, each R'' is methylene.

Typically, X_1 in the formula (I') is a direct bond or is -O-, -S-, -NR'-, -S-CO-, -O-CO-, -NR'-CO- or -CO-NR'-R''-CO-O-, wherein R' and R'' are as defined above.

Preferably, X_1 in the formula (I') is a direct bond or is -O-, -S-, -S-CO-, -O-CO-, -NH-CO- or -CO-NH-CH₂-CO-O-. More preferably, X_1 is a direct bond or is -O-, -S-, -SCO- or -O-CO-.

Typically, Ar_1 in the formula (I') is heteroaryl, heterocyclyl, aryl, carbocyclyl, heteroaryl-(C₁-C₆ alkyl)-, heterocyclyl-(C₁-C₆ alkyl)-, aryl-(C₁-C₆ alkyl)- or carbocyclyl-(C₁-C₆ alkyl)-. When Ar_1 is a heteroaryl-(C₁-C₆ alkyl)-, aryl-(C₁-C₆ alkyl)-, heterocyclyl-(C₁-C₆ alkyl)- or carbocyclyl-(C₁-C₆ alkyl)- group, the alkyl moiety is typically an unsubstituted methylene or ethylene moiety. Preferably, Ar_1 is heteroaryl, heterocyclyl, carbocyclyl, aryl, heteroaryl-Y'- or aryl-Y'-, in particular heteroaryl, heterocyclyl, aryl, heteroaryl-Y'- or aryl-Y'-, wherein Y' is an unsubstituted methylene or ethylene moiety. More preferably, Ar_1 is heteroaryl, for example imidazolyl, 2-pyridyl, 3-pyridyl, benzimidazolyl, furanyl and pyrazinyl, heteroaryl-(C₁-C₂ alkyl)-, for example furanyl-methyl-, heterocyclyl, for example morpholinyl, piperazinyl, piperidyl and pyrrolidinyl, aryl, for example phenyl, aryl-(C₁-C₂ alkyl)-, for example benzyl, or carbocyclyl, for example cyclohexenyl and 2,3-dihydro-1H-indenyl.

Typically, C_2 in the formula (I') is a C₁-C₆ alkylene group. Further, C_2 is typically unsubstituted or carries one substituent at the carbon atom α to the moiety X_2 or, where X_2 is a direct bond, to the moiety C_3 , which substituent is selected from those set out above as examples of suitable alkylene substituents. Preferably, said substituent is hydroxy, halogen, C₁-C₂ alkoxy, -NH₂, -NH-(C₁-C₂ alkyl), -N(C₁-C₂ alkyl)₂ or -NHCO-(C₁-C₂ alkyl). More preferably, said substituent is hydroxy or -NH-CO-CH₃.

For the avoidance of doubt, the orientation of the group X_2 in the formula (I') is such that the left hand side of the depicted moiety is attached to C_2 and the right hand side of the depicted moiety is attached to C_3 . Thus, for example, when X_2 is -CO-NH-CH₂-CO-O-, the moiety -C₂- X_2 -C₃- is -C₂-CO-NH-CH₂-CO-O-C₃-.

Typically, each R' in the moiety X_2 is the same or different and is hydrogen or an unsubstituted phenyl or C₁-C₆ alkyl group. More typically, each R' is the same or different and is hydrogen, methyl or ethyl. Preferably, each R' in the moiety X_2 is

hydrogen. Typically, each R'' in the moiety X₂ is the same or different and is an unsubstituted C₁-C₆ alkylene group. More typically, each R'' in the moiety X₂ is methylene or ethylene. Preferably, each R'' is methylene.

Typically, X₂ in the formula (I') is a direct bond or is -O-, -S-, -NR'-, -CO-S-, -CO-O-, -CO-NR'- or -CO-NR'-R''-CO-O-, wherein R' and R'' are as defined above. Preferably, X₁ is a direct bond or is -O-, -S-, -NMe-, -NEt-, -CO-O-, -CO-NH- or -CO-NH-CH₂-CO-O-.

Typically, C₃ in the formula (I') is a C₁-C₆ alkyl group. Typically, C₃ is unsubstituted or substituted by 1, 2 or 3 substituents selected from hydroxy, -NH₂, -NH(C₁-C₄ alkyl), -N(C₁-C₄ alkyl)₂ and halogen. Preferably, C₃ is unsubstituted or carries, on a primary carbon atom (i.e. a carbon atom at the end of a chain), either (a) one hydroxy, -NMe₂ or -NEt₂ substituent or (b) 1, 2 or 3 halo substituents, which are preferably fluoro substituents.

Preferred compounds of formula (I') are those in which:

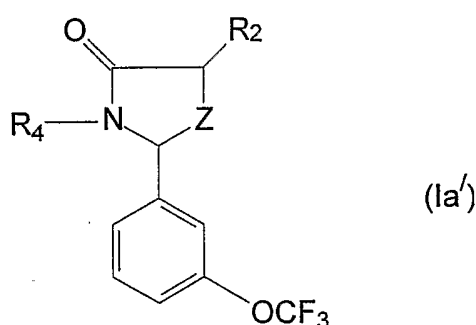
- Z is -S-, -S(O)- or -S(O)₂-;
- R₁ is hydrogen or -CH₃;
- R₂ is hydrogen, an unsubstituted C₁-C₄ alkyl group, -(CH₂)_a-CO₂H or -(CH₂)_b-CONR₅R₆ wherein a and b are 1 or 2 and either (a) R₅ is hydrogen or an unsubstituted benzyl group and R₆ is -L-R wherein L is a direct bond or an unsubstituted C₁-C₄ alkylene group and R is hydrogen or a phenyl, cyclohexenyl, piperidyl, pyridyl or benzimidazolyl group which is unsubstituted or substituted by a halogen, hydroxy, -OCH₃ or -OCH₂CH₃ substituent, or (b) R₅ and R₆, together with the N atom to which they are attached, represent a pyrrolidinyl, piperidinyl, homopiperidinyl or piperazinyl group which is unsubstituted or substituted by an unsubstituted -CHPh₂ group;
- R₃ is present at the 3-position of the phenyl ring to which it is attached, and is -OCQ₃ wherein Q is fluorine or chlorine; and
- R₄ is -CH₃, -C₁-X₁-Ar₁ or -C₂-X₂-C₃, wherein C₁, C₂, X₁, X₂, Ar₁ and C₃ are as defined above.

Further preferred compounds of formula (I') are those in which:

- Z is -S-;

- R_1 is hydrogen or $-\text{CH}_3$;
- R_2 is hydrogen or an unsubstituted C_1 - C_4 alkyl group;
- R_3 is present at the 3-position of the phenyl ring to which it is attached, and is $-\text{OCQ}_3$ wherein Q is fluorine or chlorine; and
- R_4 is $-\text{C}_1\text{-X}_1\text{-Ar}_1$ or $-\text{C}_2\text{-X}_2\text{-C}_3$, wherein C_1 , C_2 , X_1 , X_2 , Ar_1 and C_3 are as defined above.

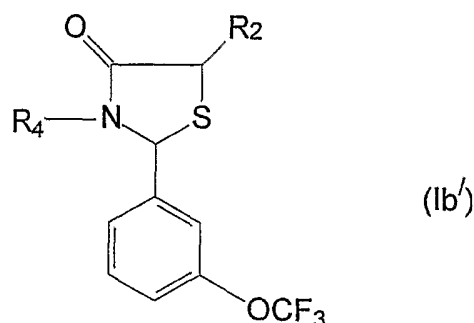
Particularly preferred compounds of formula (I') are compounds of formula (Ia')



wherein:

- Z is $-\text{S}-$, $-\text{S}(\text{O})-$ or $-\text{S}(\text{O})_2-$;
- R_2 is hydrogen, an unsubstituted C_1 - C_4 alkyl group, $-(\text{CH}_2)_a\text{-CO}_2\text{H}$ or $-(\text{CH}_2)_b\text{-CONR}_5\text{R}_6$ wherein a and b are 1 or 2 and either (a) R_5 is hydrogen or an unsubstituted benzyl group and R_6 is $-\text{L-R}$ wherein L is a direct bond or an unsubstituted C_1 - C_4 alkylene group and R is hydrogen or a phenyl, cyclohexenyl, piperidyl, pyridyl or benzimidazolyl group which is unsubstituted or substituted by a halogen, hydroxy, $-\text{OCH}_3$ or $-\text{OCH}_2\text{CH}_3$ substituent, or (b) R_5 and R_6 , together with the N atom to which they are attached, represent a pyrrolidinyl, piperidinyl, homopiperidinyl or piperazinyl group which is unsubstituted or substituted by an unsubstituted $-\text{CHPh}_2$ group;
- R_4 is an unsubstituted methyl group or is $-\text{C}_1\text{-X}_1\text{-Ar}_1$ or $-\text{C}_2\text{-X}_2\text{-C}_3$, wherein C_1 , C_2 , X_1 , X_2 , Ar_1 and C_3 are as defined above.

Further particularly preferred compounds of formula (I') are compounds of formula (Ib')



wherein:

- R₂ is hydrogen or -CH₃; and
- R₄ is -C₁-X₁-Ar₁ or -C₂-X₂-C₃, wherein C₁, C₂, X₁, X₂, Ar₁ and C₃ are as defined above.

Further preferred compounds of formulae (I'), (Ia') and (Ib') are compounds which are more active as N-type calcium channel inhibitors than as L-type calcium channel inhibitors (i.e. which are selective N-type calcium channel antagonists). Typically, such compounds have a lower IC₅₀ for inhibition of N-type calcium channels expressed by IMR32 cells than for inhibition of L-type calcium channels expressed by IMR32 cells under the same assay conditions. They may therefore involve fewer side effects than non-selective N-type calcium channel antagonists.

The above further preferred compounds of formulae (I'), (Ia') and (Ib') include compounds wherein:

Z, R₁, R₂ and R₃ are as defined above; and

R₄ is -C₁-Ar₁, or -C₂-X₂-C₃, wherein:

- C₁ is an unsubstituted C₁-C₄ alkylene group, for example a methylene or ethylene group;
- Ar₁ is an aryl group, for example a phenyl group, or a heteroaryl group, for example a 2-pyridyl or 3-pyridyl group;
- C₂ is a C₁-C₆ alkylene group, for example a methylene, ethylene or propylene group;
- X₂ is -O-, -S- or a direct bond; and
- C₃ is a C₁-C₄ alkyl group.

Typically, in said further preferred compounds, Ar₁ is an aryl or heteroaryl

group which is unsubstituted or is substituted with 1, 2 or 3 substituents selected from halogen, hydroxy, C₁-C₄ alkyl and C₁-C₄ alkoxy groups. Ar₁ is preferably an unsubstituted 2-pyridyl or 3-pyridyl group or a phenyl group which is unsubstituted or substituted with 1, 2 or 3 substituents selected from halogen, hydroxy, C₁-C₄ alkyl and C₁-C₄ alkoxy groups.

C₂ in said further preferred compounds is typically an unsubstituted C₁-C₅ alkylene group. C₃ is typically a methyl, ethyl, n-butyl and i-propyl. Preferably, C₃ is unsubstituted or carries, on a primary carbon atom (i.e. a carbon atom at the end of a chain), a hydroxy substituent.

Preferred compounds of formula (I) and formula (I') include:

- 1 2-Benzhydryl-3-pyridine-2-ylmethyl-thiazolidin-4-one;
2. 3-(2-Pyridin-2-yl-ethyl)-2-[1-(toluene-4-sulfonyl)-1H-pyrrolo-2-yl]-thiazolidin-4-one;
3. 2-(3-Cyclopentyloxy-4-methoxy-phenyl)-3-(2,3-dihydro-benzo[1,4]dioxin-2-ylmethyl)-thiazolidin-4-one;
- 4 3-Benzo[1,3]dioxol-5-ylmethyl-2-(2-trifluoromethyl-phenyl)-thiazolidin-4-one;
- 5 3-(1H-Benzoimidazol-2-ylmethyl)-2-(2,4,6-trimethyl-phenyl)-thiazolidin-4-one;
- 6 3-(2-Ethoxy-ethyl)-2-(2,4,6-triethyl-phenyl)-thiazolidin-4-one;
- 7 2-(3,5-Dimethoxy-phenyl)-3-(2-methoxy-benzyl)-thiazolidin-4-one;
- 8 3-(2,4-Difluoro-benzyl)-2-(3-methyl-thiophen-2-yl)-thiazolidin-4-one;
- 9 2-(5-Bromo-thiophen-2-yl)-3-(2-pyridin-2-yl-ethyl)-thiazolidin-4-one;
- 10 2-(4-Methylsulfonyl-phenyl)-3-(2-pyridin-2-yl-ethyl)-thiazolidin-4-one;
- 11 3-(2-Thiophen-2-yl-ethyl)-2-(4-trifluoromethyl-phenyl)-thiazolidin-4-one;
- 12 3-[2-(3,4-Dimethoxy-phenyl)-ethyl]-2-(4-ethyl-phenyl)-thiazolidin-4-one;
- 13 2-(4-Ethyl-phenyl)-3-(2-thiophen-2-yl-ethyl)-thiazolidin-4-one;
- 14 2-(3-Chloro-4-fluoro-phenyl)-3-[2-(3,4-dimethoxy-phenyl)-ethyl]-thiazolidin-4-one;
- 15 2-(3-Chloro-4-fluoro-phenyl)-3-(3-isopropoxy-propyl)-thiazolidin-4-one;
- 16 {2-[2-(3-Ethoxy-phenyl)-4-oxo-thiazolidin-3-yl]-ethyl}-carbamic acid tert-butyl ester;
- 17 3-Benzo[1,3]dioxol-5-ylmethyl-2-(3-ethoxy-phenyl)-thiazolidin-4-one;
- 18 2-(3-Bromo-4-fluoro-phenyl)-3-(2-pyridin-2-yl-ethyl)-thiazolidin-4-one;

- 19 3-Benzo[1,3]dioxol-5-ylmethyl-2-(3-bromo-4-fluoro-phenyl)-thiazolidin-4-one;
- 20 2-Benzyloxymethyl-3-(3,4,5-trifluoro-benzyl)-thiazolidin-4-one;
- 21 2-Benzyloxymethyl-3-(3,4-difluoro-benzyl)-thiazolidin-4-one;
- 22 3-(2-Fluoro-benzyl)-2-(1-phenyl-ethyl)-thiazolidin-4-one;
- 23 3-(2,3-Difluoro-benzyl)-2-(1-phenyl-ethyl)-thiazolidin-4-one;
- 24 2-sec-Butyl-3-(3,4-difluoro-benzyl)-thiazolidin-4-one;
- 25 2-(1-Ethyl-propyl)-3-(2-fluoro-benzyl)-thiazolidin-4-one;
- 26 3-(3,5-Difluoro-benzyl)-2-(1-ethyl-propyl)-thiazolidin-4-one;
- 27 2-(3-Bromo-thiophen-2-yl)-3-(2-fluoro-benzyl)-thiazolidin-4-one;
- 28 2-(3-Bromo-thiophen-2-yl)-3-(3,4-difluoro-benzyl)-thiazolidin-4-one;
- 29 2-(3-Fluoro-4-trifluoromethyl-phenyl)-3-(2-pyridin-3-yl-ethyl)-thiazolidin-4-one;
- 30 2-(3-Fluoro-4-trifluoromethyl-phenyl)-3-isobutyl-thiazolidin-4-one;
- 31 3-(2-tert-Butylsulfanyl-ethyl)-2-(3-fluoro-4-trifluoromethyl-phenyl)-thiazolidin-4-one;
- 32 3-(2-Fluoro-benzyl)-2-(3-fluoro-4-trifluoromethyl-phenyl)-thiazolidin-4-one;
- 33 2-(3-Fluoro-4-trifluoromethyl-phenyl)-3-[2-(4-hydroxy-3-methoxy-phenyl)-ethyl]-thiazolidin-4-one;
- 34 3-(2-Ethylsulfanyl-ethyl)-2-(3-fluoro-4-trifluoromethyl-phenyl)-thiazolidin-4-one;
- 35 3-(3-Butoxy-propyl)-2-(3-fluoro-4-trifluoromethyl-phenyl)-thiazolidin-4-one;
- 36 3-(2-Benzo[1,3]dioxol-5-yl-ethyl)-2-(3-fluoro-4-trifluoromethyl-phenyl)-thiazolidin-4-one;
- 37 2-(3-Fluoro-4-trifluoromethyl-phenyl)-3-(3-methylsulfanyl-propyl)-thiazolidin-4-one;
- 38 2-(3-Fluoro-4-trifluoromethyl-phenyl)-3-(5-hydroxy-4,4-dimethyl-pentyl)-thiazolidin-4-one;
- 39 3-(2-Fluoro-benzyl)-2-(5-fluoro-2-trifluoromethyl-phenyl)-thiazolidin-4-one;
- 40 3-(3,4-Difluoro-benzyl)-2-(5-fluoro-2-trifluoromethyl-phenyl)-thiazolidin-4-one;
- 41 3-(3-Butoxy-propyl)-2-(5-fluoro-2-trifluoromethyl-phenyl)-thiazolidin-4-one;
- 42 3-(2,5-Dimethoxy-benzyl)-2-(5-fluoro-2-trifluoromethyl-phenyl)-thiazolidin-

- one;
- 43 2-(5-Fluoro-2-trifluoromethyl-phenyl)-3-[2-(4-methoxy-phenoxy)-ethyl]-thiazolidin-4-one;
- 44 3-(2,3-Difluoro-benzyl)-2-(5-fluoro-2-trifluoromethyl-phenyl)-thiazolidin-4-one;
- 45 2-(1-Benzenesulfonyl-1H-pyrrol-2-yl)-3-(3,4,5-trifluoro-benzyl)-thiazolidin-4-one;
- 46 2-(1-Benzenesulfonyl-1H-pyrrol-2-yl)-3-(2-fluoro-benzyl)-thiazolidin-4-one;
- 47 2-(1-Benzenesulfonyl-1H-pyrrol-2-yl)-3-(2-pyridin-4-yl-ethyl)-thiazolidin-4-one;
- 48 2-(1-Benzenesulfonyl-1H-pyrrol-2-yl)-3-(2,2,2-trifluoro-ethyl)-thiazolidin-4-one;
- 49 2-(1-Benzenesulfonyl-1H-pyrrol-2-yl)-3-(3,4-difluoro-benzyl)-thiazolidin-4-one;
- 50 2-(1-Benzenesulfonyl-1H-pyrrol-2-yl)-3-(2,3-difluoro-benzyl)-thiazolidin-4-one;
- 51 3-[2-(3-Cyclopentyloxy-4-methoxy-phenyl)-4-oxo-thiazolidin-3-yl]-propionic acid tert-butyl ester;
- 52 2-(3-Cyclopentyloxy-4-methoxy-phenyl)-3-(4-fluoro-benzyl)-thiazolidin-4-one;
- 53 2-(3-Cyclopentyloxy-4-methoxy-phenyl)-3-(3,4-difluoro-benzyl)-thiazolidin-4-one;
- 54 2-[4-(4-Bromo-phenyl)-pyridin-3-yl]-3-(3-propoxy-propyl)-thiazolidin-4-one;
- 55 2-[4-(4-Bromo-phenyl)-pyridin-3-yl]-3-isobutyl-thiazolidin-4-one;
- 56 2-[4-(4-Bromo-phenyl)-pyridin-3-yl]-3-(3,4,5-trifluoro-benzyl)-thiazolidin-4-one;
- 57 2-[4-(4-Bromo-phenyl)-pyridin-3-yl]-3-(2-fluoro-benzyl)-thiazolidin-4-one;
- 58 2-[4-(4-Bromo-phenyl)-pyridin-3-yl]-3-(3-fluoro-benzyl)-thiazolidin-4-one;
- 59 2-[4-(4-Bromo-phenyl)-pyridin-3-yl]-3-(4-fluoro-benzyl)-thiazolidin-4-one;
- 60 2-[4-(4-Bromo-phenyl)-pyridin-3-yl]-3-(2-ethylsulfanyl-ethyl)-thiazolidin-4-one;
- 61 2-[4-(4-Bromo-phenyl)-pyridin-3-yl]-3-(3-butoxy-propyl)-thiazolidin-4-one;
- 62 2-[4-(4-Bromo-phenyl)-pyridin-3-yl]-3-(3-methylsulfanyl-propyl)-thiazolidin-

- one;
- 63 2-[4-(4-Bromo-phenyl)-pyridin-3-yl]-3-(2,5-dimethoxy-benzyl)-thiazolidin-4-one;
- 64 2-[4-(4-Bromo-phenyl)-pyridin-3-yl]-3-[2-(4-methoxy-phenoxy)-ethyl]-thiazolidin-4-one;
- 65 2-(4-Ethylsulfanyl-phenyl)-3-[2-(furan-2-ylmethylsulfanyl)-ethyl]-thiazolidin-4-one;
- 66 3-(3,4-Difluoro-benzyl)-2-(4-ethylsulfanyl-phenyl)-thiazolidin-4-one;
- 67 3-(2-Benzo[1,3]dioxol-5-yl-ethyl)-2-(4-ethylsulfanyl-phenyl)-thiazolidin-4-one;
- 68 2-(4-Ethylsulfanyl-phenyl)-3-(3-methylsulfanylpropyl)-thiazolidin-4-one;
- 69 2-(4-Ethylsulfanyl-phenyl)-3-[2-(4-methoxy-phenoxy)-ethyl]-thiazolidin-4-one;
- 70 3-(2,3-Difluoro-benzyl)-2-(4-ethylsulfanyl-phenyl)-thiazolidin-4-one;
- 71 2-(4-Methoxy-phenyl)-3-(2,3,4-trifluoro-benzyl)-thiazolidin-4-one;
- 72 3-(3-Butoxy-propyl)-2-(4-methoxy-phenyl)-thiazolidin-4-one;
- 73 2-(2-Chloro-phenyl)-3-(3,4,5-trifluoro-benzyl)-thiazolidin-4-one;
- 74 2-(2-Chloro-phenyl)-3-(2,5-difluoro-benzyl)-thiazolidin-4-one;
- 75 2-(2-Chloro-phenyl)-3-(3-fluoro-benzyl)-thiazolidin-4-one;
- 76 3-(3-Butoxy-propyl)-2-(2-chloro-phenyl)-thiazolidin-4-one;
- 77 3-(2-Benzo[1,3]dioxol-5-yl-ethyl)-2-(2-chloro-phenyl)-thiazolidin-4-one;
- 78 Thiobenzoic acid S-{2-[2-(2-methoxy-phenyl)-4-oxo-thiazolidin-3-yl]-ethyl} ester;
- 79 3-(4-Fluoro-benzyl)-2-(2-methoxy-phenyl)-thiazolidin-4-one;
- 80 3-(3,4-Difluoro-benzyl)-2-(2-methoxy-phenyl)-thiazolidin-4-one;
- 81 2-(2,3-Dimethoxy-phenyl)-3-(2-pyridin-4-yl-ethyl)-thiazolidin-4-one;
- 82 3-(3,4-Difluoro-benzyl)-2-(2,3-dimethoxy-phenyl)-thiazolidin-4-one;
- 83 3-(2,5-Dimethoxy-benzyl)-2-(2,3-dimethoxy-phenyl)-thiazolidin-4-one;
- 84 3-(3,4-Difluoro-benzyl)-2-(2,3,4-trimethoxy-phenyl)-thiazolidin-4-one;
- 85 3-(2-Benzo[1,3]dioxol-5-yl-ethyl)-2-(2,4-dimethoxy-phenyl)-thiazolidin-4-one;
- 86 2-(2,4-Dimethoxy-phenyl)-3-[2-(4-methoxy-phenoxy)-ethyl]-thiazolidin-4-one;
- 87 2-(2,5-Dimethoxy-phenyl)-3-(2,3,4-trifluoro-benzyl)-thiazolidin-4-one;
- 88 2-(2,5-Dimethoxy-phenyl)-3-[2-(4-methoxy-phenoxy)-ethyl]-thiazolidin-4-one;
- 89 3-(2,3-Difluoro-benzyl)-2-(2,5-dimethoxy-phenyl)-thiazolidin-4-one;

- 90 2-(2-Ethoxy-phenyl)-3-(2-fluoro-benzyl)-thiazolidin-4-one;
- 91 2-(2-Ethoxy-phenyl)-3-(4-methoxy-benzyl)-thiazolidin-4-one;
- 92 3-(3,4-Difluoro-benzyl)-2-(2-ethoxy-phenyl)-thiazolidin-4-one;
- 93 3-(2,5-Dimethoxy-benzyl)-2-(2-ethoxy-phenyl)-thiazolidin-4-one;
- 94 2-(2-Ethoxy-phenyl)-3-[2-(4-methoxy-phenoxy)-ethyl]-thiazolidin-4-one;
- 95 3-(2-Fluoro-benzyl)-2-o-tolyl-thiazolidin-4-one;
- 96 3-(3,4-Difluoro-benzyl)-2-o-tolyl-thiazolidin-4-one;
- 97 3-(4-Dimethylamino-benzyl)-2-o-tolyl-thiazolidin-4-one;
- 98 3-[2-(4-Methoxy-phenoxy)-ethyl]-2-o-tolyl-thiazolidin-4-one;
- 99 3-(3,4-Difluoro-benzyl)-2-(2,4,6-trimethyl-phenyl)-thiazolidin-4-one;
- 100 3-(3-Butoxy-propyl)-2-(2,4,6-triethyl-phenyl)-thiazolidin-4-one;
- 101 3-(3-Butoxy-propyl)-2-(2,4,6-triethyl-phenyl)-thiazolidin-4-one;
- 102 3-(2-tert-Butylsulfanyl-ethyl)-2-(3-chloro-phenyl)-thiazolidin-4-one;
- 103 2-(3-Chloro-phenyl)-3-(3,4,5-trifluoro-benzyl)-thiazolidin-4-one;
- 104 2-(3-Chloro-phenyl)-3-(2-fluoro-benzyl)-thiazolidin-4-one;
- 105 2-(3-Chloro-phenyl)-3-(4-fluoro-benzyl)-thiazolidin-4-one;
- 106 2-(3-Chloro-phenyl)-3-(2-ethylsulfanyl-ethyl)-thiazolidin-4-one;
- 107 3-(2-Benzo[1,3]dioxol-5-yl-ethyl)-2-(3-chloro-phenyl)-thiazolidin-4-one;
- 108 2-(3-Chloro-phenyl)-3-(3-methylsulfanyl-propyl)-thiazolidin-4-one;
- 109 2-(3-Chloro-phenyl)-3-[2-(4-methoxy-phenoxy)-ethyl]-thiazolidin-4-one;
- 110 2-(3-Chloro-phenyl)-3-(3,5-difluoro-benzyl)-thiazolidin-4-one;
- 111 3-(4-Methoxy-benzyl)-2-(3-methoxy-phenyl)-thiazolidin-4-one;
- 112 3-(3-Fluoro-benzyl)-2-(3-methoxy-phenyl)-thiazolidin-4-one;
- 113 3-(3,4-Difluoro-benzyl)-2-(3-methoxy-phenyl)-thiazolidin-4-one;
- 114 3-(3,5-Difluoro-benzyl)-2-(3-methoxy-phenyl)-thiazolidin-4-one;
- 115 3-Benzyl-2-(4-benzyloxy-3-methoxy-phenyl)-thiazolidin-4-one;
- 116 2-(4-Benzyloxy-3-methoxy-phenyl)-3-(2-methylsulfanyl-ethyl)-thiazolidin-4-one;
- 117 2-(4-Benzyloxy-3-methoxy-phenyl)-3-(3-methylsulfanyl-propyl)-thiazolidin-4-one;
- 118 2-(3,5-Dimethoxy-phenyl)-3-(3-fluoro-benzyl)-thiazolidin-4-one;
- 119 2-(4-Chloro-phenyl)-3-isobutyl-thiazolidin-4-one;

- 120 2-(4-Chloro-phenyl)-3-(2,5-difluoro-benzyl)-thiazolidin-4-one;
- 121 2-(4-Chloro-phenyl)-3-(2-phenoxy-ethyl)-thiazolidin-4-one;
- 122 2-(4-Chloro-phenyl)-3-(3,4-difluoro-benzyl)-thiazolidin-4-one;
- 123 2-(4-Chloro-phenyl)-3-[2-(4-hydroxy-3-methoxy-phenyl)-ethyl]-thiazolidin-4-one;
- 124 N-(4-{3-[2-(Furan-2-ylmethylsulfanyl)-ethyl]-4-oxo-thiazolidin-2-yl}-phenyl)-acetamide;
- 125 2-(4-Ethoxy-phenyl)-3-(3,4,5-trifluoro-benzyl)-thiazolidin-4-one;
- 126 3-(3,4-Difluoro-benzyl)-2-thiophen-2-yl-thiazolidin-4-one;
- 127 3-(2,4-Dimethoxy-benzyl)-2-(3-methyl-thiophen-2-yl)-thiazolidin-4-one;
- 128 3-(3,5-Difluoro-benzyl)-2-thiophen-3-yl-thiazolidin-4-one;
- 129 3-(2,5-Dimethoxy-benzyl)-2-quinolin-4-yl-thiazolidin-4-one;
- 130 3-(2-tert-Butylsulfanyl-ethyl)-2-(4-methylsulfanyl-phenyl)-thiazolidin-4-one;
- 131 2-(4-Methylsulfanyl-phenyl)-3-(3,4,5-trifluoro-benzyl)-thiazolidin-4-one;
- 132 3-(4-Fluoro-benzyl)-2-(4-methylsulfanyl-phenyl)-thiazolidin-4-one;
- 133 3-(3-Butoxy-propyl)-2-(4-methylsulfanyl-phenyl)-thiazolidin-4-one;
- 134 3-(2-Benzo[1,3]dioxol-5-yl-ethyl)-2-(4-methylsulfanyl-phenyl)-thiazolidin-4-one;
- 135 3-Isobutyl-2-(4-trifluoromethyl-phenyl)-thiazolidin-4-one;
- 136 3-(2-tert-Butylsulfanyl-ethyl)-2-(4-trifluoromethyl-phenyl)-thiazolidin-4-one;
- 137 3-(3-Methylsulfanyl-propyl)-2-(4-trifluoromethyl-phenyl)-thiazolidin-4-one;
- 138 2-(4-Ethyl-phenyl)-3-(2-pyridin-3-yl-ethyl)-thiazolidin-4-one;
- 139 2-(4-Ethyl-phenyl)-3-(3-fluoro-benzyl)-thiazolidin-4-one;
- 140 2-(4-Ethyl-phenyl)-3-(3-methylsulfanyl-propyl)-thiazolidin-4-one;
- 141 3-(2-tert-Butylsulfanyl-ethyl)-2-(2,3-dihydro-benzo[1,4]dioxin-6-yl)-thiazolidin-4-one;
- 142 3-(3,4-Difluoro-benzyl)-2-(2,3-dihydro-benzo[1,4]dioxin-6-yl)-thiazolidin-4-one;
- 143 2-(2,6-Dimethoxy-phenyl)-3-(2,3,4-trifluoro-benzyl)-thiazolidin-4-one;
- 144 3-(2-Benzo[1,3]dioxol-5-yl-ethyl)-2-(2,6-dimethoxy-phenyl)-thiazolidin-4-one;
- 145 Thiobenzoic acid S-{2-[2-(3-chloro-4-fluoro-phenyl)-4-oxo-thiazolidin-3-yl]-ethyl}ester;

- 146 2-(3-Chloro-4-fluoro-phenyl)-3-(2-pyridin-3-yl-ethyl)-thiazolidin-4-one;
- 147 2-(3-Chloro-4-fluoro-phenyl)-3-[2-(furan-2-ylmethylsulfanyl)-ethyl]-thiazolidin-4-one;
- 148 N-(3-{3-[2-(3-Chloro-4-fluoro-phenyl)-4-oxo-thiazolidin-3-yl]-propoxy}-phenyl)-acetamide;
- 149 2-(3-Chloro-4-fluoro-phenyl)-3-(4-fluoro-benzyl)-thiazolidin-4-one;
- 150 3-(3-Butoxy-propyl)-2-(3-chloro-4-fluoro-phenyl)-thiazolidin-4-one;
- 151 2-(3-Chloro-4-fluoro-phenyl)-3-(2,5-dimethoxy-benzyl)-thiazolidin-4-one;
- 152 2-(3-Chloro-4-fluoro-phenyl)-3-(3,5-difluoro-benzyl)-thiazolidin-4-one;
- 153 2-(2-Allyloxy-phenyl)-3-(2-benzo[1,3]dioxol-5-yl-ethyl)-thiazolidin-4-one;
- 154 2-Benzofuran-2-yl-3-[2-(furan-2-ylmethylsulfanyl)-ethyl]-thiazolidin-4-one;
- 155 2-(3-Ethoxy-phenyl)-3-(2-pyridin-3-yl-ethyl)-thiazolidin-4-one;
- 156 2-(3-Ethoxy-phenyl)-3-(3,4,5-trifluoro-benzyl)-thiazolidin-4-one;
- 157 2-(3-Ethoxy-phenyl)-3-[2-(furan-2-ylmethylsulfanyl)-ethyl]-thiazolidin-4-one;
- 158 2-(3-Ethoxy-phenyl)-3-(4-methoxy-benzyl)-thiazolidin-4-one;
- 159 3-(2,5-Difluoro-benzyl)-2-(3-ethoxy-phenyl)-thiazolidin-4-one;
- 160 2-(3-Ethoxy-phenyl)-3-(3-fluoro-benzyl)-thiazolidin-4-one;
- 161 3-(2,6-Difluoro-benzyl)-2-(3-ethoxy-phenyl)-thiazolidin-4-one;
- 162 2-(3-Ethoxy-phenyl)-3-[2-(4-hydroxy-3-methoxy-phenyl)-ethyl]-thiazolidin-4-one;
- 163 2-(3-Ethoxy-phenyl)-3-(2-ethylsulfanyl-ethyl)-thiazolidin-4-one;
- 164 3-(3-Butoxy-propyl)-2-(3-ethoxy-phenyl)-thiazolidin-4-one;
- 165 2-(3-Ethoxy-phenyl)-3-(3-methylsulfanyl-propyl)-thiazolidin-4-one;
- 166 3-(2,5-Dimethoxy-benzyl)-2-(3-ethoxy-phenyl)-thiazolidin-4-one;
- 167 2-(3-Ethoxy-phenyl)-3-[2-(4-methoxy-phenoxy)-ethyl]-thiazolidin-4-one;
- 168 3-(2,3-Difluoro-benzyl)-2-(3-ethoxy-phenyl)-thiazolidin-4-one;
- 169 2-Benzo[1,3]dioxol-4-yl-3-(3,4,5-trifluoro-benzyl)-thiazolidin-4-one;
- 170 2-Benzo[1,3]dioxol-4-yl-3-(3,4-difluoro-benzyl)-thiazolidin-4-one;
- 171 2-Benzo[1,3]dioxol-4-yl-3-(2-benzo[1,3]dioxol-5-yl-ethyl)-thiazolidin-4-one;
- 172 2-Benzo[1,3]dioxol-4-yl-3-(3,5-difluoro-benzyl)-thiazolidin-4-one;
- 173 2-(2-Chloro-4-dimethylamino-phenyl)-3-(3,4,5-trifluoro-benzyl)-thiazolidin-4-one;

- 174 2-(2-Chloro-4-dimethylamino-phenyl)-3-(3,4-difluoro-benzyl)-thiazolidin-4-one;
- 175 2-(4-tert-Butoxy-phenyl)-3-(3,4,5-trifluoro-benzyl)-thiazolidin-4-one;
- 176 2-(3-Bromo-4-fluoro-phenyl)-3-(3-methylsulfanyl-propyl)-thiazolidin-4-one;
- 177 2-(5-Chloro-thiophen-2-yl)-3-(3-methylsulfanyl-propyl)-thiazolidin-4-one;
- 178 3-(3,5-Difluoro-benzyl)-2-(2,3,4-trifluoro-phenyl)-thiazolidin-4-one;
- 179 3-(2,3-Difluoro-benzyl)-2-(2,3,4-trifluoro-phenyl)-thiazolidin-4-one;
- 180 2-(2,3-Dihydro-benzofuran-5-yl)-3-(3,4,5-trifluoro-benzyl)-thiazolidin-4-one;
- 181 2-(2,3-Dihydro-benzofuran-5-yl)-3-(2-phenoxy-ethyl)-thiazolidin-4-one;
- 182 3-(2-Benzo[1,3]dioxol-5-yl-ethyl)-2-(2,3-dihydro-benzofuran-5-yl)-thiazolidin-4-one;
- 183 2-(2,3-Dihydro-benzofuran-5-yl)-3-[2-(4-methoxy-phenoxy)-ethyl]-thiazolidin-4-one;
- 184 3-(4-Dimethylamino-benzyl)-2-(4,5-dimethyl-furan-2-yl)-thiazolidin-4-one;
- 185 2-(3-Bromo-4-fluoro-phenyl)-3-(2-pyridin-3-yl-ethyl)-thiazolidin-4-one.
- 186 5-Methyl-3-(2-pyridin-3-yl-ethyl)-2-(3-trifluoromethoxy-phenyl)-thiazolidin-4-one;
- 187 3-(3,3-Diphenyl-propyl)-2-(3-trifluoromethoxy-phenyl)-thiazolidin-4-one
- 188 2-(3-Trifluoromethoxy-phenyl)-3-(3,4,5-trimethoxy-benzyl)-thiazolidin-4-one
- 189 3-(2,2-Diphenyl-ethyl)-2-(3-trifluoromethoxy-phenyl)-thiazolidin-4-one
- 190 3-(3-Hydroxy-propyl)-2-(3-trifluoromethoxy-phenyl)-thiazolidin-4-one
- 191 3-Hexyl-2-(3-trifluoromethoxy-phenyl)-thiazolidin-4-one
- 192 3-[2-(3-Methoxy-phenyl)-ethyl]-2-(3-trifluoromethoxy-phenyl)-thiazolidin-4-one
- 193 3-Methyl-2-(3-trifluoromethoxy-phenyl)-thiazolidin-4-one
- 194 3-(2,3-Dimethoxy-benzyl)-1-oxo-2-(3-trifluoromethoxy-phenyl)-1 λ 4*-thiazolidin-4-one
- 195 3-(2,3-Dimethoxy-benzyl)-1,1-dioxo-2-(3-trifluoromethoxy-phenyl)-1 λ 6*-thiazolidin-4-one
- 196 2-(3-Bromo-4-fluoro-phenyl)-3-isobutyl-thiazolidin-4-one
- 197 3-Indan-1-yl-2-(3-trifluoromethoxy-phenyl)-thiazolidin-4-one
- 198 3-Quinolin-6-yl-2-(3-trifluoromethoxy-phenyl)-thiazolidin-4-one

- 199 2-(3-Bromo-4-fluoro-phenyl)-3-quinolin-6-yl-thiazolidin-4-one
- 200 2-(3-Chloro-phenyl)-3-(2,3-dimethoxy-benzyl)-thiazolidin-4-one
- 201 3-(2,3-Dimethoxy-benzyl)-2-(4-ethoxy-phenyl)-thiazolidin-4-one
- 202 3-(2,3-Dimethoxy-benzyl)-2-(3-methoxy-phenyl)-thiazolidin-4-one
- 203 2-(4-Chloro-phenyl)-3-(2,3-dimethoxy-benzyl)-thiazolidin-4-one
- 204 3-(2,3-Dimethoxy-benzyl)-2-phenyl-thiazolidin-4-one
- 205 3-(3-Chloro-4-fluoro-benzyl)-2-(3-trifluoromethoxy-phenyl)-thiazolidin-4-one
- 206 3-(2,2-Diphenyl-ethyl)-1-oxo-2-(3-trifluoromethoxy-phenyl)-1 λ^4 -thiazolidin-4-one
- 207 3-(2,3-Dimethoxy-benzyl)-2-(4-methoxy-phenyl)-thiazolidin-4-one
- 208 2-(3-Chloro-4-fluoro-phenyl)-3-(2,3-dimethoxy-benzyl)-thiazolidin-4-one
- 209 3-(2,3-Dimethoxy-benzyl)-2-(4-ethylsulfanyl-phenyl)-thiazolidin-4-one
- 210 3-(2,3-Dimethoxy-benzyl)-2-(4-trifluoromethoxy-phenyl)-thiazolidin-4-one
- 211 3-(2,3-Dimethoxy-benzyl)-2-(2-trifluoromethoxy-phenyl)-thiazolidin-4-one
- 212 3-(2,3-Dimethoxy-benzyl)-2-(3-trifluoromethyl-phenyl)-thiazolidin-4-one
- 213 3-(1-Phenyl-ethyl)-2-(3-trifluoromethoxy-phenyl)-thiazolidin-4-one
- 214 3-[1-(4-Methoxy-phenyl)-ethyl]-2-(3-trifluoromethoxy-phenyl)-thiazolidin-4-one
- 215 [3-(2,3-Dimethoxy-benzyl)-4-oxo-2-(3-trifluoromethoxy-phenyl)-thiazolidin-5-yl]-acetic acid
- 216 2-[3-(2,3-Dimethoxy-benzyl)-4-oxo-2-(3-trifluoromethoxy-phenyl)-thiazolidin-5-yl]-N-isobutyl-acetamide
- 217 3-(2,3-Dimethoxy-benzyl)-2-(3-trifluoromethoxy-phenyl)-thiazolidin-4-one
- 218 3-(2,3-Dimethoxy-benzyl)-2-(3-trifluoromethoxy-phenyl)-thiazolidin-4-one
- 219 3-(2,5-Difluoro-benzyl)-2-(4-ethylsulfanyl-phenyl)-thiazolidin-4-one
- 220 2-(4-Ethylsulfanyl-phenyl)-3-(4-fluoro-benzyl)-thiazolidin-4-one
- 221 3-{2-[4-Oxo-2-(3-trifluoromethoxy-phenyl)-thiazolidin-3-yl]-ethyl}-pyridinium; chloride
- 222 2-{2-[2-(3-Bromo-4-fluoro-phenyl)-4-oxo-thiazolidin-3-yl]-ethyl}-pyridinium; chloride
- 223 3-(2-Benzo[1,3]dioxol-5-yl-ethyl)-2-(3-trifluoromethoxy-phenyl)-thiazolidin-4-one

- 224 2-(3-Bromo-phenyl)-3-isobutyl-thiazolidin-4-one
- 225 2-(2-Bromo-phenyl)-3-isobutyl-thiazolidin-4-one
- 226 2-Biphenyl-3-yl-3-isobutyl-thiazolidin-4-one
- 227 N-(3-Methoxy-benzyl)-2-[3-methyl-4-oxo-2-(3-trifluoromethoxy-phenyl)-thiazolidin-5-yl]-acetamide
- 228 N-(2-Cyclohex-1-enyl-ethyl)-2-[3-methyl-4-oxo-2-(3-trifluoromethoxy-phenyl)-thiazolidin-5-yl]-acetamide
- 229 N-Isobutyl-2-[3-methyl-4-oxo-2-(3-trifluoromethoxy-phenyl)-thiazolidin-5-yl]-acetamide
- 230 2-[3-Isobutyl-4-oxo-2-(3-trifluoromethoxy-phenyl)-thiazolidin-5-yl]-N-(3-methoxy-benzyl)-acetamide
- 231 N-(2-Cyclohex-1-enyl-ethyl)-2-[3-isobutyl-4-oxo-2-(3-trifluoromethoxy-phenyl)-thiazolidin-5-yl]-acetamide
- 232 N-Isobutyl-2-[3-isobutyl-4-oxo-2-(3-trifluoromethoxy-phenyl)-thiazolidin-5-yl]-acetamide
- 233 2-[3-(2-Cyclohex-1-enyl-ethyl)-4-oxo-2-(3-trifluoromethoxy-phenyl)-thiazolidin-5-yl]-N-(4-methoxy-benzyl)-acetamide
- 234 N-(2-Cyclohex-1-enyl-ethyl)-2-[3-(2-cyclohex-1-enyl-ethyl)-4-oxo-2-(3-trifluoromethoxy-phenyl)-thiazolidin-5-yl]-acetamide
- 235 2-[3-(2-Cyclohex-1-enyl-ethyl)-4-oxo-2-(3-trifluoromethoxy-phenyl)-thiazolidin-5-yl]-N-isobutyl-acetamide
- 236 [2-(3-Bromo-4-fluoro-phenyl)-4-oxo-3-(2-pyridin-2-yl-ethyl)-thiazolidin-5-yl]-acetic acid
- 237 2-[3-(2-Cyclohex-1-enyl-ethyl)-4-oxo-2-(3-trifluoromethoxy-phenyl)-thiazolidin-5-yl]-N-(2-piperidin-1-yl-ethyl)-acetamide
- 238 2-[3-Methyl-4-oxo-2-(3-trifluoromethoxy-phenyl)-thiazolidin-5-yl]-N-(2-piperidin-1-yl-ethyl)-acetamide
- 239 2-[3-Isobutyl-4-oxo-2-(3-trifluoromethoxy-phenyl)-thiazolidin-5-yl]-N-(2-piperidin-1-yl-ethyl)-acetamide
- 240 2-{2-[2-(3-Bromo-4-fluoro-phenyl)-5-(isobutylcarbamoyl-methyl)-4-oxo-thiazolidin-3-yl]-ethyl}-pyridinium; chloride

- 241 2-(2-{2-(3-Bromo-4-fluoro-phenyl)-5-[(2-cyclohex-1-enyl-ethylcarbamoyl)-methyl]-4-oxo-thiazolidin-3-yl}-ethyl)-pyridinium; chloride
- 242 2-(2-{2-(3-Bromo-4-fluoro-phenyl)-5-[(3-methoxy-benzylcarbamoyl)-methyl]-4-oxo-thiazolidin-3-yl}-ethyl)-pyridinium; chloride
- 243 2-[2-(3-Bromo-4-fluoro-phenyl)-4-oxo-3-(2-pyridin-2-yl-ethyl)-thiazolidin-5-yl]-N-(2-piperidin-1-yl-ethyl)-acetamide; dihydrochloride
- 244 5-[2-(4-Benzhydryl-piperazin-1-yl)-2-oxo-ethyl]-2-(3-bromo-4-fluoro-phenyl)-3-(2-pyridin-2-yl-ethyl)-thiazolidin-4-one; dihydrochloride
- 245 2-{2-[5-(Isobutylcarbamoyl-methyl)-4-oxo-2-(3-trifluoromethoxy-phenyl)-thiazolidin-3-yl]-ethyl}-pyridinium; chloride
- 246 1-Benzhydryl-4-{2-[3-isobutyl-4-oxo-2-(3-trifluoromethoxy-phenyl)-thiazolidin-5-yl]-acetyl}-piperazin-1-ium; chloride
- 247 1-Benzhydryl-4-{2-[3-methyl-4-oxo-2-(3-trifluoromethoxy-phenyl)-thiazolidin-5-yl]-acetyl}-piperazin-1-ium; chloride
- 248 2-{2-[5-[(4-Methoxy-benzylcarbamoyl)-methyl]-4-oxo-2-(3-trifluoromethoxy-phenyl)-thiazolidin-3-yl]-ethyl}-pyridinium; chloride
- 249 2-[4-Oxo-3-(2-pyridin-2-yl-ethyl)-2-(3-trifluoromethoxy-phenyl)-thiazolidin-5-yl]-N-(2-piperidin-1-yl-ethyl)-acetamide; dihydrochloride
- 250 3-Methyl-5-(2-oxo-2-pyrrolidin-1-yl-ethyl)-2-(3-trifluoromethoxy-phenyl)-thiazolidin-4-one
- 251 5-(2-Azepan-1-yl-2-oxo-ethyl)-3-methyl-2-(3-trifluoromethoxy-phenyl)-thiazolidin-4-one
- 252 N-(1H-Benzoimidazol-2-yl)-2-[3-methyl-4-oxo-2-(3-trifluoromethoxy-phenyl)-thiazolidin-5-yl]-acetamide
- 253 2-[3-Methyl-4-oxo-2-(3-trifluoromethoxy-phenyl)-thiazolidin-5-yl]-N-pyridin-2-yl-acetamide
- 254 N,N-Dibenzyl-2-[3-methyl-4-oxo-2-(3-trifluoromethoxy-phenyl)-thiazolidin-5-yl]-acetamide
- 255 5-[2-(4-Benzhydryl-piperazin-1-yl)-2-oxo-ethyl]-3-(2-pyridin-2-yl-ethyl)-2-(3-trifluoromethoxy-phenyl)-thiazolidin-4-one; dihydrochloride
- 256 2-(3-Bromo-4-fluoro-phenyl)-3-(2-cyclohex-1-enyl-ethyl)-thiazolidin-4-one
- 257 2-(3-Chloro-phenyl)-3-(2-cyclohex-1-enyl-ethyl)-thiazolidin-4-one

- 258 3-(2-Cyclohex-1-enyl-ethyl)-2-(3-ethoxy-phenyl)-thiazolidin-4-one
- 259 3-(2-Cyclohex-1-enyl-ethyl)-2-(3-trifluoromethyl-phenyl)-thiazolidin-4-one
- 260 3-(2-Cyclohex-1-enyl-ethyl)-2-(3-trifluoromethoxy-phenyl)-thiazolidin-4-one
- 261 2-(3-Bromo-4-fluoro-phenyl)-3-phenethyl-thiazolidin-4-one
- 262 3-Phenethyl-2-(3-trifluoromethoxy-phenyl)-thiazolidin-4-one
- 263 2-(3-Chloro-phenyl)-3-phenethyl-thiazolidin-4-one
- 264 2-[3-(3,5-Difluoro-benzyl)-4-oxo-2-(3-trifluoromethoxy-phenyl)-thiazolidin-5-yl]-N-isobutyl-acetamide
- 265 N-(2-Cyclohex-1-enyl-ethyl)-2-[3-(3,5-difluoro-benzyl)-4-oxo-2-(3-trifluoromethoxy-phenyl)-thiazolidin-5-yl]-acetamide
- 266 2-[3-(3,5-Difluoro-benzyl)-4-oxo-2-(3-trifluoromethoxy-phenyl)-thiazolidin-5-yl]-N-(3-methoxy-benzyl)-acetamide
- 267 2-(4-Bromo-pyridin-3-yl)-3-isobutyl-thiazolidin-4-one
- 268 2-(3-Bromo-4-fluoro-phenyl)-3-[2-(6-bromo-pyridin-2-yl)-ethyl]-thiazolidin-4-one
- 269 2-(3-Bromo-pyridin-4-yl)-3-isobutyl-thiazolidin-4-one
- 270 3-[2-(4-Imidazolyl)ethyl]-2-[(3-trifluoromethoxyphenyl)]-4-thiazolidinone
- 271 [4-Oxo-2-(3-trifluoromethoxyphenyl)-3-thiazolidinyl]acetic acid, pentyl ester
- 272 3-[2-(3,4-dimethoxyphenyl)ethyl]-2-[(3-trifluoromethoxyphenyl)]-4-thiazolidinone
- 273 6-[4-Oxo-2-(3-trifluoromethoxyphenyl)-3-thiazolidinyl]-hexanoic acid, methyl ester
- 274 3-[3-(1-Imidazolyl)propyl]-2-(3-trifluoromethoxyphenyl)-4-thiazolidinone
- 275 3-(2-Pyridinyl)methyl-2-(3-trifluoromethoxyphenyl)-4-thiazolidinone
- 276 3-[2-(2-Pyridinyl)ethyl]-2-(3-trifluoromethoxyphenyl)-4-thiazolidinone
- 277 3-(Benzo[1,3]dioxol-5-yl)methyl-2-(3-trifluoromethoxyphenyl)-4-thiazolidinone
- 278 3-[2-(1H-Benzoimidazolyl)methyl]-2-(3-trifluoromethoxyphenyl)-4-thiazolidinone
- 279 3-(2,4-Difluorophenylmethyl)-2-(3-trifluoromethoxyphenyl)-4-thiazolidinone
- 280 3-[2-[4-Morpholinyl)ethyl]-2-(3-trifluoromethoxyphenyl)-4-thiazolidinone
- 281 3-[3-(4-Methyl-1-piperazinyl)propyl]-2-(3-trifluoromethoxyphenyl)-4-thiazolidinone

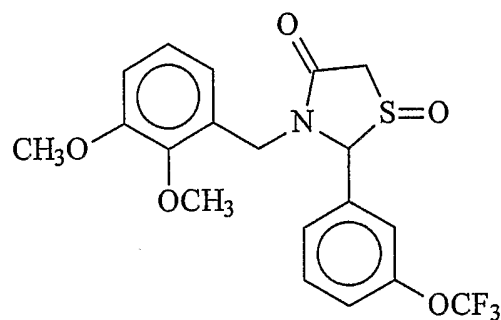
- 282 3-[3-(1-Piperidiny)propyl]-2-(3-trifluoromethoxyphenyl)-4-thiazolidinone
- 283 3-(2-Ethoxyethyl)-2-(3-trifluoromethoxyphenyl)-4-thiazolidinone
- 284 3-(6-Methoxy-3-pyridinyl)-2-(3-trifluoromethoxyphenyl)-4-thiazolidinone
- 285 3-(3-Isopropoxyphenyl)-2-(3-trifluoromethoxyphenyl)-4-thiazolidinone
- 286 3-(3-Propoxypropyl)-2-(3-trifluoromethoxyphenyl)-4-thiazolidinone
- 287 3-(2-Hydroxyethyl)-2-(3-trifluoromethoxyphenyl)-4-thiazolidinone
- 288 Thiobenzoic acid, S-{2-[4-oxo-2-(3-trifluoromethoxyphenyl)-3-thiazolidinyl]-ethyl} ester
- 289 3-Phenylmethyl-2-(3-trifluoromethoxyphenyl)-4-thiazolidinone
- 290 3-[2-(3-Pyridinyl)ethyl]-2-(3-trifluoromethoxyphenyl)-4-thiazolidinone
- 291 3-[4-(1-Pyrrolidinyl)butyl]-2-(3-trifluoromethoxyphenyl)-4-thiazolidinone
- 292 3-(3-Dimethylaminopropyl)-2-(3-trifluoromethoxyphenyl)-4-thiazolidinone
- 293 3-Isobutyl-2-(3-trifluoromethoxyphenyl)-4-thiazolidinone
- 294 3-(2-tert-Butylsulphanylethyl)-2-(3-trifluoromethoxyphenyl)-4-thiazolidinone
- 295 3-[(3,4,5-Trifluorophenyl)methyl]-2-(3-trifluoromethoxyphenyl)-4-thiazolidinone
- 296 3-[(4-Hydroxy-3-methoxyphenyl)methyl]-2-(3-trifluoromethoxyphenyl)-4-thiazolidinone
- 297 (S)-3-(2,3-Dihydroxypropyl)-2-(3-trifluoromethoxyphenyl)-4-thiazolidinone
- 298 3-{2-[2-Furanyl)methylsulphanyl]ethyl}-2-(3-trifluoromethoxyphenyl)-4-thiazolidinone
- 299 3-[(2-Fluorophenyl)methyl]-2-(3-trifluoromethoxyphenyl)-4-thiazolidinone
- 300 3-[2-(2-Hydroxyethoxy)ethyl]-2-(3-trifluoromethoxyphenyl)-4-thiazolidinone
- 301 3-[5-Methyl-2-pyrazinyl)methyl]-2-(3-trifluoromethoxyphenyl)-4-thiazolidinone
- 302 [4-Oxo-2-(3-trifluoromethoxyphenyl)-3-thiazolidinyl]acetic acid, ethyl ester
- 303 3-[2-Diethylamino)ethyl]-2-(3-trifluoromethoxyphenyl)-4-thiazolidinone
- 304 3-[(2-Dimethylamino)ethyl]-2-(3-trifluoromethoxyphenyl)-4-thiazolidinone
- 305 3-[(4-Methoxyphenyl)methyl]-2-(3-trifluoromethoxyphenyl)-4-thiazolidinone
- 306 3-(2,2,2-Trifluoroethyl)-2-(3-trifluoromethoxyphenyl)-4-thiazolidinone
- 307 3-[2-(4-Hydroxyphenyl)ethyl]-2-(3-trifluoromethoxyphenyl)-4-thiazolidinone
- 308 3-(2-Furanyl)methyl-2-(3-trifluoromethoxyphenyl)-4-thiazolidinone
- 309 3-[(3-Methoxyphenyl)methyl]-2-(3-trifluoromethoxyphenyl)-4-thiazolidinone

- 310 3-(5-Hydroxypentyl)-2-(3-trifluoromethoxyphenyl)-4-thiazolidinone
- 311 3-[(2,5-Difluorophenyl)methyl]-2-(3-trifluoromethoxyphenyl)-4-thiazolidinone
- 312 3-[(2-Phenoxy)ethyl]-2-(3-trifluoromethoxyphenyl)-4-thiazolidinone
- 313 3-[4-Oxo-2-(3-trifluoromethoxyphenyl)-3-thiazolidinyl]propionic acid, tert-butyl ester
- 314 N-Methyl-2-[4-oxo-2-(3-trifluoromethoxyphenyl)-3-thiazolidinyl]acetamide
- 315 3-[2-(2-Hydroxyethylsulphanyl)ethyl]-2-(3-trifluoromethoxyphenyl)-4-thiazolidinone
- 316 3-[3-(1-Pyrrolidinyl)propyl]-2-(3-trifluoromethoxyphenyl)-4-thiazolidinone
- 317 3-[(2,3-Dimethoxyphenyl)methyl]-2-(3-trifluoromethoxyphenyl)-4-thiazolidinone
- 318 3-{2-[5-Dimethylaminomethyl-2-furanyl)methylsulphanyl]ethyl}-2-(3-trifluoromethoxyphenyl)-4-thiazolidinone
- 319 N-(3-{3-[4-Oxo-2-(3-trifluoromethoxyphenyl)-3-thiazolidinyl]propoxy}phenyl)acetamide
- 320 3-[2-(1-Pyrrolidinyl)ethyl]-2-(3-trifluoromethoxyphenyl)-4-thiazolidinone
- 321 3-[3-(2-Oxo-1-pyrrolidinyl)propyl]-2-(3-trifluoromethoxyphenyl)-4-thiazolidinone
- 322 (2*S*)-2-Acetyl-amino-6-[4-oxo-2-(3-trifluoromethoxyphenyl)-3-thiazolidinyl]hexanoic acid methyl ester
- 323 3-[(3-Fluorophenyl)methyl]-2-(3-trifluoromethoxyphenyl)-4-thiazolidinone
- 324 3-[(4-Fluorophenyl)methyl]-2-(3-trifluoromethoxyphenyl)-4-thiazolidinone
- 325 3-(2-Methoxyethyl)-2-(3-trifluoromethoxyphenyl)-4-thiazolidinone
- 326 3-Propyl-2-(3-trifluoromethoxyphenyl)-4-thiazolidinone
- 327 3-[(3-Diethylamino)propyl]-2-(3-trifluoromethoxyphenyl)-4-thiazolidinone
- 328 3-(3-Ethoxypropyl)-2-(3-trifluoromethoxyphenyl)-4-thiazolidinone
- 329 3-[(3,4-Difluorophenyl)methyl]-2-(3-trifluoromethoxyphenyl)-4-thiazolidinone
- 330 3-[(2,4-Dimethoxyphenyl)methyl]-2-(3-trifluoromethoxyphenyl)-4-thiazolidinone
- 331 3-{[(4-Dimethylamino)phenyl]methyl}-2-(3-trifluoromethoxyphenyl)-4-thiazolidinone
- 332 3-[2-(4-Hydroxy-3-methoxyphenyl)ethyl]-2-(3-trifluoromethoxyphenyl)-4-thiazolidinone

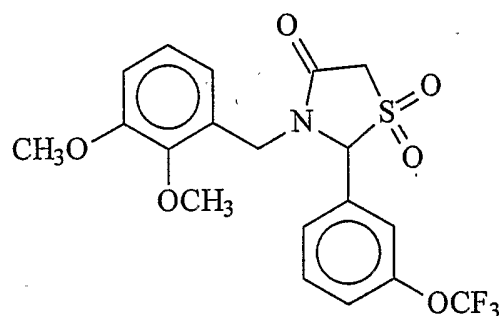
- 333 3-[(2-Ethylsulphanyl)ethyl]-2-(3-trifluoromethoxyphenyl)-4-thiazolidinone
- 334 3-[4-Oxo-2-(3-trifluoromethoxyphenyl)-3-thiazolidinyl]-propionic acid, ethyl ester
- 335 3-(3-Methoxypropyl)-2-(3-trifluoromethoxyphenyl)-4-thiazolidinone
- 336 3-(3-Butoxypropyl)-2-(3-trifluoromethoxyphenyl)-4-thiazolidinone
- 337 {2-[4-Oxo-2-(3-trifluoromethoxyphenyl)-3-thiazolidinyl]acetyl amino} acetic acid, ethyl ester
- 338 3-[4-Oxo-2-(3-trifluoromethoxyphenyl)-3-thiazolidinyl]propionic acid, methyl ester
- 339 3-[3-Methylsulphanyl]propyl]-2-(3-trifluoromethoxyphenyl)-4-thiazolidinone
- 340 3-(5-Hydroxy-4,4-dimethylpentyl)-2-(3-trifluoromethoxyphenyl)-4-thiazolidinone
- 341 (2-[4-Oxo-2-(3-trifluoromethoxyphenyl)-3-thiazolidinyl]acetyl amino} acetic acid, benzyl ester
- 342 3-[(2,5-Dimethoxyphenyl)methyl]-2-(3-trifluoromethoxyphenyl)-4-thiazolidinone
- 343 3-[2-(4-Methoxyphenoxy)ethyl]-2-(3-trifluoromethoxyphenyl)-4-thiazolidinone
- 344 3-[(3,5-Difluorophenyl)methyl]-2-(3-trifluoromethoxyphenyl)-4-thiazolidinone
- 345 3-[(2,3-Difluorophenyl)methyl]-2-(3-trifluoromethoxyphenyl)-4-thiazolidinone
- 346 2-(3-Trifluoromethoxyphenyl)-3-[(3,4,5-trimethoxyphenyl)methyl]-4-thiazolidinone
- 347 3-(3,3-Diphenylpropyl)-2-(3-trifluoromethoxyphenyl)-4-thiazolidinone
- 348 3-(2,2-Diphenylethyl)-2-(3-trifluoromethoxyphenyl)-4-thiazolidinone
- 349 3-Hexyl-2-(3-trifluoromethoxyphenyl)-4-thiazolidinone
- 350 3-(3-Hydroxypropyl)-2-(3-trifluoromethoxyphenyl)-4-thiazolidinone
- 351 5-Methyl-3-[2-(3-pyridinyl)ethyl]-2-(3-trifluoromethoxyphenyl)-4-thiazolidinone
- 352 3-[(3-methoxyphenyl)ethyl]-2-(3-trifluoromethoxyphenyl)-4-thiazolidinone and pharmaceutically acceptable salts thereof.

For the avoidance of doubt, the structures of compounds 194, 195 and 206 are as follows:

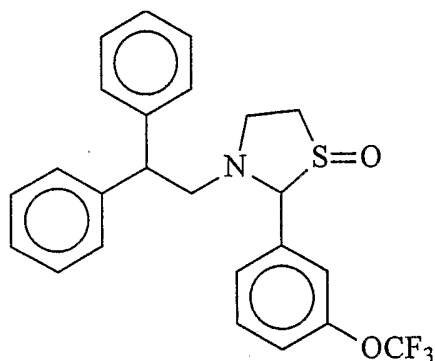
194:



195:



206:



As used herein, a pharmaceutically acceptable salt is a salt with a pharmaceutically acceptable acid or base. Pharmaceutically acceptable acids include both inorganic acids such as hydrochloric, sulfuric, phosphoric, diphosphoric, hydrobromic or nitric acid and organic acids such as citric, fumaric, maleic, malic, ascorbic, succinic, tartaric, benzoic, acetic, methanesulphonic, ethanesulphonic, benzenesulphonic or p-toluenesulphonic acid. Pharmaceutically acceptable bases include alkali metal (e.g. sodium or potassium) and alkali earth metal (e.g. calcium or

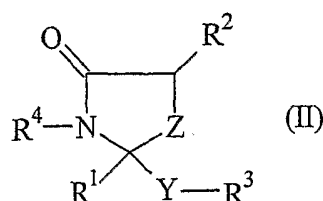
magnesium) hydroxides and organic bases such as alkyl amines, aralkyl amines or heterocyclic amines.

In a further embodiment of the invention, the compound of formula (I) is a compound wherein, when R_2 is other than hydrogen, fluorine and C_1 - C_6 alkyl, Y is $-(CR^Y_2)_q$ - and/or R_3 is hydrogen.

The compounds of the invention contain one or more chiral centre. For the avoidance of doubt, the chemical structures depicted herein are intended to embrace all stereoisomers of the compounds shown, including racemic and non-racemic mixtures and pure enantiomers and/or diastereoisomers.

Preferred compounds of the invention are optically active isomers. Thus, for example, preferred compounds of formula (I) containing only one chiral centre include an R enantiomer in substantially pure form, an S enantiomer in substantially pure form and enantiomeric mixtures which contain an excess of the R enantiomer or an excess of the S enantiomer.

The present invention also provides a pharmaceutical composition comprising a compound of formula (II), or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier or diluent,

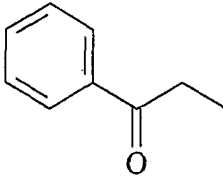
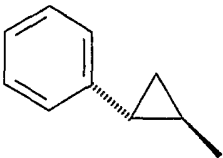
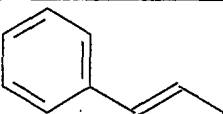
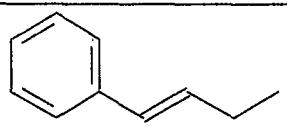
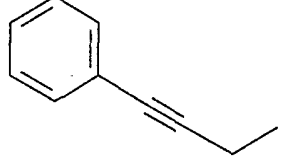
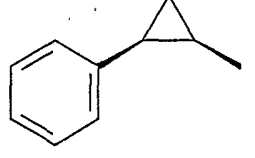
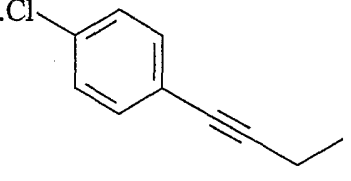
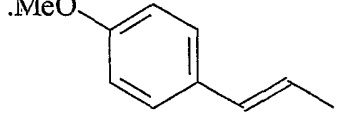


wherein R^1 , R^2 , R^3 , R^4 , Y and Z in the formula (II) are as defined above for the formula (I), provided that (i) $-YR_3$ is other than an unsubstituted pyridyl group, (ii) $-YR_3$ is other than $-\text{phenyl-O-A}_2\text{-R}$, wherein A_2 is a C_2 - C_5 alkylene group and R is 1-pyrrolidinyl, 1-piperidinyl, 4-morpholinyl, 1-piperazinyl or 4-alkyl-1-piperazinyl, (iii) R^2 is other than C_1 - C_6 alkyl, (iv) when X_1 is $-\text{O}-$, Ar_1 is other than phenyl and when X_2 is $-\text{O}-$ and C_2 is an unsubstituted C_1 - C_6 alkylene group, C_3 is other than an unsubstituted C_1 - C_6 alkyl group and (v) when Z is S and R^1 is hydrogen, R^4 and $Y-R^3$ are not defined as follows:

R ⁴	Y-R ³
-(CH ₂) ₃ -N(CH ₃) ₂	phenyl
-(CH ₂) ₃ -N(CH ₃) ₂	halophenyl
-(CH ₂) ₃ -N(CH ₃) ₂	methoxyphenyl
-(CH ₂) ₃ -N(CH ₃) ₂	(C ₁ -C ₄ alkyl)phenyl
-(CH ₂) ₃ -N(CH ₃) ₂	nitrophenyl
-(CH ₂) ₃ -N(CH ₃) ₂	aminophenyl
2-(4-methoxyphenethyl)	3-methoxyphenyl
2-(4-methylphenethyl)	4-methoxyphenyl
2-(4-methoxyphenethyl)	4-pyrrolidinylphenyl
2-(4-methoxyphenethyl)	4-benzodioxanyl
2-(4-methoxyphenethyl)	3,4-dimethoxyphenyl
2-(4-methoxyphenethyl)	4-benzodioxolanyl
2-(4-methoxyphenethyl)	3-methyl-4-methoxyphenyl
2-(3-methoxyphenethyl)	4-benzodioxolanyl
2-phenethyl	3-methoxyphenyl
2-(4-methoxyphenethyl)	4-ethylphenyl
2-(4-methoxyphenethyl)	4-isopropoxyphenyl
2-(4-methoxyphenethyl)	4-methylthiophenyl
2-(4-chlorophenethyl)	4-methoxyphenyl
2-(4-methoxyphenethyl)	4-isopropylphenyl
2-(4-methoxyphenethyl)	4-benzoxypheyl
2-(3-methoxyphenethyl)	4-(N-acetyl)aminophenyl
2-(4-methoxyphenethyl)	4-dimethylaminophenyl
2-(4-ethylphenethyl)	3-methoxyphenyl
2-(4-phenoxyphenethyl)	2-methoxyphenyl
2-(3,4-dimethoxyphenethyl)	4-ethylphenyl
2-(4-methoxyphenethyl)	3,4-dichlorophenyl
2-(3,4-dimethoxyphenethyl)	4-dimethylaminophenyl

R ⁴	Y-R ³
2-(4-methoxyphenethyl)	3,4-difluorophenyl
2-(3-bromo-4-methoxyphenethyl)	3-methoxyphenyl
2-(2,4-dichlorophenethyl)	3-methoxyphenyl
2-(4-methoxyphenethyl)	3-benzodioxolanyl
2-(4-methoxyphenethyl)	2,3-dimethyl-4-methoxyphenyl
2-(4-methoxyphenethyl)	B-naphthyl
2-(4-methoxyphenethyl)	2-thiophenyl
2-(4-methoxyphenethyl)	3-quinolinyl
2-(4-methoxyphenethyl)	phenyl
2-(4-methoxyphenethyl)	cyclohexyl
2-(4-methoxyphenethyl)	benzyl
2-(4-methoxyphenethyl)	3,5-dimethoxyphenyl
3-phenpropyl	4-dimethylaminophenyl
4-methoxybenzyl	3-methoxyphenyl
3-phenpropyl	4-ethylphenyl
4-phenbutyl	2-methoxyphenyl
n-hexyl	4-dimethylaminophenyl
4-methoxybenzyl	2-chlorophenyl
2-(4-methoxyphenethyl)	3-methoxyphenyl
2-(4-methoxyphenethyl)	4-ethylphenyl
2-(4-chlorophenethyl)	4-ethylphenyl
2-(4-methoxyphenethyl)	3-methyl-4-methoxyphenyl
2-(4-methoxyphenethyl)	4-benzodioxanyl
2-(4-bromophenethyl)	4-methoxyphenyl
2-(4-ethylphenethyl)	3-methylphenyl
2-(4-ethoxyphenethyl)	4-benzodioxolanyl
2-phenethyl	3-methyl-4-methoxyphenyl

R ⁴	Y-R ³
4-methoxybenzyl	3-methyl-4-methoxyphenyl
2-phenoxyethyl	phenyl
2-(4-methoxyphenethyl)	3,4-dimethylphenyl
2-(4-methoxyphenoxyethyl)	3,4-dimethylphenyl
2-(3-methoxyphenethyl)	4-benzodioxanyl
2-(3-methoxyphenethyl)	2,4-dichlorophenyl
n-pentyl	3-methoxyphenyl
benzyl	3,4-dimethylphenyl
2-(3-methoxyphenethyl)	4-benzodioxanyl
2-(3-methoxyphenethyl)	4-benzodioxolanyl
4-phenbutyl	3,4-dimethylphenyl
2-(3-methoxyphenethyl)	3,4-dichlorophenyl
2-(3-methoxyphenethyl)	3-methylphenyl
2-(3-methoxyphenethyl)	3-bromo-4-methoxyphenyl
2-(3-methoxyphenethyl)	β-naphthyl
2-(4-nitrophenethyl)	3,4-dimethylphenyl
2-(3-methoxyphenethyl)	2,3-dimethyl-4-methoxyphenyl
2-(4-methoxyphenethyl)	5-ethyl-2-thiophenyl
2-(3-methoxyphenethyl)	3-benzodioxolanyl
2-phenoxyethyl	4-benzodioxolanyl
2-phenoxyethyl	3,4-dimethylphenyl
2-phenoxyethyl	4-ethylphenyl
2-(4-methylphenethyl)	4-benzodioxolanyl
2-(4-methylphenethyl)	3,4-dimethylphenyl
2-(4-methylphenethyl)	4-ethylphenyl
2-phenoxyethyl	5-ethyl-2-thiophenyl
2-phenoxyethyl	5-methyl-2-thiophenyl
n-hexyl	3-methoxyphenyl

R^4	$Y-R^3$
	3,4-dimethylphenyl
	4-benzodioxolanyl
	3-methoxyphenyl
	3,4-dimethylphenyl
	3,4-dimethylphenyl
	4-ethylphenyl
	4-benzodioxolanyl
	3-methyl-4-methoxyphenyl
2-(3-methoxyphenethyl)	2,4-dichlorophenyl

Preferably, in the compound of formula (II), Z, R^1 , R^2 , R^3 and Y are as defined above for the formula (I) and R^4 is $-C_1-X_1-Ar_1'$ or $-C_2-X_2'-C_3$, or an unsubstituted C_1-C_4 alkyl group, wherein C_1 , X_1 , C_2 and C_3 are as defined above; and:

Ar₁' is heteroaryl, heterocyclyl, aryl, heteroaryl-R^a- or heterocyclyl-R^a-, wherein R^a is a C₁-C₆ alkylene group, a C₂-C₆ alkenylene group or a C₂-C₆ alkynylene group; wherein when Ar₁' is an unsubstituted phenyl group or a phenyl group substituted with one or two groups selected from methyl, ethyl, methoxy, ethoxy, phenoxy, chlorine, bromine and nitro, either both C₁ and X₁ are direct bonds or C₁ is methylene and X₁ is -O-, -S-, -NR'-, -SO-, -SO₂-, -CO-S-, -CO-O-, -CO-NR'-, -S-CO-, -O-CO-, -NR'-CO-, -CO-O-R''-CO-O-, -CO-NR'-R''-CO-O-, -CO-O-R''-CO-NR'-, -CO-NR'-R''-CO-NR'-, -O-CO-NR'- or -NR'-CO-O-, wherein each R' is the same or different and represents hydrogen, phenyl, C₁-C₆ alkyl, C₂-C₆ alkenyl or C₂-C₆ alkynyl and each R'' is the same or different and represents a C₁-C₆ alkylene group, a C₂-C₆ alkenylene group or a C₂-C₆ alkynylene group, provided that when X₁ is -O-, Ar₁' is other than phenyl; and

X₂' is -O-, -S-, -SO-, -SO₂-, -CO-, -CO-S-, -CO-O-, -CO-NR'-, -S-CO-, -O-CO-, -NR'-CO-, -CO-O-R''-CO-O-, -CO-NR'-R''-CO-O-, -CO-O-R''-CO-NR'-, -CO-NR'-R''-CO-NR'-, -NR'-CO-O- or -O-CO-NR'-, wherein each R' is the same or different and represents hydrogen, phenyl, C₁-C₆ alkyl, C₂-C₆ alkenyl or C₂-C₆ alkynyl and each R'' is the same or different and represents a C₁-C₆ alkylene group, a C₂-C₆ alkenylene group or a C₂-C₆ alkynylene group, provided that when X₂' is -O- and C₂ is an unsubstituted alkylene group, C₃ is other than an unsubstituted alkyl group;

provided that -YR₃ is other than an unsubstituted pyridyl group or -phenyl-O-A₂-R, wherein A₂ and R are as defined above, and R² is other than C₁-C₆ alkyl.

Typically, R⁴ in the compounds of formula (II) is -C₁-X₁-Ar₁' or -C₂-X₂'-C₃.

Typically, C₁ and X₁ in the compounds of formula (II) are as defined above with regard to formula (I), formula (IA) or formula (IB), with the proviso that when Ar₁' is an unsubstituted phenyl group or a phenyl group substituted with one or two groups selected from methyl, ethyl, methoxy, ethoxy, phenoxy, chlorine, bromine and nitro, either both C₁ and X₁ are direct bonds or C₁ is methylene and X₁ is -S-, -NR'-, -SO-, -SO₂-, -CO-S-, -CO-O-, -CO-NR'-, -S-CO-, -O-CO-, -NR'-CO-, -CO-O-R''-CO-O-, -CO-NR'-R''-CO-O-, -CO-O-R''-CO-NR'-, -CO-NR'-R''-CO-NR'-, -O-CO-NR'- or

-NR'-CO-O-, wherein R' and R'' are as defined above with regard to formula (I) or formula (IA). Preferably, when Ar₁' is an unsubstituted phenyl group or any substituted phenyl group which does not have at least one substituent selected from fluorine, -N(C₁-C₆ alkyl)₂, -NH-CO-(C₁-C₆ alkyl) and hydroxy, either both C₁ and X₁ are direct bonds or C₁ is methylene and X₁ is -S-, -NR'-, -SO-, -SO₂-, -CO-S-, -CO-O-, -CO-NR'-, -S-CO-, -O-CO-, -NR'-CO-, -CO-O-R''-CO-O-, -CO-NR'-R''-CO-O-, -CO-O-R''-CO-NR'-, -CO-NR'-R''-CO-NR'-, -O-CO-NR'- or -NR'-CO-O-, wherein R' and R'' are as defined above. More preferably, when Ar₁' is an unsubstituted or substituted phenyl group, either both C₁ and X₁ are direct bonds or C₁ is methylene and X₁ is -S-, -NR'-, -SO-, -SO₂-, -CO-S-, -CO-O-, -CO-NR'-, -S-CO-, -O-CO-, -NR'-CO-, -CO-O-R''-CO-O-, -CO-NR'-R''-CO-O-, -CO-O-R''-CO-NR'-, -CO-NR'-R''-CO-NR'-, -O-CO-NR'- or -NR'-CO-O-, wherein R' and R'' are as defined above.

Typically, in the compounds of formula (II), X₁ is -O-, -S-, -NR'-, -S-CO-, -O-CO-, -CO-O-, -CO-S-, -NR'-CO- or -CO-NR'-, wherein R' is as defined above. Preferably, X₁ is -O-, -S-, -S-CO-, -O-CO- or -NH-CO-. More preferably, X₁ is -O-, -S-, -S-CO- or -O-CO-. More preferably, X₁ is -S-, -S-CO- or -O-CO-.

Typically Ar₁' in the formula (II) above is heteroaryl, heterocyclyl, aryl, heteroaryl-(C₁-C₆ alkyl)- or heterocyclyl-(C₁-C₆ alkyl)-. When Ar₁' is a heteroaryl-(C₁-C₆ alkyl)- or heterocyclyl-(C₁-C₆ alkyl)- group, the alkyl moiety is typically an unsubstituted methylene or ethylene moiety. Preferably, Ar₁' is heteroaryl, heterocyclyl, aryl or heteroaryl-(C₁-C₂ alkyl)-. Preferably, when Ar₁' is aryl, it is a phenyl group fused to a 5- or 6-membered heterocyclyl ring, for example a 1,3-benzodioxolyl group or a 1,4-benzodioxanyl group. More preferably, when Ar₁' is aryl it is a 1,3-benzodioxolyl group. When Ar₁' is heteroaryl, heterocyclyl or heteroaryl-(C₁-C₂ alkyl)-, it preferably has the same meanings as the corresponding groups of Ar₁ as defined above. More preferably, Ar₁' is pyridyl, thienyl, benzimidazolyl, furanyl-methyl-, 1,4-benzodioxanyl or 1,3-benzodioxolyl.

Typically, the group Ar₁' in the formula (II) is unsubstituted or carries one or more, for example 1, 2 or 3, substituents on the cyclic group. The substituents are typically selected from halogen, for example fluorine or chlorine, C₁-C₄ alkyl, hydroxy, C₁-C₄ alkoxy, -NR'R'' and -NH-CO-R' wherein R' and R'' are selected from hydrogen

and unsubstituted C₁-C₄ alkyl. Preferred substituents are fluorine, hydroxy, methoxy, dimethylamino and -NH-CO-CH₃. More preferred substituents are fluorine, hydroxy, -N(CH₃)₂ and -NH-CO-CH₃. More preferred substituents are -N(CH₃)₂ and -NH-CO-CH₃. Typically, the substituents on a group Ar₁' are themselves unsubstituted.

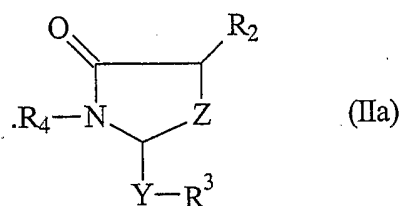
Typically, each R' in the moiety X₂' in the formula (II) above is the same or different and is hydrogen or an unsubstituted phenyl or C₁-C₆ alkyl group, preferably hydrogen, -CH₃ or -CH₂CH₃. More preferably, each R' in the moiety X₂' is hydrogen. Typically, each R'' in the moiety X₂' is an unsubstituted C₁-C₆ alkylene group, preferably -CH₂- or -CH₂-CH₂-. More preferably, each R'' is -CH₂-.

Typically, X₂' in the formula (II) above is -O-, -S-, -CO-, -CO-S-, -CO-O-, -CO-NR'-, -S-CO-, -O-CO-, -NR'-CO-, -O-CO-NR'-, -NR'-CO-O-, -S-CO- or -CO-S- wherein R' is as defined above with regard to formula (I), formula (IA) or formula (IB). Preferably, X₂' is -O-, -S-, -CO-O-, -O-CO-, -S-CO-, -CO-S- or -NH-CO-O-. Most preferably, X₂' is -O-, -S-, -CO-O- or -NH-CO-O-, for example -S-, -CO-O- or -NH-CO-O-.

When R₄ in the formula (II) above represents a C₁-C₄ alkyl group, it may be straight or branched, unsubstituted or substituted. Typically it is unsubstituted or substituted by 1, 2 or 3 substituents. Suitable substituents are those set out above as examples of suitable substituents on an alkyl group. Preferred substituents include halogen, in particular fluorine, and hydroxy. Typically, substituents on the C₁-C₄ alkyl group are themselves unsubstituted.

Typically, Y in the formula (II) above is as defined above with regard to formula (I), formula (IA) or formula (IB). Preferably, Y is a group of formula -(CR^Y)₂-, -(CH₂)_m-O-(CH₂)-, -A- or -A-X₃-(CH₂)_m wherein R^Y, m, A and X₃ are as defined above with regard to formula (I), formula (IA) or formula (IB) with the proviso that A is other than phenyl.

Examples of the most preferred compounds of formula (II) are those of formula (IIa)



wherein:

Z is -S-, -S(O)- or -S(O)₂-;

Y is a direct bond or a group of formula -(CR^y)₂-, -(CH₂)_mO(CH₂)-, -A- or -A-X₃-(CH₂)_m, wherein R^y is hydrogen, -CH₃, -CH₂-CH₃ or an unsubstituted phenyl group, wherein no more than one R^y group is phenyl; A is a phenyl, pyridyl or pyrrolyl group, which is unsubstituted or substituted with 1, 2 or 3 substituents selected from -CH₃, -CH₂-CH₃, -OCH₃, -OCH₂-CH₃, halogen and hydroxy; X₃ is -O-, -SO₂- or -NH-CO-; and m is 0 or 1;

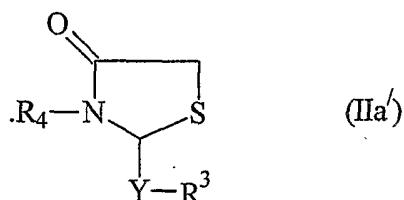
R₂ is hydrogen, -(CH₂)_a-CO₂H or -(CH₂)_b-CONR₅R₆ wherein a and b are 1 or 2 and either (a) R₅ is hydrogen or an unsubstituted benzyl group and R₆ is -L-R wherein L is a direct bond or an unsubstituted C₁-C₄ alkylene group and R is hydrogen or a phenyl, cyclohexenyl, piperidyl, pyridyl or benzimidazolyl group which is unsubstituted or substituted by a halogen, hydroxy, -OCH₃ or -OCH₂CH₃ substituent, or (b) R₅ and R₆, together with the N atom to which they are attached, represent a pyrrolidinyl, piperidinyl, homopiperidinyl or piperazinyl group which is unsubstituted or substituted by an unsubstituted -CHPh₂ group;

R₄ is -CH₃, -C₁-X₁-Ar₁' or -C₂-X₂'-C₃, wherein:

- C₁ is -(CH₂)-, -(CH₂)₂- or -(CH₂)₃-;
- X₁ is a direct bond or is -O-, -S-, -S-CO- or -O-CO-;
- Ar₁' is a pyridyl, thienyl, benzimidazolyl, furanyl-methyl-, 1,3-benzodioxolyl or 1,4-benzodioxanyl group which is unsubstituted or carries, on the cyclic moiety, 1, 2 or 3 substituents selected from fluorine, hydroxy, -OCH₃, -N(CH₃)₂ and -NH-CO-CH₃;
- C₂ is a straight chain unsubstituted C₁-C₄ alkylene group;
- X₂' is -O-, -S-, -CO-O- or -NH-CO-O-; and

- C₃ is a C₁-C₄ alkyl group which is unsubstituted or substituted on a primary carbon atom with either (a) one hydroxy or (b) 1, 2 or 3 halo substituents, provided that Y-R₃ is other than an unsubstituted pyridyl group, and when X₂' is -O-, C₃ is other than an unsubstituted C₁-C₄ alkyl group.

More preferably, the compound of formula (IIa) is a compound of formula (IIa')



wherein:

Y is a direct bond or a group of formula $-(CR^y)_2-$, $-(CH_2)_mO(CH_2)-$, -A- or $-A-X_3-(CH_2)_m$, wherein R^y is hydrogen, -CH₃, -CH₂-CH₃ or an unsubstituted phenyl group, wherein no more than one R^y group is phenyl; A is a phenyl, pyridyl or pyrrolyl group, which is unsubstituted or substituted with 1, 2 or 3 substituents selected from -CH₃, -CH₂-CH₃, -OCH₃, -OCH₂-CH₃, halogen and hydroxy; X₃ is -O-, -SO₂- or -NH-CO-; and m is 0 or 1;

R³ is hydrogen or a phenyl, thienyl, furyl, quinoliny, benzofuranyl, cyclopentyl, 1,4-benzodioxanyl, 1,3-benzodioxolyl or 2,3-dihydrobenzofuran group which is unsubstituted or substituted with 1, 2 or 3 substituents selected from halogen, C₁-C₄ alkyl, C₁-C₄ alkoxy, C₁-C₄ alkylthio, C₂-C₄ alkenyloxy, C₃-C₆ carbocyclyloxy, -NH-CO-Me and -N(CH₃)₂, the substituents on R³ being themselves unsubstituted or further substituted with 1, 2 or 3 further substituents selected from halogen and hydroxy;

R₄ is -C₁-X₁-Ar₁' or -C₂-X₂'-C₃, wherein:

- C₁ is $-(CH_2)-$, $-(CH_2)_2-$ or $-(CH_2)_3-$;
- X₁ is a direct bond or is -O-, -S-, -S-CO- or -O-CO-;
- Ar₁' is a pyridyl, thienyl, benzimidazolyl, furanyl-methyl-, 1,3-benzodioxolyl or 1,4-benzodioxanyl group which is unsubstituted or carries, on the cyclic moiety, 1, 2 or 3 substituents selected from fluorine, hydroxy, -OCH₃, -N(CH₃)₂ and -NH-CO-CH₃;
- C₂ is a straight chain unsubstituted C₁-C₄ alkylene group;

- X_2' is -O-, -S-, -CO-O- or -NH-CO-O-; and
 - C_3 is a C_1 - C_4 alkyl group which is unsubstituted or substituted on a primary carbon atom with either (a) one hydroxy or (b) 1, 2 or 3 halo substituents; and pharmaceutically acceptable salts thereof,
- provided that -Y- R_3 is other than an unsubstituted pyridyl group, and when X_2' is -O-, C_3 is other than an unsubstituted C_1 - C_4 alkyl group.

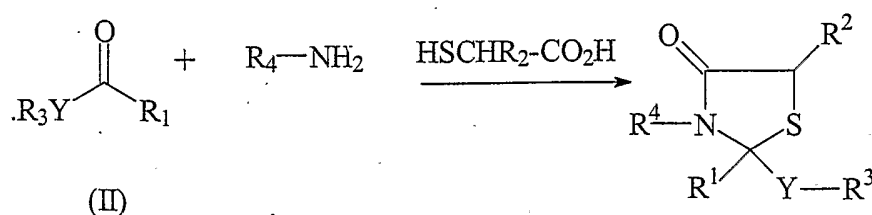
The present invention also provides a pharmaceutical composition comprising a compound of formula (I'), as defined above, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier or diluent.

For the avoidance of doubt, the said pharmaceutically acceptable carrier or diluent is not DMSO.

Said pharmaceutical composition typically contains up to 85 wt% of a compound of the invention. More typically, it contains up to 50 wt% of a compound of the invention. Preferred pharmaceutical compositions are sterile and pyrogen free. Further, the pharmaceutical compositions provided by the invention typically contain a compound of the invention which is a substantially pure optical isomer.

The compounds of formula (I) may be prepared by conventional routes, for example those set out in any of schemes 1 to 4 shown below.

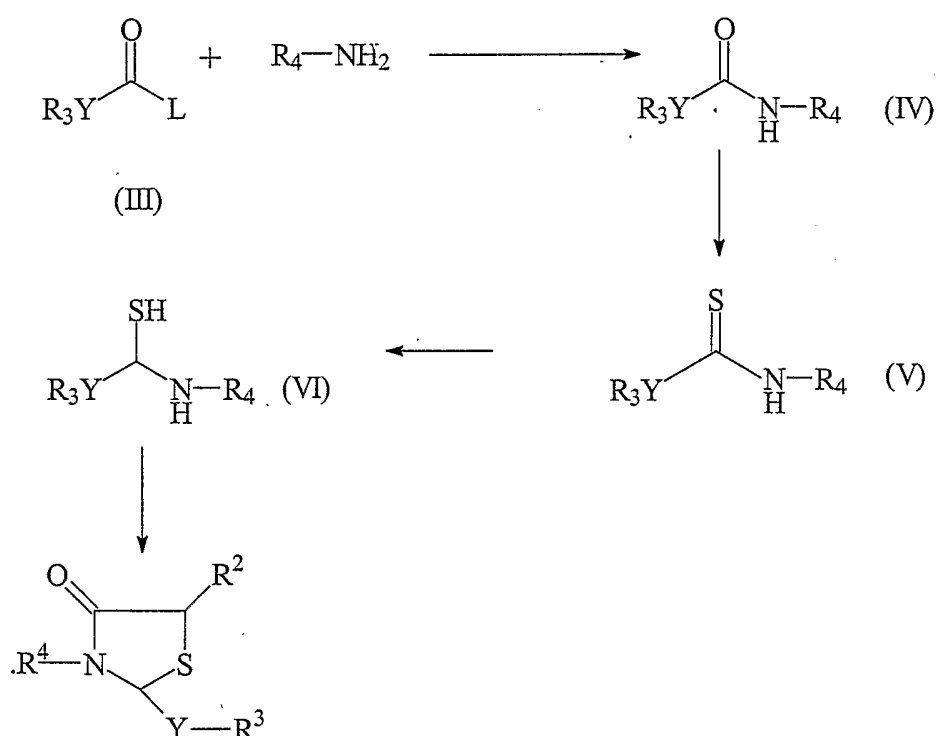
Scheme 1



In scheme (I), an aldehyde or ketone of formula (II) is reacted with an amine of formula R_4-NH_2 in the presence of $H_2S-CHR_2-CO_2H$. Typically, the reaction takes place in a solvent such as benzene or toluene at elevated temperature, for example from 80 to 100°C. A compound of formula (I) in which Z is S can be thereby prepared.

The reaction shown in scheme I can be conducted as a "one pot" reaction, or can be conducted stepwise, whereby a compound of formula (II) is reacted with an amine of formula R_4-NH_2 and the thus obtained imino intermediate is then reacted with $HSCHR_2-CO_2H$. Typically, when stepwise reaction is effected, both reaction steps take place in a solvent such as benzene or toluene at elevated temperature, for example from 80 to 100°C.

Scheme 2



Scheme 2 provides an alternate synthesis of compounds of formula (I) in which Z is S and R_1 is hydrogen. In this scheme, a compound of formula (III), in which L is a leaving group, for example a chlorine atom, is reacted with an amine of formula R_4-NH_2 under standard amide coupling reaction conditions which will be familiar to those of skill in the art. Typically, the reaction is effected in the presence of a coupling agent such as EDCI/HOBT, HATU or HBTU.

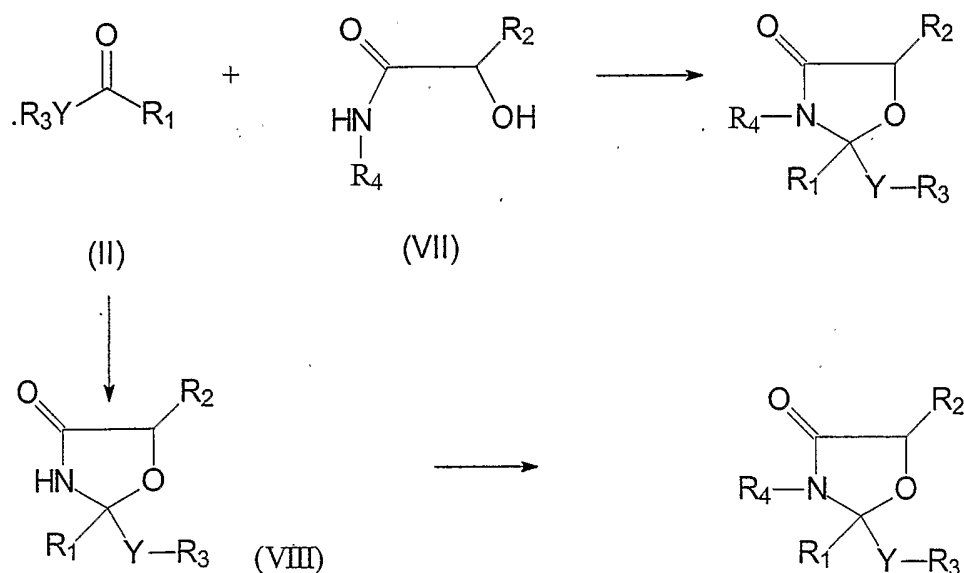
The thus obtained amide of formula (IV) can then be reacted with Lawesson's reagent under standard reaction conditions to give a compound of formula (V). The

compound of formula (V) can then be reduced by known methods to a compound of formula (VI). The compound of formula (VI) can then be reacted with $\text{ClCO-CH(R}_2\text{)Br}$, in which R_2 is as defined above, to give a compound of formula (I) in which R_1 is hydrogen and Z is S . This final reaction typically takes place in a solvent such as benzene or toluene.

Compounds of formula (I) in which Z is -S(O)- or $\text{-S(O)}_2\text{-}$ can be prepared by oxidising a corresponding compound in which Z is S . Thus, a compound of formula (I) in which Z is -S(O)- can, for example, be prepared by reacting a corresponding compound in which Z is -S- with mcpba , in a solvent such as CH_2Cl_2 at around 0°C , or with NaIO_4 in a mixture of H_2O , MeOH and dioxane.

Similarly, a compound of formula (I) in which Z is $\text{-S(O)}_2\text{-}$ can be prepared from a corresponding compound in which Z is -S- or -S(O)- by (a) reaction with hydrogen peroxide in aqueous acetic acid, (b) reaction with mcpba in CH_2Cl_2 at around 0°C , (c) reaction with NaHSO_5 in water or (d) reaction with KMnO_4 in water. All of these oxidation techniques will, of course, be familiar to those of skill in the art.

Scheme 3

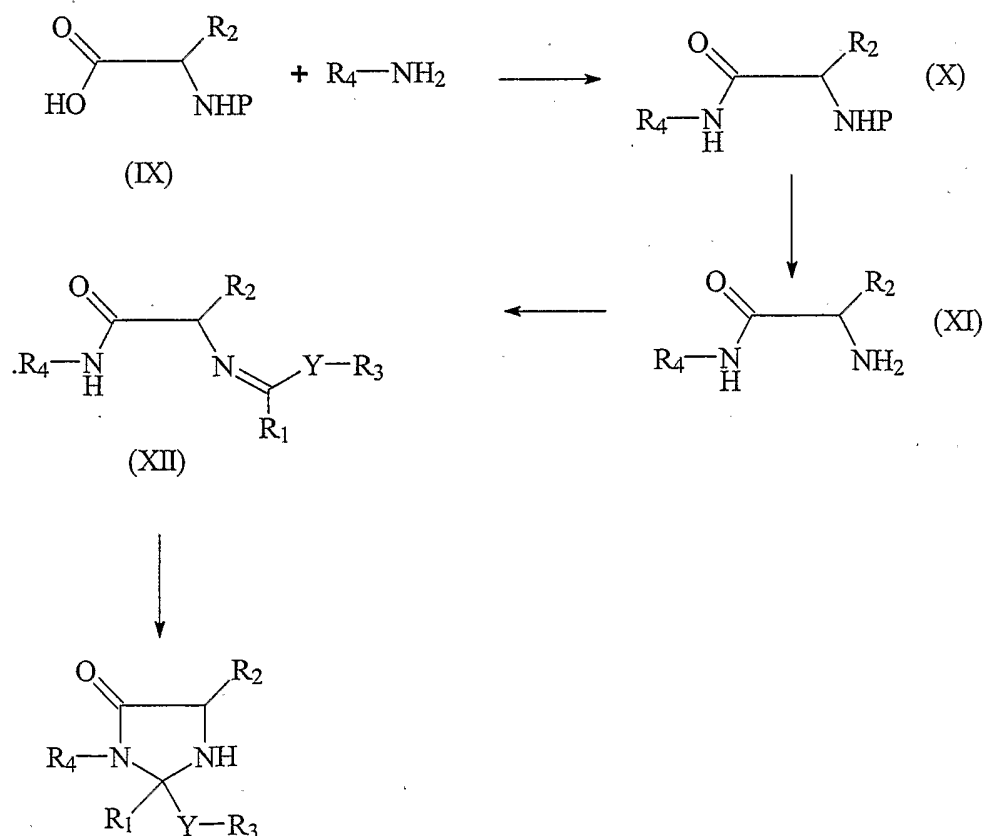


Scheme 3 provides a process for preparing compounds of formula (I) in which Z is O . In this scheme, a compound of formula (II) can be reacted with a compound of

formula (VII) under standard reaction conditions, such as those set out in Giraud *et al*, J. Org. Chem., 1998, 63, 9162-9163. The compound of formula (VII) can, if necessary, be prepared by reacting an amine of formula R_4-NH_2 with a compound $L-CO-CH(R_2)OH$, wherein L is a leaving group such as OH, under standard amide coupling reaction conditions using coupling agents such as EDCI/HOBT, HATU or HBTU which will be familiar to those of skill in the art.

A compound of formula (II) can also be reacted with $H_2N-CO-CH(R_2)OH$ under standard reaction conditions such as those set out in Giraud *et al*, to yield a compound of formula (VIII). A compound of formula (I) in which R_1 is O can then be prepared from the thus obtained intermediate of formula (VIII) by standard methods. For example, it can be prepared by reacting a compound of formula (VIII) with a compound of formula R_4-L , wherein L is a leaving group such as a chlorine atom, in the presence of a base such as NaH in a solvent such as THF at around room temperature.

Scheme 4



Scheme 4 provides a process for the preparation of compounds of the invention in which Z is -NH-. Reaction conditions for the steps set out in scheme 4 can be found, for example, in Frutos et al, Tet. Assymetry, 2001, 12, 101-104.

In Scheme 4, a compound of formula (IX), in which P represents an amino protecting group, is reacted with an amine of formula R_4-NH_2 , typically in a solvent such as THF or DMF, in the presence of a coupling agent such as EDCI/HOBT, at around 0 to 40°C. Typically, P is a Boc protecting group or a Z (benzyloxycarbonyl) protecting group.

The thus obtained compound of formula (X) can then be deprotected using standard techniques. When P is Boc, deprotection is typically effected by reaction with trifluoroacetic acid (TFA) in dichloromethane. When P is Z, deprotection is typically effected by reaction with hydrogen in the presence of a catalyst, for example 5% palladium on carbon. The thus obtained compound of formula (XI) can then be reacted with a compound of formula (II), as defined above, under standard conditions such as those set out in Frutos et al. Typically, this reaction takes place in a solvent such as CH_2Cl_2 .

Cyclisation of the thus obtained compound of formula (XII) can be effected, for example, in the presence of AcCl and MeOH to yield a compound of formula (I) in which Z is -NH-.

Compounds of formula (I) in which Z is -NR- can, of course, be prepared by reacting a corresponding compound in which Z is -NH- with a group L-R, wherein L is a leaving group, for example a halogen atom, in the presence of a coupling agent such as EDCI/HOBT, at around 0 to 40%.

Further synthetic manipulation of the compounds of formula (I), such as bromination, nitration and acylation may be carried out by conventional methods to achieve further compounds of formula (I). For example, compounds of formula (I) in which R_2 is fluorine can be prepared from corresponding compounds in which R_2 is hydrogen by reaction with $Et_3N \cdot 3HF$ in CH_3CN . Further, compounds in which R_2 is -(C₁-C₆ alkyl)-CO-NR₅R₆ can, of course, be prepared by reacting a corresponding compound in which R_2 is -(C₁-C₆ alkyl)-CO-L, wherein L is a leaving group such as a chlorine atom, with an amine HNR₅R₆.

The thus obtained compounds of formula (I) may be salified by treatment with an appropriate acid or base. Racemic mixtures obtained by any of the above processes can be resolved by standard techniques, for example elution on a chiral chromatography column.

Compounds of formulae (II), (III), (VII), (IX), $\text{HSCHR}_2\text{-CO}_2\text{H}$, $\text{Cl-CO-CH(R}_2\text{)Br}$, $\text{L-CO-CH(R}_2\text{)OH}$ and $\text{H}_2\text{N-CO-CH(R}_2\text{)OH}$ and the amines of formula $\text{R}_4\text{-NH}_2$, are known compounds, or may be prepared by analogy with known methods.

The compound of formula (I') can, of course, be prepared in the same way as the compounds of formula (I).

The compounds of the invention are found to be inhibitors of N-type calcium channels. Further, many preferred compounds of the invention exhibit selectivity over L-type calcium channels. The compounds of the invention are therefore therapeutically useful.

The compounds of the invention may be administered in a variety of dosage forms. Thus, they can be administered orally, for example as tablets, troches, lozenges, aqueous or oily suspensions, dispersible powders or granules. Preferred pharmaceutical compositions of the invention are compositions suitable for oral administration, for example tablets and capsules.

The compounds of the invention may also be administered parenterally, whether subcutaneously, intravenously, intramuscularly, intrasternally, transdermally or by infusion techniques. The compounds may also be administered as suppositories.

One preferred route of administration is inhalation. The major advantages of inhaled medications are their direct delivery to the area of rich blood supply in comparison to many medications taken by oral route. Thus, the absorption is very rapid as the alveoli have an enormous surface area and rich blood supply and first pass metabolism is bypassed.

Preferred pharmaceutical compositions of the invention therefore include those suitable for inhalation. The present invention also provides an inhalation device containing such a pharmaceutical composition. Typically said device is a metered dose inhaler (MDI), which contains a pharmaceutically acceptable chemical propellant to push the medication out of the inhaler. Typically, said propellant is a fluorocarbon.

Further preferred inhalation devices include nebulizers. Nebulizers are devices capable of delivering fine liquid mists of medication through a "mask" that fits over the nose and mouth, using air or oxygen under pressure. They are frequently used to treat those with asthma who cannot use an inhaler, including infants, young children and acutely ill patients of all ages.

Said inhalation device can also be, for example, a rotary inhaler or a dry powder inhaler, capable of delivering a compound of the invention without a propellant.

Typically, said inhalation device contains a spacer. A spacer is a device which enables individuals to inhale a greater amount of medication directly into the lower airways, where it is intended to go, rather than into the throat. Many spacers fit on the end of an inhaler; for some, the canister of medication fits into the device. Spacers with withholding chambers and one-way valves prevent medication from escaping into the air. Many people, especially young children and the elderly, may have difficulties coordinating their inhalation with the action necessary to trigger a puff from a metered dose inhaler. For these patients, use of a spacer is particularly recommended.

Another preferred route of administration is intranasal administration. The nasal cavity's highly permeable tissue is very receptive to medication and absorbs it quickly and efficiently, more so than drugs in tablet form. Nasal drug delivery is less painful and invasive than injections, generating less anxiety among patients. Drugs can be delivered nasally in smaller doses than medication delivered in tablet form. By this method absorption is very rapid and first pass metabolism is bypassed, thus reducing inter-patient variability. Nasal delivery devices further allow medication to be administered in precise, metered doses. Thus, the pharmaceutical compositions of the invention are typically suitable for intranasal administration. Further, the present invention also provides an intranasal device containing such a pharmaceutical composition.

A further preferred route of administration is transdermal administration. The present invention therefore also provides a transdermal patch containing a compound of the invention, or a pharmaceutically acceptable salt thereof. Also preferred is sublingual administration. The present invention therefore also provides a sub-lingual tablet comprising a compound of the invention or a pharmaceutically acceptable salt thereof.

A compound of the invention is typically formulated for administration with a pharmaceutically acceptable carrier or diluent. For example, solid oral forms may contain, together with the active compound, diluents, e.g. lactose, dextrose, saccharose, cellulose, corn starch or potato starch; lubricants, e.g. silica, talc, stearic acid, magnesium or calcium stearate, and/or polyethylene glycols; binding agents; e.g. starches, arabic gums, gelatin, methylcellulose, carboxymethylcellulose or polyvinyl pyrrolidone; disaggregating agents, e.g. starch, alginic acid, alginates or sodium starch glycolate; effervescing mixtures; dyestuffs; sweeteners; wetting agents, such as lecithin, polysorbates, laurylsulphates; and, in general, non toxic and pharmacologically inactive substances used in pharmaceutical formulations. Such pharmaceutical preparations may be manufactured in known manner, for example, by means of mixing, granulating, tableting, sugar coating, or film coating processes.

Liquid dispersions for oral administration may be syrups, emulsions and suspensions. The syrups may contain as carriers, for example, saccharose or saccharose with glycerine and/or mannitol and/or sorbitol.

Suspensions and emulsions may contain as carrier, for example a natural gum, agar, sodium alginate, pectin, methylcellulose, carboxymethylcellulose, or polyvinyl alcohol. The suspension or solutions for intramuscular injections may contain, together with the active compound, a pharmaceutically acceptable carrier, e.g. sterile water, olive oil, ethyl oleate, glycols, e.g. propylene glycol, and if desired, a suitable amount of lidocaine hydrochloride.

Solutions for injection or infusion may contain as carrier, for example, sterile water or preferably they may be in the form of sterile, aqueous, isotonic saline solutions.

The compounds of the present invention are therapeutically useful in the treatment or prevention of conditions mediated by N-type calcium channels. Accordingly, the present invention provides the use of a compound of the formula (I), or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for use in the treatment or prevention of a condition mediated by N-type calcium channels. Also provided is a method of treating a patient suffering from or susceptible to a condition mediated by N-type calcium channels, which method comprises administering to said patient an effective amount of a compound of formula (I), or a pharmaceutically acceptable salt thereof.

These compounds are useful as calcium channel antagonists thereby inhibiting in a subject the onset of a disorder whose alleviation is mediated by the reduction of calcium ion influx into cells whose actions contribute to the disorder.

N-type calcium channels are known to be closely involved in the mediation of pain transmission. Typically, the compounds of the invention are therefore used as analgesic agents. N-type calcium channels have been identified as being particularly important in the transmission of pain signals in the spinal cord (Chaplan S.R., Pogrel J.W., Yaksh T.L. *J. Pharm. Exp. Ther.*, 1994, 269, 1117-1123; Diaz, A., Dickenson, A.H. *Pain*, 1997, 69, 93-100). Indeed, a series of recent clinical studies has provided confirmation of the important role of N-type calcium channels in pain transmission (Mathur, V.S.; McGuire, D.; Bowersox, S.S.; Miljanich, G.P.; Luther, R.R. *Pharmaceutical News*, 1998, 5, 25-29). The compounds of the invention are accordingly particularly effective in alleviating pain. Typically, therefore, said medicament is for use in alleviating pain and said patient is suffering from or susceptible to pain. The compounds of the invention are effective in alleviating both chronic and acute pain.

Acute pain is generally understood to be a constellation of unpleasant sensory, perceptual and emotional experiences of certain associate autonomic (reflex) responses, and of psychological and behavioural reactions provoked by injury or disease. A discussion of acute pain can be found at Halpern (1984) *Advances in Pain Research and Therapy*, Vol.7, p.147. Tissue injury provokes a series of noxious stimuli which are transduced by nociceptors to impulses transmitted to the spinal cord and then to the upper part of the nervous system. Examples of acute pains which can be alleviated with the compounds of the invention include musculoskeletal pain, for example joint pain, lower back pain and neck pain, dental pain, post-operative pain, obstetric pain, for example labour pain, acute headache, neuralgia, myalgia, and visceral pain.

Chronic pain is generally understood to be pain that persists beyond the usual course of an acute disease or beyond a reasonable time for an injury to heal. A discussion of chronic pain can be found in the Halpern reference given above. Chronic pain is sometimes a result of persistent dysfunction of the nociceptive pain system. Examples of chronic pains which can be alleviated with the compounds of the invention include trigeminal neuralgia, post-herpetic neuralgia (a form of chronic pain

accompanied by skin changes in a dermatomal distribution following damage by acute Herpes Zoster disease), diabetic neuropathy, causalgia, "phantom limb" pain, pain associated with osteoarthritis, pain associated with rheumatoid arthritis, pain associated with cancer, pain associated with HIV, neuropathic pain, migraine and other conditions associated with chronic cephalic pain, primary and secondary hyperalgesia, inflammatory pain, nociceptive pain, tabes dorsalis, spinal cord injury pain, central pain, post-herpetic pain, noncardiac chest pain, irritable bowel syndrome and pain associated with bowel disorders and dyspepsia.

Some of the chronic pains set out above, for example, trigeminal neuralgia, diabetic neuropathic pain, causalgia, phantom limb pain and central post-stroke pain, have also been classified as neurogenic pain. One non-limiting definition of neurogenic pain is pain caused by dysfunction of the peripheral or central nervous system in the absence of nociceptor stimulation by trauma or disease. The compounds of the invention can, of course, be used to alleviate or reduce the incidence of neurogenic pain.

Since blockers of N-type calcium channels inhibit the release of excitatory amino acids, they can be used *inter alia* to inhibit damage to neuronal cells during anoxia, and function as neuroprotective agents, useful in the treatment of cerebral ischaemia or central nervous system injuries (Cox, B.; Denyer, J.C. *Expert Opinion on Therapeutic Patents*, 1998, 8, 1237-1250). The compounds can also be utilised for the treatment of eye diseases (Chu, T-C; Potter, D.E. *Research Communications in Pharmacology and Toxicology*, 2001, 6, 263-275).

Examples of cerebral ischaemias which can be treated or prevented with the compounds of the invention include transient ischaemic attack, stroke, for example thrombotic stroke, ischaemic stroke, embolic stroke, haemorrhagic stroke or lacunar stroke, subarachnoid haemorrhage, cerebral vasospasm, peri-natal asphyxia, drowning, cardiac arrest and subdural haematoma.

Examples of central nervous system injuries which can be treated with the compounds of the invention include traumatic brain injury, neurosurgery (surgical trauma), neuroprotection for head injuries, raised intracranial pressure, cerebral oedema, hydrocephalus and spinal cord injury.

Examples of eye diseases which can be treated or prevented with the compounds of the invention include drug-induced optic neuritis, cataract, diabetic neuropathy,

ischaemic retinopathy, retinal haemorrhage, retinitis pigmentosa, acute glaucoma, in particular acute normal tension glaucoma, chronic glaucoma, in particular chronic normal tension glaucoma, macular degeneration, retinal artery occlusion and retinitis.

By virtue of their inhibition of neurotransmitter release the compounds of the invention can be used in the treatment of seizure disorders. Examples of seizure disorders which can be treated or prevented with the compounds of the invention include epilepsy and post-traumatic epilepsy, partial epilepsy (simple partial seizures, complex partial seizures, and partial seizures secondarily generalised seizures), generalised seizures, including generalised tonic/clonic seizures (grand mal), absence seizures (petit mal), myoclonic seizures, atonic seizures, clonic seizures, and tonic seizures, Lennox Gastaut, West Syndrome (infantile spasms), multiresistant seizures and seizure prophylaxis (antiepileptogenic).

Furthermore the compounds of the invention can be utilised in the treatment of tinnitus, itch such as pruritoceptive, neuropathic, neurogenic and psychogenic itch, as well as urinary tract disorders such as urinary incontinence, and irritable bowel syndrome.

The compounds of the invention may also have application in disorders which are generally associated with blocking of L-type calcium channels, such as cardiovascular, antiasthmatic and antibronchoconstriction disorders for example in the prevention and treatment of disorders such as hypersensitivity, allergy, asthma, bronchospasm, dysmenorrhea, esophageal spasm, premature labour, gastrointestinal motility disorders and cardiovascular disorders wherein the cardiovascular disorder is selected from the group consisting of hypertension, myocardial ischemia, angina, congestive heart failure, myocardial infarction and stroke.

The compounds of the invention may, where appropriate, be used prophylactically to reduce the incidence of such conditions.

A therapeutically effective amount of a compound of the invention is administered to a patient. A typical dose is from about 0.001 to 50 mg per kg of body weight, according to the activity of the specific compound, the age, weight and conditions of the subject to be treated, the type and severity of the disease and the frequency and route of administration. Preferably, daily dosage levels are from 5 mg to 2 g.

The following Examples illustrate the invention. They do not, however, limit the invention in any way. In this regard, it is important to understand that the particular assays used in the Examples section are designed only to provide an indication of activity in inhibiting N-type calcium channels. There are many assays available to determine the activity of given compounds as N-type calcium channel antagonists, and a negative result in any one particular assay is therefore not determinative.

EXAMPLES

Example 1 (compound 2)

3-(2-Pyridin-2-yl-ethyl)-2-[1-(toluene-4-sulfonyl)-1H-pyrrol-2-yl]-thiazolidin-4-one

1-(*p*-Toluenesulfonyl)pyrrole-2-carboxaldehyde (50 mg, 0.2 mmol) was dissolved in anhydrous THF (0.3 ml) in a deep well plate. 2-(2-Aminoethyl)pyridine (25 mg, 0.2 mmol, 1 equiv) was also dissolved in anhydrous THF (0.3 ml) and added to the aldehyde solution. Thioglycolic acid (0.05 ml, 0.72 mmol, 3.6 equiv) and triethyl orthoformate (0.125 ml, 0.75 mmol, 3.8 equiv) were added to the reaction well and the plate placed in a CEM MARS 5 microwave. After irradiating at 60°C for 30 minutes at 300 W, the solvent was removed in a Genevac. The residue was then dissolved in DCM (1 ml) and washed with 7% aqueous potassium carbonate solution (2 x 1 ml) followed by water (1 x 1 ml). The solvent was removed and the sample dried in a Genevac to constant mass to give the desired 3-(2-pyridin-2-yl-ethyl)-2-[1-(toluene-4-sulfonyl)-1H-pyrrol-2-yl]-thiazolidin-4-one (15 mg, 0.04 mmol, 20%; ES+ 428, DAD (254 nm) 98%).

Example 2 (compound 18)

2-(3-Bromo-4-fluoro-phenyl)-3-(2-pyridin-2-yl-ethyl)-thiazolidin-4-one

A stirring solution of 3-bromo-4-fluorobenzaldehyde (Lancaster, 13473) (100mg, 0.49mmol), 2-(2-aminoethyl)pyridine (Lancaster, 5627) (60mg, 0.49mmol) and mercaptoacetic acid (Aldrich, 47,534-3) (45mg, 0.49mmol) in benzene (3 ml) was heated to reflux for 17h. The reaction mixture was evaporated to dryness and the remaining oil was dissolved in ethyl acetate. The solution was washed with 2M NaOH (2 x) then brine, dried (MgSO₄) and evaporated to dryness to give a yellow oil. Purification by column chromatography gave the title compound as a yellow oil.

¹H NMR (400 MHz, CDCl₃) δ 2.90-3.15 (3H), 3.58-3.62 (1H), 3.72-3.76 (1H), 3.99-4.06 (1H), 5.42-5.43 (1H), 7.07-7.11 (1H), 7.13-7.17 (3H), 7.37-7.39 (1H), 7.59-7.63 (1H), 8.49-8.51 (1H);

Mass spectrum (ES+) m/z 383 (M + 2H).

Example 3 (compound 185)**2-(3-Bromo-4-fluoro-phenyl)-3-(2-pyridin-3-yl-ethyl)-thiazolidin-4-one**

The title compound was prepared using a procedure analogous to that described in Preparation Example 2 using 3-bromo-4-fluorobenzaldehyde, mercaptoacetic acid and 3-(2-aminoethyl)pyridine (Lancaster, 16311) in benzene.

HPLC retention time, 3.38 min (Solvent: MeCN/H₂O/0.05% NH₄OH, 5-95% gradient H₂O – 6 min. Column: Phenomenex 50 x 3.00 mm i.d., C18 reverse phase. Flow rate: 1.5 ml/min.)

Mass spectrum (ES+) m/z 383 (M + 2H).

Compounds 1, 3 to 17 and 19 to 184 were prepared by analogous methods.

Example 4**3-[(2,3-Dimethoxyphenyl)methyl]-2-(3-trifluoromethoxyphenyl)-4-thiazolidinone**

A stirring solution of 3-(trifluoromethoxy)benzaldehyde (Aldrich, 34,648-9) (1.05g, 5.5mmol), 2,3-dimethoxybenzylamine (Aldrich, 18,985-5) (0.92g, 5.5mmol) and mercaptoacetic acid (Aldrich, 47,534-3) (0.51g, 5.5mmol) in benzene (30 ml) was heated to reflux for 17 h. The reaction mixture was evaporated to dryness and the remaining oil was dissolved in EtOAc. The solution was washed with sat. aq. NaHCO₃ followed by 10% aq. HCl and brine, dried (MgSO₄). MgSO₄ was removed by filtration and the filtrate was evaporated to dryness to afford a yellow oil. Purification by column chromatography gave the title compound as a yellow oil (2.14g, 94%);

¹H NMR (400 MHz, CDCl₃) δ 3.63 (3H), 3.68-3.76 (2H), 3.83-3.87 (4H), 5.00-5.04 (1H), 5.48 (2H), 6.71-6.74 (1H), 6.85-6.87 (1H), 6.96-7.00 (1H), 7.08 (1H), 7.17-7.20 (2H), 7.38-7.42 (1H); Mass spectrum (ES+) m/z 414 (M + H).

Example 5**3-(5-Hydroxypentyl)-2-(3-trifluoromethoxyphenyl)-4-thiazolidinone**

The title compound was prepared according to the procedure described in Example 4 using 3-(trifluoromethoxy)benzaldehyde, mercaptoacetic acid and 5-amino-1-pentanol (Aldrich, 12,304-8) in benzene.

HPLC retention time, 3.41 min (Solvent: MeCN/H₂O/0.05% NH₄OH, 5-95% gradient H₂O – 6 min. Column: Phenomenex 50 x 3.00 mm i.d., C18 reverse phase. Flow rate: 1.5 ml/min.). Mass spectrum (ES+) m/z 350 (M + H).

Example 6

2-(3-Trifluoromethoxyphenyl)-3-(3,4,5-trimethoxybenzyl)-4-thiazolidinone

The title compound was prepared according to the procedure described in Example 4 using 3-(trifluoromethoxy)benzaldehyde, mercaptoacetic acid and 3,4,5-trimethoxybenzylamine (Aldrich, 33,893-1) in benzene.

HPLC retention time, min (Solvent: MeCN/H₂O/0.05% NH₄OH, 5-95% gradient H₂O – 6 min. Column: Phenomenex 50 x 3.00 mm i.d., C18 reverse phase. Flow rate: 1.5 ml/min.); Mass spectrum (ES+) m/z (M + H).

Example 7

3-(3,3-Diphenylpropyl)-2-(3-trifluoromethoxyphenyl)-4-thiazolidinone

The title compound was prepared according to the procedure described in Example 4 using 3-(trifluoromethoxy)benzaldehyde, mercaptoacetic acid and 3,3-diphenylpropylamine (Aldrich, 13,629-8) in benzene.

HPLC retention time, min (Solvent: MeCN/H₂O/0.05% NH₄OH, 5-95% gradient H₂O – 6 min. Column: Phenomenex 50 x 3.00 mm i.d., C18 reverse phase. Flow rate: 1.5 ml/min.). Mass spectrum (ES+) m/z (M + H).

Example 8

3-(2,2-Diphenylethyl)-2-(3-trifluoromethoxyphenyl)-4-thiazolidinone

The title compound was prepared according to the procedure described in Example 4 using 3-(trifluoromethoxy)benzaldehyde, mercaptoacetic acid and 2,2-diphenylethylamine (Aldrich, D20,670-9) in benzene.

HPLC retention time, 4.47 min (Solvent: MeCN/H₂O/0.05% NH₄OH, 5-95% gradient H₂O – 6 min. Column: Phenomenex 50 x 3.00 mm i.d., C18 reverse phase. Flow rate: 1.5 ml/min.) Mass spectrum (ES+) m/z 444 (M + H).

Example 9**3-(5-Hydroxy-4,4-dimethylpentyl)-2-(3-trifluoromethoxyphenyl)-4-thiazolidinone**

The title compound was prepared according to the procedure described in Example 4 using 3-(trifluoromethoxy)benzaldehyde, mercaptoacetic acid and 5-amino-2,2-dimethylpentanol (Frinton Laboratories) in benzene.

HPLC retention time, 5.82 min (Solvent: MeCN/H₂O/0.05% NH₄OH, 5-95% gradient H₂O – 10 min. Column: Phenomenex 50 x 3.00 mm i.d., C18 reverse phase. Flow rate: 1.5 ml/min). Mass spectrum (ES+) m/z 378 (M + H).

Example 10**3-Hexyl-2-(3-trifluoromethoxyphenyl)-4-thiazolidinone**

The title compound was prepared according to the procedure described previously using 3-(trifluoromethoxy)benzaldehyde, mercaptoacetic acid and hexylamine (Aldrich, 21,970-3) in benzene.

HPLC retention time, 7.17 min (Solvent: MeCN/H₂O/0.05% NH₄OH, 5-95% gradient H₂O – 10 min. Column: Phenomenex 50 x 3.00 mm i.d., C18 reverse phase. Flow rate: 1.5 ml/min.) Mass spectrum (ES+) m/z 348 (M + H).

Example 11**3-(3-Hydroxypropyl)-2-(3-trifluoromethoxyphenyl)-4-thiazolidinone**

The title compound was prepared according to the procedure described in Example 4 using 3-(trifluoromethoxy)benzaldehyde, mercaptoacetic acid and 3-amino-1-propanol (Lancaster, 8654) in benzene.

HPLC retention time, 4.77 min (Solvent: MeCN/H₂O/0.05% NH₄OH, 5-95% gradient H₂O – 10 min. Column: Phenomenex 50 x 3.00 mm i.d., C18 reverse phase. Flow rate: 1.5 ml/min.). Mass spectrum (ES+) m/z 322 (M + H).

Example 12**3-(2-Pyridin-3-ylethyl)-2-(3-trifluoromethoxyphenyl)-4-thiazolidinone**

A stirring solution of 3-(trifluoromethoxy)benzaldehyde (Aldrich, 34,648-9) (2.34g, 16.4mmol), 3-(2-aminoethyl)pyridine (Lancaster, 16311) (1.00g, 8.18 mmol) and mercaptoacetic acid (Aldrich, 47,534-3) (0.51g, 5.5 mmol) in benzene (30 ml) was

heated to reflux for 3h. The reaction mixture was evaporated to dryness and the remaining oil was dissolved in EtOAc. The solution was washed with sat. aq. NaHCO₃ (2 x) and brine, dried (MgSO₄) and evaporated to dryness to afford a yellow oil. Purification by column chromatography gave the title compound as a yellow oil (1.26g, 42%).

¹H NMR (400 MHz, CDCl₃) δ 2.68 (1H), 2.80-2.97 (2H), 3.67 (1H), 3.76-3.87 (2H), 5.40 (1H), 7.09 (1H), 7.16-7.23 (3H), 7.40-7.45 (2H), 8.34 (1H), 8.48 (1H);

Mass spectrum (ES+) m/z 369 (M + H).

Examples 13 to 23

The following compounds were prepared by processes analogous to those set out above.

EXAMPLE	COMPOUND
13	3-[2-(4-Hydroxy-3-methoxyphenyl)ethyl]-2-(3-trifluoromethoxyphenyl)-4-thiazolidinone
14	3-[2-(2-Pyridinyl)ethyl]-2-(3-trifluoromethoxyphenyl)-4-thiazolidinone
15	3-(3-Butoxypropyl)-2-(3-trifluoromethoxyphenyl)-4-thiazolidinone
16	3-[3-Methylsulphanyl propyl]-2-(3-trifluoromethoxyphenyl)-4-thiazolidinone
17	3-[2-(3,4-dimethoxyphenyl)ethyl]-2-[(3-trifluoromethoxyphenyl)]-4-thiazolidinone
18	3-[(2,4-Dimethoxyphenyl)methyl]-2-(3-trifluoromethoxyphenyl)-4-thiazolidinone
19	3-[(2-Ethylsulphanyl)ethyl]-2-(3-trifluoromethoxyphenyl)-4-thiazolidinone
20	3-[(2-Fluorophenyl)methyl]-2-(3-trifluoromethoxyphenyl)-4-thiazolidinone
21	3-[(2,3-Difluorophenyl)methyl]-2-(3-trifluoromethoxyphenyl)-4-thiazolidinone
22	3-[2-(4-Methoxyphenoxy)ethyl]-2-(3-trifluoromethoxyphenyl)-4-thiazolidinone
23	3-[(3-Fluorophenyl)methyl]-2-(3-trifluoromethoxyphenyl)-4-thiazolidinone
24	2-(3-Trifluoromethoxyphenyl)-3-[(3,4,5-trimethoxyphenyl)methyl]-4-thiazolidinone
25	3-(3,3-Diphenylpropyl)-2-(3-trifluoromethoxyphenyl)-4-thiazolidinone
26	3-(2,2-Diphenylethyl)-2-(3-trifluoromethoxyphenyl)-4-thiazolidinone

27	3-Hexyl-2-(3-trifluoromethoxyphenyl)-4-thiazolidinone
28	3-(3-Hydroxypropyl)-2-(3-trifluoromethoxyphenyl)-4-thiazolidinone
29	5-Methyl-3-[2-(3-pyridinyl)ethyl]-2-(3-trifluoromethoxyphenyl)-4-thiazolidinone
30	3-(3-methoxyphenyl)-2-(3-trifluoromethoxyphenyl)-4-thiazolidinone

Activity Example 1

N-type calcium channel inhibition in IMR32 cells

The human neuroblastoma cell line IMR32 has been used by a number of groups to investigate calcium ion channels either by electrophysiological or fluorescent techniques in low throughput assays (Carbone, E., *et al.* (1990) *Pflügers Arch* 416:170-179; Rafferty, M., *et al.* (2000) Patent WO 00/06559; Seko, T., *et al.*, (2001) *Bioorg Med Chem Lett* 11:2067-2070).

It has been shown that undifferentiated IMR32 cells constitutively express L-type calcium channels, whilst differentiated IMR32 cells express both N- and L-type channels. Therefore, undifferentiated IMR32 cells can be used to assay the L-type calcium channel and differentiated cells assayed in the presence of 5 μ M nitrendipine can be used to study the N-type channels.

The Molecular Devices Corp FLEXstationTM was utilised to develop a medium throughput assay with undifferentiated and differentiated IMR32 cells labelled with Fluo-4. Opening of voltage-activated calcium channels was stimulated by depolarisation of cells with KCl, which was added by the FLEXstation's fluidics system. The resulting influx of calcium into the cells was recorded by an increase in fluorescence. The assays were validated with known ion channel blockers.

IMR32 cells were grown in EMEM supplemented with 10% foetal bovine serum, 2 mM lutamine, 1% NEAA, 100 U/ml penicillin and 100 μ g/ml streptomycin. To differentiate the IMR32 cells, 1 mM dibutyryl cAMP and 2.5 μ M bromodeoxyuridine were added to the cell culture media and cells maintained for 7-9 days.

Cells were detached from tissue culture surfaces using an enzyme free cell dissociation buffer (Invitrogen) after washing with a Ca^{2+} / Mg^{2+} free Hanks buffered

saline solution (HBSS). The cells were then resuspended in assay buffer (HBSS containing $\text{Ca}^{2+}/\text{Mg}^{2+}$ and supplemented with 20 mM HEPES, pH 7.4) to give a total volume of 40 ml. 2 μM Fluo-4 and 50 μM probenecid were added and then the cells were incubated at 25 °C for 30 min. Following centrifugation in a Heraeus Megafuge 1.0 (rotor 2704) for 1 min at 1000 rpm, the cell pellet was resuspended in 40 ml assay buffer supplemented with 50 μM probenecid and incubated at 25 °C for a further 30 min. The cells were centrifuged as before and again resuspended in assay buffer supplemented with probenecid. 200,000 cells were aliquoted into each well of a 96-well plate containing 0.001-100 μM compound to be tested (for the N-type assay 5 μM nitrendipine was also added to each well), in triplicate. The final volume of compound and cells in assay buffer was 200 μl . The plate containing cells was centrifuged at 300 rpm for 1 min with no brake in a Heraeus Labofuge 400E (rotor 8177).

The plate was then assayed using the FLEXstation (Molecular Devices Corp). The excitation and emission wavelengths were 494 and 525 nm, respectively. The calcium response was stimulated by the addition of 50 μl 250 mM KCl (50 mM final concentration) by the FLEXstation fluidics system. SOFTmax Pro (Molecular Devices Corp) was used to calculate the change in fluorescence caused by calcium influx for each well and hence the IC_{50} for each compound. The results are shown in the Tables below.

Table 1

Compound*	$\text{IC}_{50}(\mu\text{M})$ (N-type calcium channels)	$\text{IC}_{50}(\mu\text{M})$ (L-type calcium channels)	Selectivity
1	12.03	14.42	1.20
2	1.74	3.65	2.10
3	1.06	1.88	1.77
4	2.69	1.27	0.47
5	5.62	4.79	0.85
6	7.57	2.9	0.38

Compound [*]	IC ₅₀ (μ M) (N-type calcium channels)	IC ₅₀ (μ M) (L-type calcium channels)	Selectivity
7	3.9	3.77	0.97
8	2.97	4.5	1.52
9	8.79	7.38	0.84
10	4.27	7.87	1.84
11	2.61	2.98	1.14
12	3.84	4.11	1.07
13	2.95	2.14	0.73
14	1.24	2.36	1.90
15	3.72	6.23	1.67
16	2.07	3.99	1.93
17	2.03	1.63	0.80
18**	1.47	4.41	3.00
18**	0.919	3.5	3.81
18**	2.62	19.83	7.57
19	2.51	1.64	0.65
20	1.34	2.21	1.65
21	4.41	3.17	0.72
22	5.75	9.22	1.6
23	1.49	2.91	1.96
24	4.05	3.83	0.95
25	4.5	4.23	0.94
26	5.75	6.82	1.19
27	2.68	2.7	1.01
28	1.58	1	0.63
29	2.89	12.21	4.22
30	1.59	6.38	4.01
31	2.38	4.1	1.72
32	1.31	2.49	1.90

Compound*	IC ₅₀ (μ M) (N-type calcium channels)	IC ₅₀ (μ M) (L-type calcium channels)	Selectivity
33	9.39	5.4	0.58
34	3.56	9.98	3.56
35	3.2	5.6	1.75
36	1.81	2.69	1.49
37	2.26	6.09	2.69
38	1.58	1.12	0.71
39	4.31	3.62	0.84
40	2.78	3.26	1.17
41	2.62	2.51	0.96
42	3.8	3.75	0.99
43	6.08	8.74	1.44
44	3.5	2	0.57
45	3.44	3.26	0.95
46	2.56	1.47	0.57
47	4.94	7.23	1.46
48	2.6	4.43	1.70
49	2.69	1.55	0.58
50	3.15	2.46	0.78
51	3.49	2.11	0.60
52	2.86	2.44	0.85
53	2.62	2.52	0.96
54	1.83	4.34	2.37
55	0.57	5.33	9.35
56	3.75	4.28	1.14
57	0.93	0.87	0.94
58	3.18	3.9	1.23
59	2.55	1.82	0.71
60	1.83	15.55	8.50

Compound*	IC ₅₀ (μ M) (N-type calcium channels)	IC ₅₀ (μ M) (L-type calcium channels)	Selectivity
61	3.05	3.44	1.13
62	0.75	2.17	2.89
63	2.33	3.23	1.39
64	1.65	1.53	0.93
65	5.98	5.74	0.96
66	0.78	1.72	2.21
67	1.52	4.28	2.82
68	5.03	4.49	0.89
69	1.74	2.08	1.20
70	0.6	1.78	2.97
71	1.03	3.82	3.71
72	6.19	9.05	1.46
73	3.16	1.2	0.38
74	2.93	2.06	0.70
75	3.39	7.08	2.09
76	3.44	3.56	1.03
77	3.08	2.13	0.69
78	2.09	1.04	0.50
79	3.13	4.87	1.56
80	3.07	2.16	0.70
81	30	100	3.33
82	3.45	3.5	1.01
83	4.31	2.57	0.60
84	4.34	3.7	0.85
85	4.23	5.99	1.42
86	3.19	3.63	1.14
87	1.96	0.89	0.45
88	2.26	2.21	0.98

Compound*	IC ₅₀ (μ M) (N-type calcium channels)	IC ₅₀ (μ M) (L-type calcium channels)	Selectivity
89	3.79	2.6	0.69
90	3.13	1.25	0.40
91	2.47	1.02	0.41
92	2.83	2.77	0.98
93	6.56	5.63	0.86
94	3.48	2.71	0.78
95	7.58	4.88	0.64
96	1.75	2.64	1.51
97	5.77	5.8	1.01
98	4.27	2.92	0.68
99	2.76	2.66	0.96
100	2.47	2.98	1.21
101	2.35	5.23	2.23
102	1.98	5.17	2.61
103	5.04	3.99	0.79
104	2.56	3.87	1.51
105	4.04	9.39	2.32
106	2.65	3.97	1.50
107	0.6	1.7	2.83
108	2.13	2.37	1.11
109	1.6	3.75	2.34
110	1.8	3.4	1.89
111	7.48	8.35	1.12
112	3.51	7.25	2.07
113	2.89	3.57	1.24
114	0.82	3.93	4.79
115	4.17	4	0.96
116	2.78	1.07	0.38

Compound*	IC ₅₀ (μ M) (N-type calcium channels)	IC ₅₀ (μ M) (L-type calcium channels)	Selectivity
117	1.29	4.65	3.60
118	4.12	4.28	1.04
119	2.92	4.24	1.45
120	0.88	1.04	1.18
121	5.99	1.4	0.23
122	3.89	1.52	0.39
123	3.49	4.23	1.21
124	12.41	9.87	0.80
125	0.86	2.6	3.02
126	2.54	5.72	2.52
127	4.04	3.65	0.90
128	4.04	3.73	0.92
129	5.29	3.48	0.66
130	2.56	5.42	2.12
131	1.23	1.98	1.61
132	9.35	3.14	0.34
133	4.08	4.27	1.05
134	0.68	5.16	7.59
135	2.99	3.84	1.28
136	2.9	2.82	0.97
137	5.45	4.76	0.87
138	5.01	8.65	1.73
139	5.25	2.5	0.48
140	2.8	1.78	0.64
141	4.68	4.23	0.90
142	4.04	2.55	0.63
143	4.95	4.2	0.85
144	3.98	4.34	1.09

Compound*	IC ₅₀ (μ M) (N-type calcium channels)	IC ₅₀ (μ M) (L-type calcium channels)	Selectivity
145	1.15	0.7	0.61
146	5.83	22.15	3.80
147	3.07	2.43	0.79
148	0.77	1.55	2.01
149	3.35	3.33	0.99
150	6.02	1.76	0.29
151	1.79	3.07	1.72
152	3	3.74	1.25
153	3.76	3.81	1.01
154	5.81	4.56	0.78
155	7.13	18.1	2.54
156	1.67	1.36	0.81
157	9.86	3.52	0.36
158	2.8	2.45	0.88
159	0.93	1.69	1.82
160	3.96	2.52	0.64
161	4.22	3.57	0.85
162	4.57	6.69	1.46
163	2.53	4.58	1.81
164	3.23	2.44	0.76
165	1.39	5.56	4.00
166	3.33	4.13	1.24
167	3.19	2.26	0.71
168	1.58	2.94	1.86
169	2.24	2.3	1.03
170	1.16	1.1	0.95
171	2.08	1.72	0.83
172	2.92	3.88	1.33

Compound*	IC ₅₀ (μ M) (N-type calcium channels)	IC ₅₀ (μ M) (L-type calcium channels)	Selectivity
173	2.18	1.65	0.76
174	0.97	2.86	2.95
175	2.97	2.45	0.82
176	2.4	5.25	2.19
177	4.06	2.81	0.69
178	4.03	4.35	1.08
179	1.43	2.78	1.94
180	1.45	3.6	2.48
181	3.36	1.7	0.51
182	7.2	7.21	1.00
183	2.97	6.85	2.31
184	6.46	6.35	0.98
185	2.78	3.2	1.15
186	1.55	4.20	
187	2.17	1.21	
188	2.79	5.06	
189	1.74	0.83	
190	8.55	21.88	
191	0.83	2.13	
192	0.90	1.14	
193	7.27	31.10	
194	7.40	14.31	
195	2.71	2.88	
196	2.94	3.39	
197	1.27	2.68	
198	4.25	2.26	
199	3.29	2.67	
200	2.54	0.75	

Compound*	IC ₅₀ (μ M) (N-type calcium channels)	IC ₅₀ (μ M) (L-type calcium channels)	Selectivity
201	3.51	1.60	
202	2.91	4.07	
203	2.33	1.80	
204	5.44	7.62	
205	1.27	2.62	
206	1.66	1.19	
207	4.73	7.41	
208	1.19	2.48	
209	1.31	1.99	
210	1.89	2.23	
211	1.49	1.76	
212	0.56	1.17	
213	0.47	2.56	
214	1.22	3.67	
216	1.24	1.77	
217	0.81	2.28	
218	1.05	2.27	
219	1.62	1.87	
220	2.04	1.56	
221	1.57	4.24	
222	1.65	4.16	
223	0.48	0.46	
224	1.90	6.91	
225	3.06	7.61	
226	1.15	1.17	
227	1.18	0.91	
228	0.38	0.47	
229	3.31	11.02	

Compound*	IC ₅₀ (μ M) (N-type calcium channels)	IC ₅₀ (μ M) (L-type calcium channels)	Selectivity
230	1.04	0.51	
231	0.71	0.29	
232	1.66	1.30	
233	0.79	0.69	
234	1.22	0.59	
235	0.52	0.91	
237	2.52	0.78	
238	12.26	>30	
239	6.35	4.42	
240	1.33	2.58	
241	0.64	0.41	
242	0.70	0.71	
243	9.31	>30	
244	0.55	0.78	
245	1.29	1.94	
246	0.00	3.50	
247	0.93	0.97	
248	0.69	0.64	
249	6.43	6.87	
250	14.20	17.55	
251	3.94	4.42	
252	1.80	4.32	
253	2.12	4.11	
254	1.24	2.13	
255	0.67	1.09	
256	0.57	1.06	
257	0.57	1.56	
258	0.52	1.24	

Compound*	IC ₅₀ (μ M) (N-type calcium channels)	IC ₅₀ (μ M) (L-type calcium channels)	Selectivity
259	0.54	1.29	
260	0.68	2.47	
261	0.84	1.48	
262	0.74	1.46	
263	0.93	1.79	
264	0.41	0.46	
265	0.33	0.47	
266	0.36	0.46	
268	1.28	2.89	

* Compound numbers in this Table correspond to those set out in the list of preferred compounds in the description.

** 3 different measurements were taken using the same assay.

5

Table 2

Compound	IC ₅₀ (L-type calcium channels)	IC ₅₀ (N-type calcium channels)	Selectivity
Example 4	2.00 μ M	1.00 μ M	2.00
Example 9	13.99 μ M	1.68 μ M	8.33
Example 12	11.49 μ M	2.06 μ M	5.58
Example 13	5.03 μ M	2.74 μ M	1.84
Example 14	4.38 μ M	1.49 μ M	2.94
Example 15	3.09 μ M	0.84 μ M	3.68
Example 16	3.35 μ M	1.24 μ M	2.70
Example 17	1.63 μ M	0.67 μ M	2.43
Example 18	3.50 μ M	1.21 μ M	2.89
Example 19	4.64 μ M	1.86 μ M	2.49
Example 20	4.26 μ M	1.53 μ M	2.78

Example 21	4.20 μ M	2.56 μ M	1.64
Example 22	2.15 μ M	2.37 μ M	0.91
Example 23	2.14 μ M	1.50 μ M	1.43
Example 24	3.19 μ M	2.92 μ M	1.09
Example 25	1.13 μ M	2.37 μ M	0.48
Example 26	1.09 μ M	3.23 μ M	0.34
Example 27	1.07 μ M	0.54 μ M	1.98
Example 28	18.64 μ M	9.47 μ M	1.97
Example 29	4.14 μ M	1.59 μ M	2.60
Example 30	1.13 μ M	0.90 μ M	1.26

Activity Example 2

Inflammation-induced hyperalgesia in experimental animals

Chronic inflammatory conditions produce a state of hyperalgesia, which is evident from a few hours to days after administration of an inflammatory stimulus.

Freund's complete adjuvant (FCA containing heat-killed *Mycobacterium tuberculosis*) and carrageenan have been well documented to produce this state in laboratory animals following intraplantar injection. In particular intraplantar injection of FCA in the rat is associated with the development of persistent hyperalgesia within a few hours, which is confined to the ipsilateral paw.

Methodology

The method used was based on that described by Iadarola *et al.* Brain Res. 1998, 455, 205-212. Animals received a unilateral, intraplantar injection of saline. At various time points post-administration of inflammatory stimulus the following parameter was measured:

Oedema

The displacement volume (ml) of each hindpaw was assessed using plethysmometer.

Mechanical hyperalgesia

To assess the development of mechanical hyperalgesia, paw withdrawal threshold of both ipsilateral and contralateral paws was determined using an algometer (Ugo Basile, Italy). An increasing weight was applied to each paw until a withdrawal reflex was elicited.

The results are shown in the Table below. The figures quoted show the reversal achieved 3 hours after administration of compound 18 (2-(3-bromo-4-fluoro-phenyl)-3-(2-pyridin-2-yl-ethyl)-thiazolidin-4-one).

Vehicle only	1 mg/kg active compound	10 mg/kg active compound	30 mg/kg active compound
2.5%	18.1	46.8	47.1

Activity Example 3

Allodynia in experimental animals

Allodynia, an extreme tenderness or hypersensitivity of the skin resulting from nerve damage, was examined in the model of neuropathic pain induced by partial ligation of the sciatic nerve as described by Seltzer *et al.* (Seltzer Z., Dubner, R. and Shir, Y., 1990. A novel behavioural model of neuropathic pain disorders produced in rats by partial sciatic nerve injury. *Pain* **43**, 205-218). Briefly, Wistar rats (120-140 g) were anaesthetized, the left sciatic nerve was exposed at mid-thigh level through a small incision and 1/3 to 1/2 of the nerve thickness was tightly ligated within a 7.0 silk suture. The wound was closed with a single muscle suture and skin clips. The animals were allowed to recover and evaluated 12-15 days following surgery.

Tactile allodynia was assessed in rats by measuring withdrawal thresholds to calibrated von Frey hairs with intensities ranging from 1 to 15 g. Filaments exerting a force above 15 g were not used as they produced lifting of the paws. On the day of the experiment animals were placed in a perspex chamber with mesh metal floor and allowed to acclimatise for 15 - 30 min. Starting with the lowest filament force, von Frey hairs were applied perpendicular to the mid plantar surface of the both hind paws, with sufficient force to cause slight bending against the paw and held for 5 seconds. A positive response was noted if the paw was sharply withdrawn or there was flinching upon removal of the hair. If no response was noted to any trial the process was repeated with the next higher force hair and the filament which produced a positive response was denoted as the threshold. Withdrawal thresholds were determined prior to and up to 6 h following drug or vehicle administration.

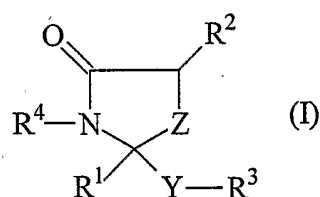
Results are shown in the Tables below. The figures quoted show the reversal of allodynia achieved 1 hour after subcutaneous administration of compound 18 and 3 hours after the administration compound 119 respectively:

3 mg/kg active compound	10 mg/kg active compound	30 mg/kg active compound
17	53	63

3 mg/kg active compound	10 mg/kg active compound	30 mg/kg active compound
24	41	58

CLAIMS

1. Use, in the manufacture of a medicament for use in the treatment or prevention of a condition mediated by N-type calcium channels, of a compound of formula (I) or a pharmaceutically acceptable salt thereof,



wherein:

Z is -S-, -S(O)-, -SO₂-, -O- or -NR- wherein R is hydrogen, C₁-C₆ alkyl or -CO-(C₁-C₆ alkyl);

R¹ is hydrogen or C₁-C₆ alkyl;

R² is hydrogen, fluorine, C₁-C₆ alkyl, -(C₁-C₆ alkyl)-CO₂H or -(C₁-C₆ alkyl)-CO-NR₅R₆, wherein either (a) R₅ is hydrogen, aryl or -(C₁-C₆ alkyl)-aryl and R₆ is -L-R wherein L is a direct bond, a C₁-C₆ alkylene group, a C₂-C₆ alkenylene group or a C₂-C₆ alkynylene group and R is hydrogen, aryl, heteroaryl, carbocyclyl or heterocyclyl or (b) R₅ and R₆, together with the nitrogen atom to which they are attached, represent a moiety -Het₁-Het₂, wherein Het₁ is a heterocyclyl or heteroaryl group and Het₂ is hydrogen, aryl, heteroaryl, -CH(aryl)₂ or -CH(heteroaryl)₂;

Y is -(CR^y₂)_q-, -(CR^y₂)_m-X₄-(CR^y₂)_n-, -(CR^y₂)_m-A-(CR^y₂)_m- or -(CR^y₂)_m-A-(CR^y₂)_p-X₃-(CR^y₂)_m, wherein:

- p, q, m and n are each independently an integer of 0 to 4;
- A is aryl, heteroaryl, carbocyclyl or heterocyclyl;
- X₃ is -O-, -S-, -NR'-, -S(O)-, -SO₂-, -O-CO-, -S-CO-, -NR'-CO-, -CO-O-, -CO-S- or -CO-NR' wherein R' is hydrogen, C₁-C₆ alkyl, C₂-C₆ alkenyl or C₂-C₆ alkynyl;
- X₄ is -O-, -S-, -NR'-, -S(O)- or -SO₂- wherein R' is hydrogen, C₁-C₆ alkyl, C₂-C₆ alkenyl or C₂-C₆ alkynyl;

- each R^y is the same or different and is hydrogen, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, aryl or heteroaryl;

R³ is hydrogen, aryl, heteroaryl, heterocyclyl or carbocyclyl; and

R₄ is methyl, -C₁-X₁-Ar₁ or -C₂-X₂-C₃, wherein:

- C₁ is a direct bond, a C₁-C₆ alkylene group, a C₂-C₆ alkenylene group or a C₂-C₆ alkynylene group;
- X₁ is a direct bond when C₁ is a direct bond and, when C₁ is a C₁-C₆ alkylene group, C₂-C₆ alkenylene group or C₂-C₆ alkynylene group, represents a direct bond or -O-, -S-, -NR'-, -SO-, -SO₂-, -CO-, -CO-S-, -CO-O-, -CO-NR'-, -S-CO-, -O-CO-, -NR'-CO-, -CO-O-R''-CO-O-, -CO-NR'-R''-CO-O-, -CO-O-R''-CO-NR'-, -CO-NR'-R''-CO-NR'-, -O-CO-NR'- or -NR'-CO-O-, wherein each R' is the same or different and represents hydrogen, phenyl, C₁-C₆ alkyl, C₂-C₆ alkenyl or C₂-C₆ alkynyl and each R'' is the same or different and represents a C₁-C₆ alkylene group, a C₂-C₆ alkenylene group or a C₂-C₆ alkynylene group;
- Ar₁ is heteroaryl, heterocyclyl, aryl, carbocyclyl, heteroaryl-R^a-, heterocyclyl-R^a-, aryl-R^a- or carbocyclyl-R^a-, wherein R^a is a C₁-C₆ alkylene group, a C₂-C₆ alkenylene group or a C₂-C₆ alkynylene group;
- C₂ is a C₁-C₆ alkylene group, a C₂-C₆ alkenylene group or a C₂-C₆ alkynylene group;
 - X₂ is a direct bond or -O-, -S-, -NR'-, -SO-, -SO₂-, -CO-, -CO-S-, -CO-O-, -CO-NR'-, -S-CO-, -O-CO-, -NR'-CO-, -CO-O-R''-CO-O-, -CO-NR'-R''-CO-O-, -CO-O-R''-CO-NR'-, -CO-NR'-R''-CO-NR'-, -NR'-CO-O- or -O-CO-NR'-, wherein each R' is the same or different and represents hydrogen, phenyl, C₁-C₆ alkyl, C₂-C₆ alkenyl or C₂-C₆ alkynyl and each R'' is the same or different and represents a C₁-C₆ alkylene group, a C₂-C₆ alkenylene group or a C₂-C₆ alkynylene group; and
- C₃ is a C₁-C₆ alkyl group, a C₂-C₆ alkenyl group or a C₂-C₆ alkynyl group, wherein:
 - the alkyl, alkylene, alkenyl, alkenylene, alkynyl and alkynylene groups and moieties in the R¹ to R⁴ substituents are unsubstituted or carry 1, 2 or 3 unsubstituted substituents selected from aryl, hydroxy, C₁-C₆ alkoxy, C₁-C₆ alkylthio, -NH₂, -NH(C₁-C₆ alkyl), -N(C₁-C₆ alkyl)₂, halogen, cyano, nitro, -NHCO-(C₁-C₆ alkyl),

-CO-NH-(C₁-C₆ alkyl), -CO-O-(C₁-C₆ alkyl) and -O-CO-(C₁-C₆ alkyl) substituents; and

- the aryl, heteroaryl, carbocyclyl and heterocyclyl groups and moieties in the R¹ to R⁴ substituents are unsubstituted or carry 1, 2 or 3 substituents selected from halogen, C₁-C₆ alkyl, C₁-C₆ alkoxy, C₁-C₆ alkylthio, C₃-C₆ carbocyclyl, C₃-C₆ carbocyclyoxy, C₃-C₆ carbocyclylthio, C₂-C₆ alkenyl, C₂-C₆ alkenyloxy, C₂-C₆ alkenylthio, C₂-C₆ alkenynyl, C₂-C₆ alkynyloxy, C₂-C₆ alkynylthio, hydroxy, -NH₂, -NH(C₁-C₆ alkyl), -N(C₁-C₆ alkyl)₂, cyano, nitro, -NH-CO-(C₁-C₆ alkyl), -CO-NH-(C₁-C₆ alkyl), -CO-O-(C₁-C₆ alkyl) and -O-CO-(C₁-C₆ alkyl) substituents, said substituents being unsubstituted or substituted by 1, 2 or 3 further unsubstituted substituents selected from halogen, hydroxy, C₁-C₆ alkoxy, C₁-C₆ alkylthio, -NH₂, -NH(C₁-C₆ alkyl), -N(C₁-C₆ alkyl)₂, -NH-CO-(C₁-C₆ alkyl), -CO-NH-(C₁-C₆ alkyl) and -O-CO-(C₁-C₆ alkyl) substituents.

2. Use according to claim 1, wherein R₂ is hydrogen, fluorine or C₁-C₆ alkyl and R₄ is -C₁-X₁-Ar₁ or -C₂-X₂-C₃ wherein C₁, X₁, Ar₁, C₂, X₂ and C₃ are as defined in claim 1.

3. Use according to claim 1, wherein R₂ represents hydrogen, fluorine, C₁-C₄ alkyl, -(C₁-C₄ alkyl)-CO₂H or -(C₁-C₄ alkyl)-CONR₅R₆, wherein either (a) R₅ is hydrogen, aryl or -(C₁-C₂ alkyl)-aryl and R₆ is -L-R wherein L is a direct bond or a C₁-C₄ alkylene group and R is hydrogen, aryl, carbocyclyl, heterocyclyl or heteroaryl or (b) R₅ and R₆, together with the nitrogen atom to which they are attached, represent a moiety -Het₁-Het₂, wherein Het₁ is a heterocyclyl group and Het₂ is hydrogen, aryl or -CH(aryl)₂.

4. Use according to claim 3, wherein R₂ represents hydrogen, an unsubstituted C₁-C₄ alkyl group, -(CH₂)_a-CO₂H or -(CH₂)_b-CONR₅R₆ wherein a and b are 1 or 2 and either (a) R₅ is hydrogen or an unsubstituted benzyl group and R₆ is -L-R wherein L is a direct bond or an unsubstituted C₁-C₄ alkylene group and R is hydrogen or a phenyl, cyclohexenyl, piperidyl, pyridyl or benzimidazolyl group which is unsubstituted or substituted by a halogen, hydroxy, -OCH₃ or -OCH₂CH₃ substituent, or (b) R₅ and R₆, together with the N atom to which they are attached, represent a pyrrolidinyl, piperidinyl, homopiperidinyl or piperazinyl group which is unsubstituted or substituted by an unsubstituted -CHPh₂ group.

5. Use according to any one of the preceding claims, wherein:

- the alkyl, alkylene, alkenyl, alkenylene, alkynyl and alkynylene groups and moieties in the R^1 to R^4 substituents are unsubstituted or carry 1, 2 or 3 unsubstituted substituents selected from hydroxy, halogen, C_1 - C_2 alkoxy, $-NH_2$, $-NH(C_1-C_2 \text{ alkyl})$ and $-N(C_1-C_2 \text{ alkyl})_2$ substituents; and
- the aryl, heteroaryl, carbocyclyl and heterocyclyl groups and moieties in the R^1 to R^4 substituents are unsubstituted or carry 1, 2 or 3 substituents selected from C_1 - C_4 alkyl, C_1 - C_4 alkoxy, C_1 - C_4 alkylthio, C_5 - C_6 carbocycloxy, C_2 - C_4 alkenyloxy, halogen, hydroxy, $-NH_2$, $-NH(C_1-C_2 \text{ alkyl})$, $-N(C_1-C_2 \text{ alkyl})_2$ and $-NH-CO-(C_1-C_2 \text{ alkyl})$ substituents, the substituents on an aryl or heteroaryl group or moiety being unsubstituted or substituted with 1, 2 or 3 further substituents which are halo substituents and the substituents on a carbocyclyl or heterocyclyl group or moiety being unsubstituted.

6. Use according to any one of the preceding claims, wherein the alkyl groups and moieties in substituents R^1 to R^4 are unsubstituted or carry 1, 2 or 3 substituents selected from fluorine and hydroxy groups.

7. Use according to any one of the preceding claims, wherein, when Ar_1 is a heteroaryl or heterocyclyl group it is attached via a carbon-atom.

8. Use according to any one of the preceding claims, wherein Z is $-S-$, $-S(O)-$ or $-S(O)_2-$.

9. Use according to any one of the preceding claims, wherein R_1 is hydrogen or $-CH_3$.

10. Use according to any one of the preceding claims, wherein R_2 is hydrogen or an unsubstituted C_1 - C_4 alkyl group.

11. Use according to any one of the preceding claims, wherein each R^y is the same or different and is hydrogen or an unsubstituted C_1 - C_4 alkyl or phenyl group.

12. Use according to any one of the preceding claims, wherein A is an aryl or heteroaryl group which is unsubstituted or substituted with 1, 2 or 3 substituents selected from unsubstituted C_1 - C_4 alkyl, C_1 - C_4 alkoxy, halogen, hydroxy, NH_2 , $NH(C_1-C_2 \text{ alkyl})$ and $N(C_1-C_2 \text{ alkyl})_2$ groups.

13. Use according to any one of the preceding claims, wherein X_3 is $-O-$, $-S-$, $-SO-$, $-SO_2-$ or $-NH-CO-$.

14. Use according to any one of the preceding claims, wherein p is 0 or 1; and/or q is 0, 1, 2 or 3; and/or m is 0 or 1; and/or n is 1 or 2.
15. Use according to any one of the preceding claims, wherein X₄ is -S- or -O-.
16. Use according to any one of the preceding claims, wherein Y is a direct bond or a group of formula -(CR^y)₂-, -(CH₂)_mO(CH₂)_n-, -A- or -A-X₃-(CH₂)_m- wherein R^y, A, X₃, m and n are as defined in any one of the preceding claims.
17. Use according to any one of the preceding claims wherein R₃ is hydrogen or an aryl, heteroaryl or carbocyclyl group which is unsubstituted or substituted by 1, 2 or 3 substituents selected from halogen, hydroxy, C₁-C₆ alkyl, C₁-C₆ alkoxy, C₁-C₆ alkylthio, C₂-C₆ alkenyl, C₂-C₆ alkenyloxy, C₂-C₆ alkenylthio, C₂-C₆ alkynyl, C₂-C₆ alkynyloxy, C₂-C₆ alkynylthio, C₃-C₆ carbocyclyl, C₃-C₆ carbocycliloxy, C₃-C₆ carbocyclylthio, -NH-CO-(C₁-C₆ alkyl), -CO-NH-(C₁-C₆ alkyl) and -NR'R'' wherein R' and R'' are each independently hydrogen or a C₁-C₆ alkyl group, the substituents on R₃ being themselves unsubstituted or further substituted with 1, 2 or 3 further substituents selected from halogen and hydroxy.
18. Use according to any one of claims 1 and 2 to 17, wherein R₄ is -CH₃ or is -C₁-X₁-Ar₁ or -C₂-X₂-C₃.
19. Use according to any one of the preceding claims, wherein C₁ is an unsubstituted C₁-C₄ alkylene group.
20. Use according to any one of the preceding claims, wherein X₁ is a direct bond or is -O-, -S-, -S-CO-, -O-CO- or -NH-CO-.
21. Use according to any one of the preceding claims, wherein Ar₁ is a heteroaryl, heterocyclyl, aryl, carbocyclyl or heteroaryl-(C₁-C₂ alkyl)- group which is unsubstituted or carries, on the cyclic moiety, 1, 2 or 3 unsubstituted groups selected from halogen, C₁-C₄ alkyl, hydroxy, C₁-C₄ alkoxy, -NR'R'' and -NH-CO-R' wherein R' and R'' are the same or different and are selected from hydrogen and unsubstituted C₁-C₄ alkyl.
22. Use according to claim 21, wherein, when Ar₁ is a heteroaryl group it is a thienyl group, when Ar₁ is a heteroaryl-(C₁-C₂ alkyl)- group it is a thienyl-methyl- or furanyl-methyl- group and when Ar is a heterocyclyl group it is a morpholinyl, 1,4-benzodioxanyl or 1,3-benzodioxanyl group.

23. Use according to claim 21, wherein Ar_1 is a pyridyl, thienyl, benzimidazolyl, furanyl-methyl-, 1,4-benzodioxanyl, phenyl, cyclohexenyl, quinolinyl, 2,3-dihydro-1H-indenyl, 1,3-benzodioxolyl or 1,3-benzodioxanyl group which is unsubstituted or carries, on the cyclic moiety, 1, 2 or 3 substituents selected from fluorine, hydroxy, $-OCH_3$, $-N(CH_3)_2$ and $-NH-CO-CH_3$.

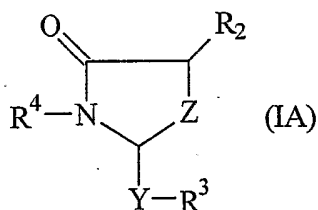
24. Use according to any one of the preceding claims, wherein C_2 is an unsubstituted C_1-C_4 alkylene group.

25. Use according to any one of the preceding claims, wherein X_2 is a direct bond or $-O-$, $-S-$, $-CO-O-$, $-O-CO-$, $-S-CO-$, $-CO-S-$ or $-NH-CO-$.

26. Use according to any one of the preceding claims, wherein C_3 is a C_1-C_4 alkyl group which is unsubstituted or substituted with 1, 2 or 3 unsubstituted groups selected from hydroxy, $-NH_2$, $-NH(C_1-C_2 \text{ alkyl})$, $-N(C_1-C_2 \text{ alkyl})_2$ and halogen.

27. Use according to claim 26, wherein C_3 is unsubstituted or carries, on a primary carbon atom, either (a) one hydroxy or (b) 1, 2 or 3 halo substituents.

28. Use according to claim 1, wherein the compound of formula (I) is a thiazolidinone derivative of formula (IA) or a pharmaceutically acceptable salt thereof:



wherein:

Z is $-S-$, $-S(O)-$ or $-S(O)_2-$;

R_2 represents hydrogen, an unsubstituted C_1-C_4 alkyl group, $-(CH_2)_a-CO_2H$ or $-(CH_2)_b-CONR_5R_6$ wherein a and b are 1 or 2 and either (a) R_5 is hydrogen or an unsubstituted benzyl group and R_6 is $-L-R$ wherein L is a direct bond or an unsubstituted C_1-C_4 alkylene group and R is hydrogen or a phenyl, cyclohexenyl, piperidyl, pyridyl or benzimidazolyl group which is unsubstituted or substituted by a halogen, hydroxy, $-OCH_3$ or $-OCH_2CH_3$ substituent, or (b) R_5 and R_6 , together with the N atom to which they are attached, represent a pyrrolidinyl, piperidinyl, homopiperidinyl or

piperazinyl group which is unsubstituted or substituted by an unsubstituted -CHPh₂ group;

Y is a direct bond or a group of formula $-(CR^Y)_2-$, $-(CH_2)_mO(CH_2)-$, $-A-$ or $-A-X_3-(CH_2)_m$, wherein R^Y is hydrogen, $-CH_3$, $-CH_2-CH_3$ or an unsubstituted phenyl group, wherein no more than one R^Y group is phenyl; A is a phenyl, pyridyl or pyrrolyl group, which is unsubstituted or substituted with 1, 2 or 3 substituents selected from $-CH_3$, $-CH_2-CH_3$, $-OCH_3$, $-OCH_2-CH_3$, halogen and hydroxy; X_3 is $-O-$, $-SO_2-$ or $-NH-CO-$; and m is 0 or 1;

R^3 is hydrogen or a phenyl, thienyl, furyl, quinolinyl, benzofuranyl, cyclopentyl, 1,4-benzodioxanyl, 1,3-benzodioxolyl or 2,3-dihydrobenzofuran group which is unsubstituted or substituted with 1, 2 or 3 substituents selected from halogen, C_1-C_4 alkyl, C_1-C_4 alkoxy, C_1-C_4 alkylthio, C_2-C_4 alkenyloxy, C_3-C_6 carbocyclyloxy, $-NH-CO-Me$ and $-N(CH_3)_2$, the substituents on R^3 being themselves unsubstituted or further substituted with 1, 2 or 3 further substituents selected from halogen and hydroxy;

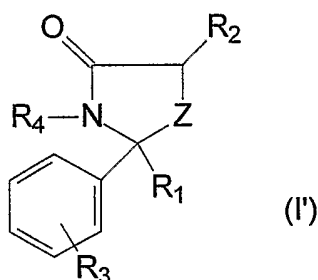
R_4 is an unsubstituted methyl group or is $-C_1-X_1-Ar_1$ or $-C_2-X_2-C_3$, wherein:

- C_1 is $-(CH_2)-$, $-(CH_2)_2-$ or $-(CH_2)_3-$;
- X_1 is a direct bond or is $-O-$, $-S-$, $-S-CO-$ or $-O-CO-$;
- Ar_1 is a phenyl, pyridyl, thienyl, benzimidazolyl, furanyl-methyl-, cyclohexenyl, quinolinyl, 2,3-dihydro-1H-indenyl, 1,3-benzodioxolyl, 1,3-benzodioxanyl or 1,4-benzodioxanyl group, which is unsubstituted or carries, on the cyclic moiety, 1, 2 or 3 substituents selected from fluorine, hydroxy, $-OCH_3$, $-N(CH_3)_2$ and $-NH-CO-CH_3$;
- C_2 is a straight chain unsubstituted C_1-C_4 alkylene group;
- X_2 is a direct bond or is $-O-$, $-S-$, $-CO-O-$ or $-NH-CO-O-$; and
- C_3 is C_1-C_4 alkyl group which is unsubstituted or substituted on a primary carbon atom with either (a) one hydroxy or (b) 1, 2 or 3 halo substituents.

29. Use according to claim 28 wherein, when Ar_1 is a pyridyl or benzimidazolyl group it is attached via a carbon atom.

30. Use according to claim 28, wherein Ar_1 is a phenyl, thienyl, furanyl-methyl-, 1,3-benzodioxanyl or 1,4-benzodioxanyl group, which is unsubstituted or carries, on the cyclic moiety, 1, 2 or 3 substituents selected from fluorine, hydroxy, $-OCH_3$, $-N(CH_3)_2$ and $-NH-CO-CH_3$.

31. Use, in the manufacture of a medicament for use in the treatment or prevention of a condition mediated by N-type calcium channels, of a compound of formula (I') or a pharmaceutically acceptable salt thereof,



wherein:

Z is -S-, -S(O)-, -SO₂-, -O- or -NR- wherein R is hydrogen, C₁-C₆ alkyl or -CO-(C₁-C₆ alkyl);

R₁ is hydrogen or C₁-C₆ alkyl;

R² is hydrogen, fluorine, C₁-C₆ alkyl, -(C₁-C₆ alkyl)-CO₂H or -(C₁-C₆ alkyl)-CO-NR₅R₆, wherein either (a) R₅ is hydrogen, aryl or -(C₁-C₆ alkyl)-aryl and R₆ is -L-R wherein L is a direct bond, a C₁-C₆ alkylene group, a C₂-C₆ alkenylene group or a C₂-C₆ alkynylene group and R is hydrogen, aryl, heteroaryl, carbocyclyl or heterocyclyl or (b) R₅ and R₆, together with the nitrogen atom to which they are attached, represent a moiety -Het₁-Het₂, wherein Het₁ is a heterocyclyl or heteroaryl group and Het₂ is hydrogen, aryl, heteroaryl, -CH(aryl)₂ or -CH(heteroaryl)₂;

R₃ is -SCQ₃ or -OCQ₃ wherein Q is halogen; and

R₄ is methyl, -C₁-X₁-Ar₁ or -C₂-X₂-C₃, wherein

- C₁ is a direct bond, a C₁-C₆ alkylene group, a C₂-C₆ alkenylene group or a C₂-C₆ alkynylene group;
- X₁ is a direct bond when C₁ is a direct bond and, when C₁ is a C₁-C₆ alkylene group, C₂-C₆ alkenylene group or C₂-C₆ alkynylene group, represents a direct bond or -O-, -S-, -NR'-, -SO-, -SO₂-, -CO-, -CO-S-, -CO-O-, -CO-NR'-, -S-CO-, -O-CO-, -NR'-CO-, -CO-O-R''-CO-O-, -CO-NR'-R''-CO-O-, -CO-O-R''-CO-NR'-, -CO-NR'-R''-CO-NR'-, -OCO-NR'- or -NR'-CO-O- wherein each R' is the same or different and represents hydrogen, phenyl, C₁-C₆ alkyl, C₂-C₆ alkenyl or

- C₂-C₆ alkynyl and each R'' is the same or different and represents a C₁-C₆ alkylene group, a C₂-C₆ alkenylene group or a C₂-C₆ alkynylene group;
- Ar₁ is heteroaryl, heterocyclyl, aryl, carbocyclyl, heteroaryl-Y-, heterocyclyl-Y-, aryl-Y- or carbocyclyl-Y-, wherein each Y is the same or different and represents a C₁-C₆ alkylene, C₂-C₆ alkenylene or C₂-C₆ alkynylene group;
 - C₂ is a C₁-C₆ alkylene group, a C₂-C₆ alkenylene group or a C₂-C₆ alkynylene group;
 - X₂ is a direct bond or -O-, -S-, -NR'-, -SO-, -SO₂-, -CO-, -CO-S-, -CO-O-, -CO-NR'-, -S-CO-, -O-CO-, -NR'-CO-, -CO-O-R''-CO-O-, -CO-NR'-R''-CO-O-, -CO-O-R''-CO-NR'-, -CO-NR'-R''-CO-NR'-, -OCO-NR'- or -NR'-CO-O- wherein each R' is the same or different and represents hydrogen, phenyl, C₁-C₆ alkyl, C₂-C₆ alkenyl or C₂-C₆ alkynyl and each R'' is the same or different and represents a C₁-C₆ alkylene group, a C₂-C₆ alkenylene group or a C₂-C₆ alkynylene group; and
 - C₃ is a C₁-C₆ alkyl group, a C₂-C₆ alkenyl group or a C₂-C₆ alkynyl group.

wherein:

- the alkyl, alkylene, alkenyl, alkenylene, alkynyl and alkynylene groups and moieties in the R₁ to R₄ substituents are unsubstituted or carry 1, 2 or 3 unsubstituted substituents selected from aryl, hydroxy, C₁-C₆ alkoxy, C₁-C₆ alkylthio, -NH₂, -NH(C₁-C₆ alkyl), -N(C₁-C₆ alkyl)₂, halogen, cyano, nitro, -NHCO-(C₁-C₆ alkyl), -CO-NH-(C₁-C₆ alkyl), -CO-O-(C₁-C₆ alkyl) and -O-CO-(C₁-C₆ alkyl);
- the aryl and heteroaryl groups and moieties in the R₁ to R₄ substituents are unsubstituted or carry 1, 2 or 3 substituents selected from halogen, C₁-C₆ alkyl, C₁-C₆ alkoxy, C₁-C₆ alkylthio, hydroxy, C₁-C₄ alkylendioxy, -NH₂, -NH(C₁-C₆ alkyl), -N(C₁-C₆ alkyl)₂, cyano, nitro, -NH-CO-(C₁-C₆ alkyl), -CO-NH-(C₁-C₆ alkyl), -CO-O-(C₁-C₆ alkyl) and -O-CO-(C₁-C₆ alkyl) substituents, said substituents being unsubstituted or substituted by 1, 2 or 3 further unsubstituted substituents selected from halogen, hydroxy, C₁-C₆ alkoxy, C₁-C₆ alkylthio, -NH₂, -NH(C₁-C₆ alkyl), -N(C₁-C₆ alkyl)₂, -NH-CO-(C₁-C₆ alkyl), -CO-NH-(C₁-C₆ alkyl) and -O-CO-(C₁-C₆ alkyl); and
- the carbocyclyl and heterocyclyl groups and moieties in the R₁ to R₄ substituents are unsubstituted or carry 1, 2 or 3 substituents selected from halogen, C₁-C₆ alkyl, C₁-C₆ alkoxy, C₁-C₆ alkylthio, hydroxy, C₁-C₄ alkylendioxy, -NH₂,

-NH(C₁-C₆ alkyl), -N(C₁-C₆ alkyl)₂, cyano, nitro, oxo, -NH-CO-(C₁-C₆ alkyl), -CO-NH-(C₁-C₆ alkyl), -CO-O-(C₁-C₆ alkyl) and -O-CO-(C₁-C₆ alkyl) substituents, said substituents being unsubstituted or substituted by 1, 2 or 3 further unsubstituted substituents selected from halogen, hydroxy, C₁-C₆ alkoxy, C₁-C₆ alkylthio, -NH₂, -NH(C₁-C₆ alkyl), -N(C₁-C₆ alkyl)₂, -NH-CO-(C₁-C₆ alkyl), -CO-NH-(C₁-C₆ alkyl) and -O-CO-(C₁-C₆ alkyl).

32. Use according to claim 31, wherein R₂ is hydrogen, fluorine or C₁-C₆ alkyl and R₄ is -C₁-X₁-Ar₁ or -C₂-X₂-C₃ wherein C₁, X₁, Ar₁, C₂, X₂ and C₃ are as defined in claim 31.

33. Use according to claim 31 or 32, wherein:

- the alkyl, alkylene, alkenyl, alkenylene, alkynyl and alkynylene groups and moieties in the R₁ to R₄ substituents are unsubstituted or carry 1, 2 or 3 unsubstituted substituents selected from phenyl, hydroxy, halogen, C₁-C₂ alkoxy, -NH₂, -NH(C₁-C₂ alkyl), -N(C₁-C₂ alkyl)₂ and -NHCO-(C₁-C₂ alkyl);
- the aryl and heteroaryl groups and moieties in the R₁ to R₄ substituents are unsubstituted or carry 1, 2 or 3 substituents selected from C₁-C₄ alkyl, C₁-C₄ alkoxy, C₁-C₄ alkylthio, halogen, hydroxy, methylenedioxy, -NH₂, -NH(C₁-C₂ alkyl), -N(C₁-C₂ alkyl)₂, -NH-CO-(C₁-C₂ alkyl) and -O-CO-(C₁-C₂ alkyl) substituents, said substituents being unsubstituted or substituted either (a) with one further substituent selected from unsubstituted C₁-C₂ alkoxy, -NH-(C₁-C₂ alkyl) and -N(C₁-C₂ alkyl)₂ groups or (b) with 1, 2 or 3 further substituents which are halo substituents; and
- the carbocyclyl and heterocyclyl groups and moieties in the R₁ to R₄ substituents are unsubstituted or carry 1, 2 or 3 substituents selected from C₁-C₄ alkyl, C₁-C₄ alkoxy, C₁-C₄ alkylthio, halogen, hydroxy, methylenedioxy, -NH₂, -NH(C₁-C₂ alkyl), -N(C₁-C₂ alkyl)₂, oxo, -NH-CO-(C₁-C₂ alkyl) and -O-CO-(C₁-C₂ alkyl) substituents, said substituents being unsubstituted or substituted either (a) with one further substituent selected from unsubstituted C₁-C₂ alkoxy, -NH-(C₁-C₂ alkyl) and -N(C₁-C₂ alkyl)₂ groups or (b) with 1, 2 or 3 further substituents which are halo substituents.

34. Use according to any one of claims 31 to 33, wherein R₂ is as defined in claim 3 or 4.

35. Use according to any one of claims 31 to 34, wherein Z is -S-, -S(O)- or

-S(O)₂- and/or R₁ is hydrogen or -CH₃ and/or R₂ is hydrogen or an unsubstituted C₁-C₄ alkyl group.

36. Use according to any one of claims 31 to 35, wherein the R₃ group is present at the 3-position of the phenyl ring to which it is attached.

37. Use according to any one of claims 31 to 36, wherein C₁ is a direct bond or a C₁-C₄ alkylene group which is unsubstituted when X₁ is other than a direct bond and, when X₁ is a direct bond, is unsubstituted or substituted at the carbon atom α to the moiety Ar₁ by one substituent selected from phenyl, hydroxy, halogen, C₁-C₂ alkoxy, -NH₂, -NH(C₁-C₂ alkyl), -N(C₁-C₂ alkyl)₂ and -NHCO-(C₁-C₂ alkyl).

38. Use according to claim 37 wherein the substituent α to the moiety X₁ is a phenyl group.

39. Use according to any one of claims 31 to 38, wherein X₁ is a direct bond or is -O-, -S-, -NR'-, -S-CO-, -O-CO-, -NR'-CO- or -CO-NR'-R''-CO-O-, wherein each R' is the same or different and is hydrogen, -CH₃ or -CH₂CH₃ and R'' is -CH₂- or -CH₂-CH₂-.

40. Use according to claim 39, wherein X₁ is a direct bond or is -O-, -S-, -S-CO-, -O-CO-, -NH-CO- or -CO-NH-CH₂-CO-O-.

41. Use according to any one of claims 31 to 40 wherein Ar₁ is heteroaryl, heterocyclyl, carbocyclyl, aryl, heteroaryl-(CH₂)_n- or aryl-(CH₂)_n- wherein n is 1 or 2.

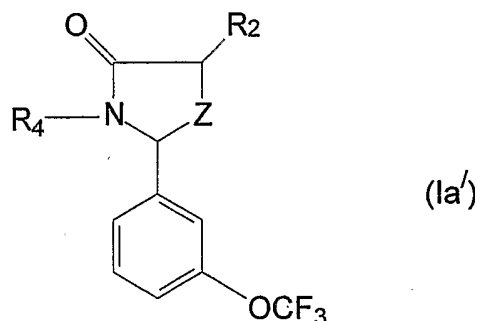
42. Use according to any one of claims 31 to 41, wherein C₂ is unsubstituted or carries one substituent at the carbon atom α to the moiety X₂ or, where X₂ is a direct bond, to the moiety C₃, which substituent is selected from hydroxy, halogen, C₁-C₂ alkoxy, -NH₂, -NH(C₁-C₂ alkyl), -N(C₁-C₂ alkyl)₂ and -NHCO-(C₁-C₂ alkyl).

43. Use according to claim 42, wherein said substituent is hydroxy or -NH-COCH₃.

44. Use according to any one of claims 31 to 43 wherein X₂ is a direct bond or is -O-, -S-, -NR'-, -CO-S-, -CO-O-, -CO-NR'- or -CO-NR'-R''-CO-O- wherein each R' is the same or different and is hydrogen, -CH₃ or -CH₂CH₃ and R'' is -CH₂- or -CH₂-CH₂-.

45. Use according to any one of claims 31 to 44, wherein C₃ is unsubstituted or substituted by one, two or three substituents selected from hydroxy, -NH₂, -NH(C₁-C₄ alkyl), -N(C₁-C₄ alkyl)₂ and halogen.

46. Use according to claim 31, wherein the compound of formula (I') is a compound of formula (Ia')



wherein:

- Z is -S-, -S(O)- or -S(O)₂-;
- R₂ is hydrogen, an unsubstituted C₁-C₄ alkyl group, -(CH₂)_a-CO₂H or -(CH₂)_b-CONR₅R₆ wherein a and b are 1 or 2 and either (a) R₅ is hydrogen or an unsubstituted benzyl group and R₆ is -L-R wherein L is a direct bond or an unsubstituted C₁-C₄ alkylene group and R is hydrogen or a phenyl, cyclohexenyl, piperidyl, pyridyl or benzimidazolyl group which is unsubstituted or substituted by a halogen, hydroxy, -OCH₃ or -OCH₂CH₃ substituent, or (b) R₅ and R₆, together with the N atom to which they are attached, represent a pyrrolidinyl, piperidinyl, homopiperidinyl or piperazinyl group which is unsubstituted or substituted by an unsubstituted -CHPh₂ group;
- R₄ is an unsubstituted methyl group or is -C₁-X₁-Ar₁ or -C₂-X₂-C₃, wherein C₁, C₂, X₁, X₂, Ar₁ and C₃ are as defined in any one of claims 31 to 45.

47. Use according to claim 46, wherein Z is S, R₂ is hydrogen or -CH₃ and R₄ is -C₁-X₁-Ar₁ or C₂-X₂-C₃ wherein C₁, C₂, X₁, X₂, Ar₁ and C₃ are as defined in any one of claims 31 to 45.

48. Use according to any one of claims 31 to 46, wherein:
Z, R₁, R₂ and R₃ are as defined in any one of claims 31 to 47; and
R₄ is an unsubstituted methyl group or is -C₁-Ar, or -C₂-X₂-C₃, wherein:

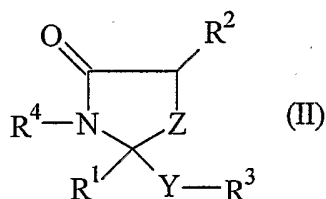
- C₁ is an unsubstituted C₁-C₄ alkylene group;
- Ar₁ is an aryl or heteroaryl group;
- C₂ is a C₁-C₆ alkylene group;

- X_2 is -O-, -S- or a direct bond; and
- C_3 is a C_1 - C_4 alkyl group.

49. Use according to claim 48, wherein (a) Ar_1 is an unsubstituted 2-pyridyl or 3-pyridyl group or a phenyl group which is unsubstituted or substituted with 1, 2 or 3 substituents selected from halogen, hydroxy, C_1 - C_4 alkyl and C_1 - C_4 alkoxy substituents, and/or (b) C_2 is an unsubstituted C_1 - C_5 alkylene group, and/or (c) C_3 is unsubstituted or carries, on a primary carbon atom, a hydroxy substituent.

50. Use according to any one of claims 1 to 30, wherein the compound of formula (I) is a compound wherein, when R_2 is other than hydrogen, fluorine and C_1 - C_6 alkyl, Y is $-(CR^y_2)_q-$, and/or R^3 is hydrogen.

51. A pharmaceutical composition comprising a compound of formula (II), or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier or diluent,

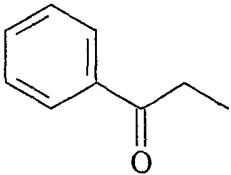


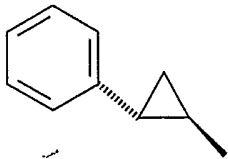
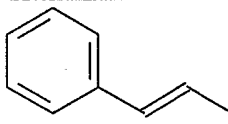
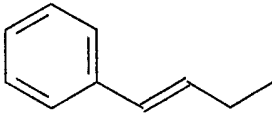
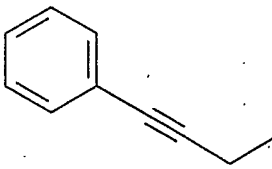
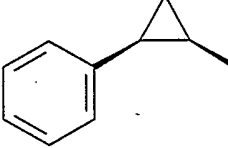
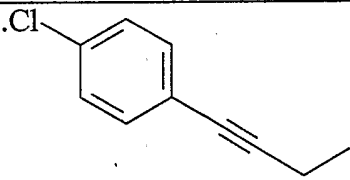
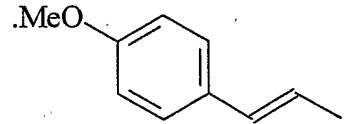
wherein R^1 , R^2 , R^3 , R^4 , Y and Z in the formula (II) are as defined in any one of claims 1 to 30, provided that (i) $-YR_3$ is other than an unsubstituted pyridyl group, (ii) $-YR_3$ is other than $-phenyl-O-A_2-R$, wherein A_2 is a C_2 - C_5 alkylene group and R is 1-pyrrolidinyl, 1-piperidinyl, 4-morpholinyl, 1-piperazinyl or 4-alkyl-1-piperazinyl, (iii) R^2 is other than C_1 - C_6 alkyl, (iv) when X_1 is -O-, Ar_1 is other than phenyl and when X_2 is -O- and C_2 is an unsubstituted C_1 - C_6 alkylene group, C_3 is other than an unsubstituted C_1 - C_6 alkyl group and (v) when Z is S and R^1 is hydrogen, R^4 and $Y-R^3$ are not defined as follows:

R^4	$Y-R^3$
$-(CH_2)_3-N(CH_3)_2$	phenyl
$-(CH_2)_3-N(CH_3)_2$	halophenyl

R ⁴	Y-R ³
-(CH ₂) ₃ -N(CH ₃) ₂	methoxyphenyl
-(CH ₂) ₃ -N(CH ₃) ₂	(C ₁ -C ₄ alkyl)phenyl
-(CH ₂) ₃ -N(CH ₃) ₂	nitrophenyl
-(CH ₂) ₃ -N(CH ₃) ₂	aminophenyl
2-(4-methoxyphenethyl)	3-methoxyphenyl
2-(4-methylphenethyl)	4-methoxyphenyl
2-(4-methoxyphenethyl)	4-pyrrolidinylphenyl
2-(4-methoxyphenethyl)	4-benzodioxanyl
2-(4-methoxyphenethyl)	3,4-dimethoxyphenyl
2-(4-methoxyphenethyl)	4-benzodioxolanyl
2-(4-methoxyphenethyl)	3-methyl-4-methoxyphenyl
2-(3-methoxyphenethyl)	4-benzodioxolanyl
2-phenethyl	3-methoxyphenyl
2-(4-methoxyphenethyl)	4-ethylphenyl
2-(4-methoxyphenethyl)	4-isopropoxyphenyl
2-(4-methoxyphenethyl)	4-methylthiophenyl
2-(4-chlorophenethyl)	4-methoxyphenyl
2-(4-methoxyphenethyl)	4-isopropylphenyl
2-(4-methoxyphenethyl)	4-benzoxyphenyl
2-(3-methoxyphenethyl)	4-(N-acetyl)aminophenyl
2-(4-methoxyphenethyl)	4-dimethylaminophenyl
2-(4-ethylphenethyl)	3-methoxyphenyl
2-(4-phenoxyphenethyl)	2-methoxyphenyl
2-(3,4-dimethoxyphenethyl)	4-ethylphenyl
2-(4-methoxyphenethyl)	3,4-dichlorophenyl
2-(3,4-dimethoxyphenethyl)	4-dimethylaminophenyl
2-(4-methoxyphenethyl)	3,4-difluorophenyl
2-(3-bromo-4-methoxyphenethyl)	3-methoxyphenyl

R ⁴	Y-R ³
2-(2,4-dichlorophenethyl)	3-methoxyphenyl
2-(4-methoxyphenethyl)	3-benzodioxolanyl
2-(4-methoxyphenethyl)	2,3-dimethyl-4-methoxyphenyl
2-(4-methoxyphenethyl)	B-naphthyl
2-(4-methoxyphenethyl)	2-thiophenyl
2-(4-methoxyphenethyl)	3-quinolinyl
2-(4-methoxyphenethyl)	phenyl
2-(4-methoxyphenethyl)	cyclohexyl
2-(4-methoxyphenethyl)	benzyl
2-(4-methoxyphenethyl)	3,5-dimethoxyphenyl
3-phenpropyl	4-dimethylaminophenyl
4-methoxybenzyl	3-methoxyphenyl
3-phenpropyl	4-ethylphenyl
4-phenbutyl	2-methoxyphenyl
n-hexyl	4-dimethylaminophenyl
4-methoxybenzyl	2-chlorophenyl
2-(4-methoxyphenethyl)	3-methoxyphenyl
2-(4-methoxyphenethyl)	4-ethylphenyl
2-(4-chlorophenethyl)	4-ethylphenyl
2-(4-methoxyphenethyl)	3-methyl-4-methoxyphenyl
2-(4-methoxyphenethyl)	4-benzodioxanyl
2-(4-bromophenethyl)	4-methoxyphenyl
2-(4-ethylphenethyl)	3-methylphenyl
2-(4-ethoxyphenethyl)	4-benzodioxolanyl
2-phenethyl	3-methyl-4-methoxyphenyl
4-methoxybenzyl	3-methyl-4-methoxyphenyl
2-phenoxyethyl	phenyl
2-(4-methoxyphenethyl)	3,4-dimethylphenyl

R ⁴	Y-R ³
2-(4-methoxyphenoxyethyl)	3,4-dimethylphenyl
2-(3-methoxyphenethyl)	4-benzodioxanyl
2-(3-methoxyphenethyl)	2,4-dichlorophenyl
n-pentyl	3-methoxyphenyl
Benzyl	3,4-dimethylphenyl
2-(3-methoxyphenethyl)	4-benzodioxanyl
2-(3-methoxyphenethyl)	4-benzodioxolanyl
4-phenbutyl	3,4-dimethylphenyl
2-(3-methoxyphenethyl)	3,4-dichlorophenyl
2-(3-methoxyphenethyl)	3-methylphenyl
2-(3-methoxyphenethyl)	3-bromo-4-methoxyphenyl
2-(3-methoxyphenethyl)	β-naphthyl
2-(4-nitrophenethyl)	3,4-dimethylphenyl
2-(3-methoxyphenethyl)	2,3-dimethyl-4-methoxyphenyl
2-(4-methoxyphenethyl)	5-ethyl-2-thiophenyl
2-(3-methoxyphenethyl)	3-benzodioxolanyl
2-phenoxyethyl	4-benzodioxolanyl
2-phenoxyethyl	3,4-dimethylphenyl
2-phenoxyethyl	4-ethylphenyl
2-(4-methylphenethyl)	4-benzodioxolanyl
2-(4-methylphenethyl)	3,4-dimethylphenyl
2-(4-methylphenethyl)	4-ethylphenyl
2-phenoxyethyl	5-ethyl-2-thiophenyl
2-phenoxyethyl	5-methyl-2-thiophenyl
n-hexyl	3-methoxyphenyl
	3,4-dimethylphenyl

R^4	$Y-R^3$
	4-benzodioxolanyl
	3-methoxyphenyl
	3,4-dimethylphenyl
	3,4-dimethylphenyl
	4-ethylphenyl
	4-benzodioxolanyl
	3-methyl-4-methoxyphenyl
2-(3-methoxyphenethyl)	2,4-dichlorophenyl

52. A pharmaceutical composition according to claim 51, wherein, in the compound of formula (II), Z, R^1 , R^2 , R^3 and Y are as defined in any one of claims 1 to 30, and R^4 is $-C_1-X_1-Ar_1'$ or $-C_2-X_2'-C_3$, or an unsubstituted C_1-C_4 alkyl group, wherein C_1 , X_1 , C_2 and C_3 are as defined in any one of claims 1 to 30, and:

- Ar_1' is heteroaryl, heterocyclyl, aryl, heteroaryl- R^a - or heterocyclyl- R^a -, wherein R^a is a C_1-C_6 alkylene group, a C_2-C_6 alkenylene group or a C_2-C_6 alkynylene group; wherein when Ar_1' is an unsubstituted phenyl group or a phenyl group

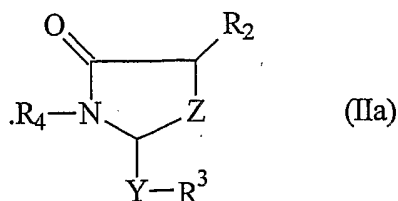
substituted with one or two groups selected from methyl, ethyl, methoxy, ethoxy, phenoxy, chlorine, bromine and nitro, either both C_1 and X_1 are direct bonds or C_1 is methylene and X_1 is -O-, -S-, -NR'-, -SO-, -SO₂-, -CO-S-, -CO-O-, -CO-NR'-, -S-CO-, -O-CO-, -NR'-CO-, -CO-O-R''-CO-O-, -CO-NR'-R''-CO-O-, -CO-O-R''-CO-NR'-, -CO-NR'-R''-CO-NR'-, -O-CO-NR'- or -NR'-CO-O-, wherein each R' is the same or different and represents hydrogen, phenyl, C_1 - C_6 alkyl, C_2 - C_6 alkenyl or C_2 - C_6 alkynyl and each R'' is the same or different and represents a C_1 - C_6 alkylene group, a C_2 - C_6 alkenylene group or a C_2 - C_6 alkynylene group, provided that when X_1 is -O-, Ar_1' is other than phenyl; and X_2' is -O-, -S-, -SO-, -SO₂-, -CO-, -CO-S-, -CO-O-, -CO-NR'-, -S-CO-, -O-CO-, -NR'-CO-, -CO-O-R''-CO-O-, -CO-NR'-R''-CO-O-, -CO-O-R''-CO-NR'-, -CO-NR'-R''-CO-NR'-, -NR'-CO-O- or -O-CO-NR'-, wherein each R' is the same or different and represents hydrogen, phenyl, C_1 - C_6 alkyl, C_2 - C_6 alkenyl or C_2 - C_6 alkynyl and each R'' is the same or different and represents a C_1 - C_6 alkylene group, a C_2 - C_6 alkenylene group or a C_2 - C_6 alkynylene group, provided that when X_2' is -O- and C_2 is an unsubstituted alkylene group, C_3 is other than an unsubstituted alkyl group;

provided that -YR₃ is other than an unsubstituted pyridyl group or -phenyl-O-A₂-R, wherein A₂ and R are as defined in claim 51 and R₂ is other than C_1 - C_6 alkyl.

53. A composition according to claim 52, wherein R_4 in the formula (II) is - C_1 - X_1 - Ar_1' or - C_2 - X_2' - C_3 .

54. A composition according to claim 52 or 53, wherein Ar_1' in the formula (II) is heteroaryl, heterocyclyl, heteroaryl-(C_1 - C_2 alkyl)- or a phenyl group fused to a heterocyclyl ring, each of which is unsubstituted or carries, on the cyclic moiety, 1, 2 or 3 unsubstituted groups selected from halogen, C_1 - C_4 alkyl, hydroxy, C_1 - C_4 alkoxy, -NR'R'' and -NH-CO-R' wherein R' and R'' are selected from hydrogen and unsubstituted C_1 - C_4 alkyl.

55. A composition according to claim 51, wherein the compound of formula (II) is a compound of formula (IIa)



wherein:

Z is -S-, -S(O)- or -S(O)₂-;

Y is a direct bond or a group of formula -(CR^y)₂-, -(CH₂)_mO(CH₂)-, -A- or -A-X₃-(CH₂)_m, wherein R^y is hydrogen, -CH₃, -CH₂-CH₃ or an unsubstituted phenyl group, wherein no more than one R^y group is phenyl; A is a phenyl, pyridyl or pyrrolyl group, which is unsubstituted or substituted with 1, 2 or 3 substituents selected from -CH₃, -CH₂-CH₃, -OCH₃, -OCH₂-CH₃, halogen and hydroxy; X₃ is -O-, -SO₂- or -NH-CO-; and m is 0 or 1;

R₂ is hydrogen, -(CH₂)_a-CO₂H or -(CH₂)_b-CONR₅R₆ wherein a and b are 1 or 2 and either (a) R₅ is hydrogen or an unsubstituted benzyl group and R₆ is -L-R wherein L is a direct bond or an unsubstituted C₁-C₄ alkylene group and R is hydrogen or a phenyl, cyclohexenyl, piperidyl, pyridyl or benzimidazolyl group which is unsubstituted or substituted by a halogen, hydroxy, -OCH₃ or -OCH₂CH₃ substituent, or (b) R₅ and R₆, together with the N atom to which they are attached, represent a pyrrolidinyl, piperidinyl, homopiperidinyl or piperazinyl group which is unsubstituted or substituted by an unsubstituted -CHPh₂ group;

R₄ is -CH₃, -C₁-X₁-Ar₁' or -C₂-X₂'-C₃, wherein:

- C₁ is -(CH₂)-, -(CH₂)₂- or -(CH₂)₃-;
- X₁ is a direct bond or is -O-, -S-, -S-CO- or -O-CO-;
- Ar₁' is a pyridyl, thienyl, benzimidazolyl, furanyl-methyl-, 1,3-benzodioxolyl or 1,4-benzodioxanyl group which is unsubstituted or carries, on the cyclic moiety, 1, 2 or 3 substituents selected from fluorine, hydroxy, -OCH₃, -N(CH₃)₂ and -NH-CO-CH₃;
- C₂ is a straight chain unsubstituted C₁-C₄ alkylene group;
- X₂' is -O-, -S-, -CO-O- or -NH-CO-O-; and

- C₃ is a C₁-C₄ alkyl group which is unsubstituted or substituted on a primary carbon atom with either (a) one hydroxy or (b) 1, 2 or 3 halo substituents, provided that Y-R₃ is other than an unsubstituted pyridyl group, and when X₂' is -O-, C₃ is other than an unsubstituted C₁-C₄ alkyl group.

56. A pharmaceutical composition comprising a compound of formula (I'), as defined in any one of claims 31 to 49, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier or diluent.

57. A pharmaceutical composition according to any one of claims 51 to 56, which is in the form of a tablet, capsule, troche, lozenge, aqueous or oily suspension, dispersible powder or granules or a sub-lingual tablet.

58. A pharmaceutical composition according to any one of claims 51 to 56, which is in a format suitable for parenteral, intranasal or transdermal administration or administration by inhalation.

59. A pharmaceutical composition according to any one of claims 51 to 58 which composition contains a pharmaceutically acceptable salt of a compound of formula (II) or (I').

60. A pharmaceutical composition according to any one of claims 51 to 59, which contains a compound of formula (II) or (I') which is a substantially pure optical isomer.

61. A compound of formula (II), as defined in any one of claims 51 to 55, a compound of formula (I'), as defined in any one of claims 31 to 49, or a pharmaceutically acceptable salt thereof, for use in the treatment of the human or animal body.

62. A method of treating a patient suffering from or susceptible to a condition mediated by N-type calcium channels, which method comprises administering to said patient an effective amount of a compound according to any one of claims 1 to 52, or a pharmaceutically acceptable salt thereof.

63. Use according to any one of claims 1 to 50, or a method according to claim 62, wherein said condition mediated by N-type calcium channels is pain.

INTERNATIONAL SEARCH REPORT

Internal application No
PCT/GB 03/03673

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 A61K31/427 A61K31/381 A61K31/343 A61K31/496 A61K31/4436
A61K31/4425 A61K31/44 A61K31/341 A61K31/4709 A61K31/4184
A61K31/4025 A61K31/352 A61P25/04

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 A61K

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, PAJ, CHEM ABS Data, MEDLINE, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X Y	EP 0 705 816 A (CHUGAI PHARMACEUTICAL CO LTD) 10 April 1996 (1996-04-10) page 3, line 1 - line 34 page 3, line 35 - page 4, line 19 examples 1-66	1-30, 62, 63 31-50, 56, 59-61
X Y	EP 0 799 614 A (CHUGAI PHARMACEUTICAL CO LTD) 8 October 1997 (1997-10-08) tables 18-57	1-30, 62, 63 31-50
X Y	WO 99 62891 A (ICAGEN INC ; LILLY CO ELI (US)) 9 December 1999 (1999-12-09) examples 1-86 page 1	1-30, 62, 63 56, 59-61
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☒ Further documents are listed in the continuation of box C.

☒ 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.

G document member of the same patent family

Date of the actual completion of the international search

22 October 2003

Date of mailing of the international search report

07/11/2003

Name and mailing address of the ISA

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Authorized officer

Giacobbe, S.

INTERNATIONAL SEARCH REPORT

Inter Application No
PCT/GB 03/03673

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	PATENT ABSTRACTS OF JAPAN vol. 0061, no. 69 (C-122), 2 September 1982 (1982-09-02) & JP 57 085380 A (HISAMITSU PHARMACEUT CO INC), 28 May 1982 (1982-05-28) abstract example 6	56, 59-61
X	US 3 377 355 A (SURREY ALEXANDER R) 9 April 1968 (1968-04-09) column 1, paragraph 1 column 5, lines 10,52 column 7, line 37 column 8, line 64 column 9, line 21 column 10, lines 7,13,26,28,55,68 claim 13	56, 59-61
X	RAVENS, URSULA ET AL: "Drugs preventing Na ⁺ and Ca ²⁺ overload" PHARMACOLOGICAL RESEARCH; ISSN: 1043-6618, vol. 39, no. 3, 1999, pages 169-174, XP0001155908	1-30, 62, 63
Y	figure 4 page 171, column 2, line 3 - page 172, column 1, line 3	31-50
X	PREVITERA, TINDARA ET AL: "3,3'-Bi-'1,3-thiazolidine-4-one! system. VII. Synthesis and SARS of some 2-heteroaryl derivatives with antiinflammatory and related activities" FARMACO; ISSN: 0014-827X, vol. 49, no. 1, 1994, pages 33-40, XP0009019619	1-30, 62, 63
Y	abstract tables 1,2,7,8 page 38, column 2, paragraph 4-6	31-50
A	EP 0 325 496 A (SUMITOMO PHARMA) 26 July 1989 (1989-07-26) examples 80-89,116-121,128,142-160,190,195,196 abstract	56, 59-61
A	PATENT ABSTRACTS OF JAPAN vol. 1997, no. 11, 28 November 1997 (1997-11-28) & JP 9 187300 A (SUMITOMO PHARMACEUT CO LTD), 22 July 1997 (1997-07-22) abstract	56, 59-61

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INTERNATIONAL SEARCH REPORT

Intern Application No
PCT/GB 03/03673

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	PATENT ABSTRACTS OF JAPAN vol. 1996, no. 03, 29 March 1996 (1996-03-29) & JP 7 304689 A (SUMITOMO PHARMACEUT CO LTD), 21 November 1995 (1995-11-21) abstract -----	56,59-61
A	PATENT ABSTRACTS OF JAPAN vol. 1998, no. 01, 30 January 1998 (1998-01-30) & JP 9 227411 A (SUMITOMO PHARMACEUT CO LTD), 2 September 1997 (1997-09-02) abstract -----	56,59-61
P,A	WO 03 008398 A (EURO CELTIQUE SA ; KYLE DONALD J (US); SUN QUN (US)) 30 January 2003 (2003-01-30) paragraph '0008! paragraph '0017! - paragraph '0026! paragraph '0034! -----	56,59-61

INTERNATIONAL SEARCH REPORT

Int. application No.
PCT/GB 03/03673

Box I Observations where certain claims were found unsearchable (Continuation of item 1 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.: 62
because they relate to subject matter not required to be searched by this Authority, namely:
Although claim 62 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.: 51-55
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:
see FURTHER INFORMATION sheet PCT/ISA/210
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 II Observations where unity of invention is lacking (Continuation of item 2 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.

Continuation of Box I.2

Claims Nos.: 51-55

1. Present claims 51-55 and 57 relate to an extremely large number of possible compounds. In fact, the claims contain so many variables and such a great number of disclaimers that a lack of clarity (and conciseness) within the meaning of Article 6 PCT arises to such an extent as to render a meaningful search of the claims impossible. In particular the huge number of disclaimers makes it totally impossible to define the actual scope of independent claim 51, i.e. the boundaries delimiting what is claimed from what lies outside. The same applies mutatis mutandis to its dependent claims. Consequently no Search has been performed on the subject-matter of these claims.

2. Present claims 1-50, 56 and 58-63 relate to an extremely large number of possible compounds. Support within the meaning of Article 6 PCT and disclosure within the meaning of Article 5 PCT is to be found, however, for only a very small proportion of them. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Consequently, the search has been carried out for those parts of the claims which appear to be supported and disclosed, namely those parts defined by the examples. In particular the Search has been performed for the compounds where

- a) Z=S
- b) R₁=H
- c) R₂=H, F or C₁-C₆ alkyl
- d) Y=-(CR_y2)q- wherein R_y=H and q=0
- e) R₃ is not H
- f) R₄=-C₁-X₁-Ar₁ where C₁ and Ar₁ are as claimed and X₁ is a bond, alkylene or O, S or N or R₄=-C₂-X₂-C₃ where C₂ and C₃ are as claimed and X₂ is a bond or O, S or N.

These values should encompass all the examples presented in the description and define therefore a range which is supported. Since however no claim was drafted encompassing this subject-matter no claim could be searched completely. The attention is further drawn to the fact that it is possible that the Applicant might later not be in the position of drafting an allowable claim to this subject-matter without contravening the requirement that the application as filed may not be amended so as to introduce new subject-matter: defining new boundaries to a Markush formula may implicate just that (new selection).

The applicant's attention is drawn to the fact that claims relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the

claims are amended following receipt of the search report or during any Chapter II procedure. If the application proceeds into the regional phase before the EPO, the applicant is reminded that a search may be carried out during examination before the EPO (see EPO Guideline C-VI, 8.5), should the problems which led to the Article 17(2) declaration be overcome.

INTERNATIONAL SEARCH REPORT

Internal application No
PCT/GB 03/03673

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