The invention relates to novel N-(2-methylphenyl-1-cyclopentyl)sulphonamide derivatives of formula (I) and salts thereof: wherein R₁, R₂, R₃, R₄, R₅, R₆, R₇, R₈, p, R₉ and R₁₀ are as defined in the description. The invention also relates to the use of the derivatives in treating diseases and conditions mediated by potentiation of the glutamate receptor, compositions containing the derivatives and processes for their preparation.
**Compounds which potentiate the AMPA receptor and uses thereof in medicine**

This invention relates to potentiation of the AMPA receptor by novel N-(2-methyl-phenyl-cyclopentyl)sulphonamide derivatives.

Glutamate receptors, which mediate the majority of fast excitatory neurotransmission in the mammalian central nervous system (CNS), are activated by the excitatory amino acid, L-glutamate (for review see Watkins JC, Krogsgaard-Larsen P, Honore T (1990) Trends Pharmacol Sci 11: 25-33).

Glutamate receptors can be divided into two distinct families. The G-protein or second messenger-linked "metabotropic" glutamate receptor family which can be subdivided into three groups (Group I, mGlu1 and mGlu5; Group II, mGlu2 and mGlu3; Group III, mGlu4, mGlu6, mGlu7, mGlu8) based on sequence homology and intracellular transduction mechanisms (for review see Conn PJ and Pinn JP (1997) Ann Rev Pharmacol Toxicol 37: 205-237). The "ionotropic" glutamate receptor family, which directly couple to ligand-gated cation channels, can be subdivided into at least three subtypes based on depolarizing activation by selective agonists, N-methyl-D-aspartate (NMDA), α-amino-3-hydroxy-5-methylisoxazole-4-propionic acid (AMPA) and kainic acid (KA) (for review see Dingledine R, Borges K, Bowie D and Traynelis S (1999) Pharmacol. Rev. 51: 7-61).

Native AMPA receptors (AMPAR) exist as heterotetramers consisting of combinations of four different protein subunits (GluR1-4) (for review see Bettler B and Muller C (1995) Neuropharmacology 34: 123-139.). Receptor subunit diversity is increased further as each subunit can undergo alternative splicing of a 38 amino acid sequence in the extracellular region just before the fourth membrane spanning domain M4. Such editing results in so-called 'flip' and 'flop' receptor isoforms which differ in kinetic and pharmacological properties (Sommer B, Keinanen K, Verdoon TA, Wisden W, Burnashev N, Herb A, Kohler M, Takagi T, Sakmann B, Seeburg PH (1990) Science 249: 1580-1585).

Additionally, post-transcriptional editing of GluR2 mRNA changes a neutral glutamine to a positively charged arginine within M2. In normal humans >99% GluR2 is edited in this way. AMPAR containing such edited GluR2 subunit exhibit low calcium permeability (Burnashev N, Monyer H, Seeburg PH, Sakmann B (1992) Neuron 8: 189-198). There is a suggestion, however, that the number of AMPAR with high calcium permeability is elevated in certain disease-associated conditions (Weiss JH, and Sensi SL (2000) Trends in Neurosci 23: 365-371).

AMPAR depolarization removes voltage dependent Mg$^{2+}$ block of NMDA receptors which in turn leads to NMDA receptor activation, an integral stage in the induction of Long Term Potentiation ("LTP") (Bliss TVP, Collingridge GL (1993) Nature 361: 31-9). LTP is a
physiological measure of increased synaptic strength following a repetitive stimulus or activity, such as occurs during learning.

It has been reported that direct activation of glutamate receptors by agonists, in conditions where glutamate receptor function is reduced, increases the risk of excitotoxicity and additional neuronal damage. AMPAR positive allosteric modulators do not activate the receptor directly. However, when the ligand (L-glutamate or AMPA) is present AMPAR modulators increase receptor activity. Thus, AMPA receptor modulators enhance synaptic function when glutamate is released and is able to bind at post-synaptic receptor sites.


Compounds which act as AMPA receptor positive allosteric modulators are known, for example in international patent application WO2006/015828.

We have discovered a class of novel N-(2- methyl-phenyl-cyclopentyl)sulphonamide derivatives that potentiate the AMPA receptor.

According to a first aspect, the invention provides a compound of formula (I), or a salt thereof:

\[
\text{\text{(I)}}
\]
wherein

R is C-\(\text{^galkyl}\), haloC-\(\text{^\mu galkyl}\), C-\(\text{^2 galkenyl}\), amino, monoC-\(\text{^4alkylamino}\) or diC-\(\text{^4alkylamino}\);  
R, R3, R4, ... the one or more heteroatoms may be in an aromatic ring, or in a non-aromatic ring or in both types of rings.

each R\(^9\), which may be the same or different, is C-\(\text{^\mu galkyl}\), haloC-\(\text{^\mu galkyl}\) and C-\(\text{^4alkoxy}\);  
p is 0, 1 or 2;  
R\(^9\) is halo; or phenyl or aromatic heterocyclyl, either of which is optionally substituted by one or more groups independently selected from the group consisting of: halogen, haloC-\(\text{^\mu galkyl}\), C-\(\text{^4alkoxy}\), haloC-\(\text{^4alkoxy}\), cyano, -(CH\(^2\))\(\text{\_qNR}^9\text{\text{\_aSC>2R}^9\text{\text{\_b}}\)}, -(CH\(^2\))\(\text{\_qNR}^9\text{\text{\_a(C=O)R}^9\text{\text{\_d}}\)}, -(CH\(^2\))\(\text{\_qNR}^9\text{\text{\_a(C=O)N(R}^9\text{\text{\_c)}_\text{\_2}}\)}, -(CH\(^2\))\(\text{\_q(C=O)R}^9\text{\text{\_d}}\) and -(CH\(^2\))\(\text{\_qSO}\text{\_2R}^9\text{\text{\_b}}\); where R\(\text{\_a}\) and each R\(\text{\_c}\), which may be the same or different, is hydrogen or C-\(\text{^\_galkyl}\); R\(\text{\_b}\) is C-\(\text{^\_galkyl}\) or haloC-\(\text{^\_galkyl}\); R\(\text{\_d}\) is C-\(\_\text{\_galkyl}\), C-\(\text{^4alkoxy}\) or haloC-\(\_\text{\_galkyl}\); or R\(\text{\_a}\) and R\(\text{\_b}\), R\(\text{\_a}\) and R\(\text{\_c}\), or R\(\text{\_a}\) and R\(\text{\_d}\) together with the interconnecting atoms, may form a 5- or 6-membered ring; and q is 0, 1, or 2.

Unless otherwise indicated, any alkyl group may be straight or branched and is of 1 to 6 carbon atoms, preferably 1 to 4 and particularly 1 to 3 carbon atoms.

Unless otherwise indicated, any alkenyl group may be straight or branched and is of 2 to 6 carbon atoms and may contain up to 3 double bonds which may be conjugated, for example vinyl, allyl and butadienyl.

Halo is fluoro, chloro, bromo or iodo. For example, halo is selected from fluoro and chloro.

The term aromatic heterocyclyl as used herein describes a carbocyclic group, containing 1 to 4 heteroatoms independently selected from oxygen, nitrogen and sulphur and which contains at least one aromatic ring system. The aromatic heterocyclyl group may, for example, be monocyclic or bicyclic. It may also be tricyclic. A monocyclic aromatic heterocyclyl group may, for example, contain 5 to 7 ring atoms. A bicyclic aromatic heterocyclyl group may, for example, contain 7 to 12 ring atoms. In the case of bicyclic aromatic heterocyclyl groups, one ring or both rings may be aromatic. In the case of only one ring being aromatic, the one or more heteroatoms may be in the aromatic ring, in the non-aromatic ring or in both rings. A tricyclic aromatic heterocyclyl group may, for example, contain 10 to 14 ring atoms. In the case of tricyclic aromatic heterocyclyl groups, one, two or three rings may be aromatic. In the case of not all of the rings being aromatic, the one or more heteroatoms may be in an aromatic ring, or in a non-aromatic ring or in both types of rings.
Examples of monocyclic aromatic heterocyclyl groups are furyl, thienyl, pyrrolyl, imidazolyl, oxazolyl, thiazolyl, imidazolyl, pyrazolyl, isoxazolyl, isothiazolyl, oxadiazolyl, triazolyl, thiadiazolyl, pyridazinyl, pyridyl, pyrimidinyl, pyrazinyl, tetrazolyl, triazinyl, oxazepinyl, thiazepinyl, and diazepinyl.

In addition, the term heterocyclyl includes fused bicyclic heterocyclyl groups in which both rings are aromatic, for example benzimidazolyl, benzoxazolyl, imidazopyridinyl, benzoazinyl, benzothiazinyl, oxazolopyridinyl, benzofuranyl, quinolinyl, quinazolinyl, quinoxalinyl, dihydroquinazolinyl, benzothiazolyl, phthalimido, benzofuranyl, benzodiazepinyl, indolyl, benzodioxany1 and isoindolyl.

Examples of bicyclic aromatic heterocyclyl groups in which only one ring is aromatic include phenyl fused with a diazabicycloalkane group, for example ethanoquinoxaliny1.

Examples of tricyclic aromatic heterocyclyl groups include carbazolyl, acridinyl, phenazinyl, phenothiazinyl, phenoxazinyl, thianthrenyl, anthraceninyl, acenaphthleninyl, fluoreninyl and phenanthreninyl and the like.

In an embodiment \( R^1 \) is \( C_{1-g} \) alkyl. In a further embodiment \( R^1 \) is isopropyl or ethyl.

In an embodiment \( R^2, R^3, R^4, R^5, R^6, R^7 \) and \( R^{10} \), which may be the same or different, are hydrogen, halogen or \( C_{1-g} \) alkyl. In a further embodiment \( R^2, R^3, R^4, R^5, R^6, R^7 \) and \( R^{10} \), which may be the same or different, are hydrogen, fluorine or methyl.

In an embodiment, when present, each \( R^8 \), which may be the same or different, is or \( C_{1-g} \) alkyl or halogen. In a further embodiment, when present, each \( R^8 \), which may be the same or different, is methyl or fluorine.

In an embodiment, \( p \) is 0.

In an embodiment, \( R^9 \) is phenyl or aromatic heterocyclyl, optionally substituted with one or more groups independently selected from the group consisting of: halogen, cyano, \(-(CH_2)_qNR9as0_{2}R^\beta_{b} \) and \(-(CH_2)_qSO_{2}R^\beta_{b} \); where \( R^\beta_{a} \) and each \( R^\beta_{C} \), which may be the same or different, is hydrogen or \( C_{1-g} \) alkyl; \( R^\beta_{b} \) is \( C_{1-g} \) alkyl or halo\( C_{1-g} \) alkyl; \( R^\beta_{d} \) is \( C_{1-g} \) alkyl, \( C_{1-g} \) alkoxy or halo\( C_{1-g} \)alkyl; or \( R^\beta_{a} \) and \( R^\beta_{b} \), \( R^\beta_{a} \) and \( R^\beta_{c} \), or \( R^\beta_{a} \) and \( R^\beta_{d} \) together with the interconnecting atoms, may form a 5- or 6-membered ring; and \( q \) is 0, 1, or 2.

In an embodiment, \( R^9 \) is a phenyl, optionally substituted with one or more groups independently selected from the group consisting of: cyano, \(-(CH_2)_qNR^9aSO_{2}R^9b_{b} \), \(-(CH_2)_qNR^9a(C=O)R^9b_{d} \), \(-(CH_2)_qNR^9a(C=O)NR^9a(C=O)(R^9C)_2 \), \(-(CH_2)_q(C=O)R^9d_{d} \) and \(-(CH_2)_qSO_{2}R^9b_{b} \); where \( R^9a \) and each \( R^9c \), which may be the same or different, is
hydrogen or C₂alkyl; R⁹ is C₁alkyl, C₁.galkyl or haloC₂alkyl; R⁹d is C₁.galkyl, C₁.4alkoxy or haloC₂alkyl; or R⁹a and R⁹b, R⁹a and R⁹c, or R⁹a and R⁹d together with the interconnecting atoms, may form a 5- or 6-membered ring; and q is 0, 1, or 2.

In an embodiment, R⁹ is a pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, thienyl, imidazolyl, pyrrolyl, oxazolyl or pyrazolyl, optionally substituted with one or more groups independently selected from the group consisting of: cyano or halogen.

In an embodiment, R⁹ is iodo or bromo.

Because of the presence of the cyclopentyl ring, compounds of formula (I) possess at least two chiral centres, namely the attachment points of the sulphonamide and the phenyl ring on the cyclopentyl ring. The compounds may exist in four stereoisomers - a pair of diastereomers (cis and trans), each comprising a pair of enantiomers with respect to the chiral centres in the cyclopentane. It will also be appreciated, in common with most biologically active molecules that the level of biological activity may vary between the individual diastereoisomers of a given molecule. It is intended that the scope of the invention includes all individual stereoisomers (diastereoisomers and enantiomers) and all mixtures thereof, including but not limited to racemic mixtures, which demonstrate appropriate biological activity with reference to the procedures described herein.

In an embodiment, the sulphonamide and phenyl substituents on the cyclopentyl ring are in a trans arrangement relative to each other.

Individual enantiomers of various of the example compounds have been prepared. As at the date of filing, the absolute stereochemistry of the individual isomers has not been established. The individual isomers are identified by chiral HPLC retention times or by the chiral HPLC retention times of the intermediate starting materials from which they were prepared. Herein, a compound that has been prepared in racemic form has the suffix "racemic" and a compound that has been prepared in chiral form has the suffix "enantiomer 1" or "enantiomer 2". In one embodiment a compound of the invention in chiral form has at least 80% e.e. In another a compound of the invention in chiral form has at least 90% e.e., for example at least 95% e.e. In another embodiment the isomers correspond to at least 98% e.e, for example at least 99% e.e.

In an embodiment, the compound according to the first aspect is of formula (Ia) or a salt thereof:
wherein \( R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, p, R^9 \) and \( R^{10} \) are as defined for formula (I).

In an embodiment,

5 \( R^1 \) is C1-6 alkyl;

5 \( R^2, R^3, R^4, R^5, R^6, R^7 \) and \( R^{10} \) are hydrogen, halogen, or C1-6 alkyl;

p is 0 and

5 \( R^9 \) is phenyl, pyridyl or thienyl, optionally substituted with one or more groups independently selected from the group consisting of: halogen, cyano, -(CH\(_2\))\(_q\)NR\(_9\)a, -(CH\(_2\))\(_q\)NR\(_9\)(C=O)R\(_9\)d, -(CH\(_2\))\(_q\)NR\(_9\)a(C=O)N(R\(_9\)C\(_2\)), -(CH\(_2\))\(_q\) (C=O)R\(_9\)d and -(CH\(_2\))\(_q\)SO\(_2\)R\(_9\)b, where \( R^9 \)a and each \( R^9 \)c, which may be the same or different, is hydrogen or C-1,galkyl; \( R^9 \)d, C-1,galkyl or haloC-1,galkyl; \( R^9 \)d is C-1,6 alkyl, C-1,4 alkoxy or haloC-1,6 alkyl; or \( R^9 \)a and \( R^9 \)d, \( R^9 \)a and \( R^9 \)d together with the interconnecting atoms, may form a 5- or 6-membered ring; and q is 0, 1, or 2.

Examples of compounds of formula (I) are:

C/s.-N-[2-[(3'-[(methylsulfonyl) amino]-4-biphenylmethyl)cyclopentyl]-2-propanesulfonamide (example 1),

C/s.-N-[2-[(3'-[(methylsulfonyl)-4-biphenylmethyl)cyclopentyl]-2-propanesulfonamide (example 2),

C/s.-N-[2-[(4-(3-thienyl)phenylmethyl)cyclopentyl]-2-propanesulfonamide (example 3),

C/s.-N-[2-[(4'-cyanof-4-biphenylmethyl)cyclopentyl]-2-propanesulfonamide (example 4),

C/s.-N-[2-[(4'-iododiphenyl)methyl)cyclopentyl]-2-propanesulfonamide (example 5),

C/s.-N-[2-[(4'-iodophenyl)methyl)cyclopentyl]ethaneanesulfonamide (example 6) and

C/s.-N-[2-[(2'-fluoro-4-biphenylmethyl)cyclopentyl]-2-propanesulfonamide (example 7)

and salts thereof.

For the avoidance of doubt, unless otherwise indicated, the term substituted means substituted by one or more defined groups. In the case where groups may be selected from a number of alternative groups, the selected groups may be the same or different.

For the avoidance of doubt, the term independently means that where more than one substituent is selected from a number of possible substituents, those substituents may be the same or different.

In one embodiment, an appropriate compound of formula (I) may be in the form of a salt. In one embodiment, the present invention provides a compound of formula (I) or a
pharmaceutically acceptable salt. Suitable pharmaceutically acceptable salts of the compounds of formula (I) include acid salts, for example sodium, potassium, calcium, magnesium and tetraalkylammonium and the like, or mono- or di-basic salts with the appropriate acid for example organic carboxylic acids such as acetic, lactic, tartaric, malic, isethionic, lactobionic and succinic acids; organic sulfonic acids such as methanesulfonic, ethanesulfonic, benzenesulfonic and p-toluensulfonic acids and inorganic acids such as hydrochloric, sulfuric, phosphoric and sulfamic acids and the like. Other salt forms that are not pharmaceutically acceptable, for example a salt that is useful as an intermediate, also form part of the present invention.

Furthermore, some of the crystalline forms of the compounds of structure (I) may exist as polymorphs, which are included in the present invention.

Some of the compounds of this invention may be crystallised or recrystallised from solvents such as aqueous and organic solvents. In such cases solvates may be formed. This invention includes within its scope stoichiometric solvates including hydrates as well as compounds containing variable amounts of solvent (including water) where non-stoichiometric solvates (hydrates in the case of water) may be produced by processes such as lyophilisation).

It will be appreciated by those skilled in the art that certain protected derivatives of compounds of formula (I), which may be made prior to a final deprotection stage, may not possess pharmacological activity as such, but may, in certain instances, be administered orally or parenterally and thereafter metabolised in the body to form compounds of the invention which are pharmacologically active. Such derivatives may therefore be described as "prodrugs". Further, certain compounds of the invention may act as prodrugs of other compounds of the invention. All protected derivatives and prodrugs of compounds of the invention are included within the scope of the invention. Examples of suitable pro-drugs for the compounds of the present invention are described in Drugs of Today, Volume 19, Number 9, 1983, pp 499 - 538 and in Topics in Chemistry, Chapter 31, pp 306 - 316 and in "Design of Prodrugs" by H. Bundgaard, Elsevier, 1985, Chapter 1 (the disclosures in which documents are incorporated herein by reference). It will further be appreciated by those skilled in the art, that certain moieties, known to those skilled in the art as "pro-moieties", for example as described by H. Bundgaard in "Design of Prodrugs" (the disclosure in which document is incorporated herein by reference) may be placed on appropriate functionalities when such functionalities are present within compounds of the invention. Preferred prodrugs for compounds of the invention include : esters, carbonate esters, hemi-esters, phosphate esters, nitro esters, sulfate esters, sulfoxides, amides, carbamates, azo-compounds, phosphamides, glycosides, ethers, acetals and ketals.
Hereinafter, compounds, their pharmaceutically acceptable salts, their solvates and prodrugs, defined in any aspect of the invention (except Intermediate compounds in chemical processes) are referred to as "compounds of the invention".

The compounds of the invention may exist in one or more tautomeric forms. All tautomers and mixtures thereof are included in the scope of the present invention.

Since the compounds of the invention are intended for use in pharmaceutical compositions it will readily be understood that they are each preferably provided in substantially pure form, for example at least 60% pure, more suitably at least 75% pure and preferably at least 85%, especially at least 98% pure (% are on a weight for weight basis). Impure preparations of the compounds may be used for preparing the more pure forms used in the pharmaceutical compositions; these less pure preparations of the compounds should contain at least 1%, more suitably at least 5% and preferably from 10 to 59% of a compound of the invention.

Compounds of the invention may be prepared in a variety of ways. In the following reaction schemes and hereafter, unless otherwise stated R¹ to R¹⁰, p and q are as defined in the first aspect. These processes form further aspects of the invention.

Throughout the specification, general formulae are designated by Roman numerals (I), (II), (III), (IV) etc. Subsets of these general formulae are defined as (Ia), (Ib), (Ic) etc .... (IVa), (IVb), (IVc) etc.

Compounds of general formula (I) may be prepared by coupling compounds of formula (II) where X is a leaving group such as halogen (preferably bromine) with boronic acid derivatives of formula (III) according to reaction scheme 1. Typical coupling conditions comprise heating a compound of formula (II), a compound of formula (III), a base (such as cesium carbonate), triphenylphosphine, and palladium (II) acetate in a mixture of 1,4-dioxan and water at about 80 degC.

Scheme 1

Compounds of formula (Na), i.e. compounds of formula (II) where X is iodine, may be prepared from compounds of formula (IV) according to reaction scheme 2. Typical
reaction conditions require treatment of (IV) with strong acid such as sulfuric acid and glacial acetic acid followed by treatment with periodic acid and iodine.

Scheme 2

![Scheme 2](image)

Compounds of formula (IV) may be prepared from compounds of formula (V) according to reaction scheme 3. Typical reaction conditions are adding sulfonyl chloride (VI) to an ice-cooled mixture of (V) and a base (such as diisopropylamine) in a suitable solvent (such as dichloromethane) and then warming the mixture gradually to room temperature.

Scheme 3

![Scheme 3](image)

Compounds of formula (V) may be prepared using procedures available to the skilled person (Chem Berichte 119(8), 2668-77, 1986).

Further details for the preparation of compounds of formula (I) are found in the examples section hereinafter.

The compounds of the invention may be prepared singly or as compound libraries comprising at least 2, for example 5 to 1,000 compounds, for example 10 to 100 compounds. Libraries of compounds of the invention may be prepared by a combinatorial 'split and mix' approach or by multiple parallel synthesis using either solution phase or solid phase chemistry, by procedures known to those skilled in the art. Thus according to a further aspect there is provided a compound library comprising at least 2 compounds of the invention.
Compounds of the invention may be administered in combination with other therapeutic agents, for example an antipsychotic (such as olanzapine, risperidone, clozapine, ziprazidone and talnetant).

The compounds of the invention may be administered in conventional dosage forms prepared by combining a compound of the invention with standard pharmaceutical carriers or diluents according to conventional procedures well known in the art. These procedures may involve mixing, granulating and compressing or dissolving the ingredients as appropriate to the desired preparation.

The pharmaceutical compositions of the invention may be formulated for administration by any route, and include those in a form adapted for oral, topical or parenteral administration to mammals including humans.

The compositions may be formulated for administration by any route. The compositions may be in the form of tablets, capsules, powders, granules, lozenges, creams or liquid preparations, such as oral or sterile parenteral solutions or suspensions.

The topical formulations of the present invention may be presented as, for instance, ointments, creams or lotions, eye ointments and eye or ear drops, impregnated dressings and aerosols, and may contain appropriate conventional additives such as preservatives, solvents to assist drug penetration and emollients in ointments and creams.

The formulations may also contain compatible conventional carriers, such as cream or ointment bases and ethanol or oleyl alcohol for lotions. Such carriers may be present as from about 1% up to about 98% of the formulation. More usually they will form up to about 80% of the formulation.

Tablets and capsules for oral administration may be in unit dose presentation form, and may contain conventional excipients such as binding agents, for example syrup, acacia, gelatin, sorbitol, tragacanth, or polyvinylpyrrolidone; fillers, for example lactose, sugar, maize-starch, calcium phosphate, sorbitol or glycine; tableting lubricants, for example magnesium stearate, talc, polyethylene glycol or silica; disintegrants, for example potato starch; or acceptable wetting agents such as sodium lauryl sulphate. The tablets may be coated according to methods well known in normal pharmaceutical practice. Oral liquid preparations may be in the form of, for example, aqueous or oily suspensions, solutions, emulsions, syrups or elixirs, or may be presented as a dry product for reconstitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives, such as suspending agents, for example sorbitol, methyl cellulose, glucose syrup, gelatin, hydroxyethyl cellulose, carboxymethyl cellulose, aluminium stearate gel or hydrogenated edible fats, emulsifying agents, for example lecithin, sorbitan monooleate, or acacia; non-aqueous vehicles (which may include edible oils), for example
almond oil, oily esters such as glycerine, propylene glycol, or ethyl alcohol; preservatives, for example methyl or propyl p-hydroxybenzoate or sorbic acid, and, if desired, conventional flavouring or colouring agents.

Suppositories will contain conventional suppository bases, e.g. cocoa-butter or other glyceride.

For parenteral administration, fluid unit dosage forms are prepared utilising the compound and a sterile vehicle, for example water. The compound, depending on the vehicle and concentration used, can be either suspended or dissolved in the vehicle. In preparing solutions the compound can be dissolved in water for injection and filter sterilised before filling into a suitable vial or ampoule and sealing.

Advantageously, agents such as a local anaesthetic, preservative and buffering agents can be dissolved in the vehicle. To enhance the stability, the composition can be frozen after filling into the vial and the water removed under vacuum. The dry lyophilised powder is then sealed in the vial and an accompanying vial of water for injection may be supplied to reconstitute the liquid prior to use. Parenteral suspensions are prepared in substantially the same manner except that the compound is suspended in the vehicle instead of being dissolved and sterilisation cannot be accomplished by filtration. The compound can be sterilised by exposure to ethylene oxide before suspending in the sterile vehicle. Advantageously, a surfactant or wetting agent is included in the composition to facilitate uniform distribution of the compound.

The compositions may contain from 0.1% by weight, for example from 10-60% by weight, of the active material, depending on the method of administration. Where the compositions comprise dosage units, each unit may, for example contain from 0.1 to 20 mg of the active ingredient. For example, such a unit may contain from 1 to 10 mg. The dosage as employed for adult human treatment may, for example, range from 2 to 50 mg per day, for instance 5 to 20 mg per day depending on the route and frequency of administration (though in some instances, a dosage of 50mg to 100mg per day may be appropriate). Based on a 75kg individual, such a dosage corresponds to 0.027 to 0.667 mg/kg per day. Suitably the dosage is from 0.05 to 0.3 mg/kg per day.

It will be recognised by one of skill in the art that the optimal quantity and spacing of individual dosages of a compound of the invention will be determined by the nature and extent of the condition being treated, the form, route and site of administration, and the particular mammal being treated, and that such optimums can be determined by conventional techniques. It will also be appreciated by one of skill in the art that the optimal course of treatment, i.e. the number of doses of a compound of the invention given per day for a defined number of days, can be ascertained by those skilled in the art using conventional course of treatment determination tests.
It will be appreciated that the invention includes the following further aspects. The embodiments described in respect of the first aspect apply equally to each of these further aspects:

i) a pharmaceutical composition comprising a compound of formula (I) or a pharmaceutically acceptable salt and at least one pharmaceutically acceptable carrier or diluent;

ii) the use of a compound of formula (I) or a pharmaceutically acceptable salt in the manufacture of a medicament for treating or preventing a disease or condition caused by a reduction or imbalance in glutamate receptor function in a mammal;

iii) a compound of formula (I) or a pharmaceutically acceptable salt for use in treating or preventing a disease or condition caused by a reduction or imbalance in glutamate receptor function in a mammal;

iv) a compound of formula (I) or a pharmaceutically acceptable salt for use as a medicament; and

v) a method of treatment or prevention of a disease or condition caused by a reduction or imbalance in glutamate receptor function in a mammal comprising administering an effective amount of a compound of formula (I) or a pharmaceutically acceptable salt.

Furthermore, the invention also provides a combination product of a compound of formula (I) or a pharmaceutically acceptable salt with an antipsychotic. In addition, the invention provides:

i) a pharmaceutical composition comprising such a combination product and at least one pharmaceutically acceptable carrier or diluent;

ii) the use of such a combination in the manufacture of a medicament for treating or preventing a disease or condition caused by a reduction or imbalance in glutamate receptor function in a mammal;

iii) such a combination product for use in treating or preventing a disease or condition caused by a reduction or imbalance in glutamate receptor function in a mammal;

iv) such a combination product for use as a medicament;

v) a method of treatment or prevention of a disease or condition caused by a reduction or imbalance in glutamate receptor function in a mammal comprising administering an effective amount of such a combination product.

In the case of aspects ii), iii) and v), relevant diseases or conditions are: psychosis and psychotic disorders (including schizophrenia, schizoaffective disorder, schizophreniform diseases, brief reactive psychosis, child onset schizophrenia, "schizophrenia-spectrum" disorders such as schizoid or schizotypal personality disorders, acute psychosis, alcohol psychosis, drug-induced psychosis, autism, delerium, mania (including acute mania), manic depressive psychosis, hallucination, endogenous psychosis, organic
psychosyndrome, paranoid and delusional disorders, puerperal psychosis, and psychosis associated with neurodegenerative diseases such as Alzheimer's disease; cognitive impairment (e.g. the treatment of impairment of cognitive functions including attention, orientation, memory (i.e. memory disorders, amnesia, amnesic disorders and age-associated memory impairment) and language function, and including cognitive impairment as a result of stroke, Alzheimer's disease, Aids-related dementia or other dementia states, as well as other acute or sub-acute conditions that may cause cognitive decline such as delirium or depression (pseudodementia states) trauma, aging, stroke, neurodegeneration, drug-induced states, neurotoxic agents), mild cognitive impairment, age related cognitive impairment, autism related cognitive impairment, Down's syndrome, cognitive deficit related to psychosis, post-electroconvulsive treatment related cognitive disorders; anxiety disorders (including generalised anxiety disorder, social anxiety disorder, agitation, tension, social or emotional withdrawal in psychotic patients, panic disorder, and obsessive compulsive disorder); neurodegenerative diseases (such as Alzheimer's disease, amyotrophic lateral sclerosis, motor neurone disease and other motor disorders such as Parkinson's disease (including relief from locomotor deficits and/or motor disability, including slowly increasing disability in purposeful movement, tremors, bradykinesia, hyperkinesia (moderate and severe), akinesia, rigidity, disturbance of balance and co-ordination, and a disturbance of posture), dementia in Parkinson's disease, dementia in Huntington's disease, neuroleptic-induced Parkinsonism and tardive dyskinesias, neurodegeneration following stroke, cardiac arrest, pulmonary bypass, traumatic brain injury, spinal cord injury or the like, and demyelinating diseases such as multiple sclerosis and amyotrophic lateral sclerosis); depression (which term includes bipolar (manic) depression (including type I and type II), unipolar depression, single or recurrent major depressive episodes with or without psychotic features, catatonic features, melancholic features, atypical features (e.g. lethargy, over-eating/obesity, hypersomnia) or postpartum onset, seasonal affective disorder and dysthymia, depression-related anxiety, psychotic depression, and depressive disorders resulting from a general medical condition including, but not limited to, myocardial infarction, diabetes, miscarriage or abortion); post-traumatic stress syndrome; attention deficit disorder; attention deficit hyperactivity disorder; drug-induced (phencyclidine, ketamine and other dissociative anaesthetics, amphetamine and other psychostimulants and cocaine) disorders; Huntingdon's chorea; tardive dyskinesia; dystonia; myoclonus; spasticity; obesity; stroke; sexual dysfunction; and sleep disorders. Relevant diseases also include some forms of epilepsy.

Within the context of the present invention, the terms describing the indications used herein are classified in the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, published by the American Psychiatric Association (DSM-IV) and/or the International Classification of Diseases, 10th Edition (ICD-10). The various subtypes of the disorders mentioned herein are contemplated as part of the present invention. Numbers in brackets after the listed diseases below refer to the classification code in DSM-IV.
Within the context of the present invention, the term "psychotic disorder" includes:

Schizophrenia including the subtypes Paranoid Type (295.30), Disorganised Type (295.10), Catatonic Type (295.20), Undifferentiated Type (295.90) and Residual Type (295.60); Schizophreniform Disorder (295.40); Schizoaffective Disorder (295.70) including the subtypes Erotomanic Type, Grandiose Type, Jealous Type, Persecutory Type, Somatic Type, Mixed Type and Unspecified Type; Brief Psychotic Disorder (298.8); Shared Psychotic Disorder (297.3); Psychotic Disorder Due to a General Medical Condition including the subtypes With Delusions and With Hallucinations; Substance-Induced Psychotic Disorder including the subtypes With Delusions (293.81) and With Hallucinations (293.82); and Psychotic Disorder Not Otherwise Specified (298.9).

Compounds of the invention may also be of use in the treatment of the following disorders:

Depression and mood disorders including Major Depressive Episode, Manic Episode, Mixed Episode and Hypomanic Episode; Depressive Disorders including Major Depressive Disorder, Dysthmic Disorder (300.4), Depressive Disorder Not Otherwise Specified (311); Bipolar Disorders including Bipolar I Disorder, Bipolar II Disorder (Recurrent Major Depressive Episodes with Hypomanic Episodes) (296.89), Cyclothymic Disorder (301.13) and Bipolar Disorder Not Otherwise Specified (296.80); Other Mood Disorders including Mood Disorder Due to a General Medical Condition (293.83) which includes the subtypes With Depressive Features, With Major Depressive-like Episode, With Manic Features and With Mixed Features), Substance-Induced Mood Disorder (including the subtypes With Depressive Features, With Manic Features and With Mixed Features) and Mood Disorder Not Otherwise Specified (296.90);

Anxiety disorders including Panic Attack; Panic Disorder including Panic Disorder without Agoraphobia (300.01) and Panic Disorder with Agoraphobia (300.21); Agoraphobia; Agoraphobia Without History of Panic Disorder (300.22), Specific Phobia (300.29, formerly Simple Phobia) including the subtypes Animal Type, Natural Environment Type, Blood-Injection-Injury Type, Situational Type and Other Type), Social Phobia (Social Anxiety Disorder, 300.23), Obsessive-Compulsive Disorder (300.3), Posttraumatic Stress Disorder (309.81), Acute Stress Disorder (308.3), Generalized Anxiety Disorder (300.02), Anxiety Disorder Due to a General Medical Condition (293.84), Substance-Induced Anxiety Disorder, Separation Anxiety Disorder (309.21), Adjustment Disorders with Anxiety (309.24) and Anxiety Disorder Not Otherwise Specified (300.00);

Substance-related disorders including Substance Use Disorders such as Substance Dependence, Substance Craving and Substance Abuse; Substance-Induced Disorders
such as Substance Intoxication, Substance Withdrawal, Substance-Induced Delirium, Substance-Induced Persisting Dementia, Substance-Induced Persisting Amnestic Disorder, Substance-Induced Psychotic Disorder, Substance-Induced Mood Disorder, Substance-Induced Anxiety Disorder, Substance-Induced Sexual Dysfunction, Substance-Induced Sleep Disorder and Hallucinogen Persisting Perception Disorder (Flashbacks); Alcohol-Related Disorders such as Alcohol Dependence (303.90), Alcohol Abuse (305.00), Alcohol Intoxication (303.00), Alcohol Withdrawal (291.81), Alcohol Intoxication Delirium, Alcohol Withdrawal Delirium, Alcohol-Induced Persisting Dementia, Alcohol-Induced Persisting Amnestic Disorder, Alcohol-Induced Psychotic Disorder, Alcohol-Induced Mood Disorder, Alcohol-Induced Anxiety Disorder, Alcohol-Induced Sexual Dysfunction, Alcohol-Induced Sleep Disorder and Alcohol-Related Disorder Not Otherwise Specified (291.9); Amphetamine (or Amphetamine-Like)-Related Disorders such as Amphetamine Dependence (304.40), Amphetamine Abuse (305.70), Amphetamine Intoxication (292.89), Amphetamine Withdrawal (292.0), Amphetamine Intoxication Delirium, Amphetamine Induced Psychotic Disorder, Amphetamine-Induced Mood Disorder, Amphetamine-Induced Anxiety Disorder, Amphetamine-Induced Sexual Dysfunction, Amphetamine-Induced Sleep Disorder and Amphetamine-Related Disorder Not Otherwise Specified (292.9); Caffeine Related Disorders such as Caffeine Intoxication (305.90), Caffeine-Induced Anxiety Disorder, Caffeine-Induced Sleep Disorder and Caffeine-Related Disorder Not Otherwise Specified (292.9); Cannabis-Related Disorders such as Cannabis Dependence (304.30), Cannabis Abuse (305.20), Cannabis Intoxication (292.89), Cannabis Intoxication Delirium, Cannabis-Induced Psychotic Disorder, Cannabis-Induced Anxiety Disorder and Cannabis-Related Disorder Not Otherwise Specified (292.9); Cocaine-Related Disorders such as Cocaine Dependence (304.20), Cocaine Abuse (305.60), Cocaine Intoxication (292.89), Cocaine Withdrawal (292.0), Cocaine Intoxication Delirium, Cocaine-Induced Psychotic Disorder, Cocaine-Induced Mood Disorder, Cocaine-Induced Anxiety Disorder, Cocaine-Induced Sexual Dysfunction, Cocaine-Induced Sleep Disorder and Cocaine-Related Disorder Not Otherwise Specified (292.9); Hallucinogen-Related Disorders such as Hallucinogen Dependence (304.50), Hallucinogen Abuse (305.30), Hallucinogen Intoxication (292.89), Hallucinogen Persisting Perception Disorder (Flashbacks) (292.89), Hallucinogen Intoxication Delirium, Hallucinogen-Induced Psychotic Disorder, Hallucinogen-Induced Mood Disorder, Hallucinogen-Induced Anxiety Disorder and Hallucinogen-Related Disorder Not Otherwise Specified (292.9); Inhalant-Related Disorders such as Inhalant Dependence (304.60), Inhalant Abuse (305.90), Inhalant Intoxication (292.89), Inhalant Intoxication Delirium, Inhalant-Induced Persisting Dementia, Inhalant-Induced Psychotic Disorder, Inhalant-Induced Mood Disorder, Inhalant-Induced Anxiety Disorder and Inhalant-Related Disorder Not Otherwise Specified (292.9); Nicotine-Related Disorders such as Nicotine Dependence (305.1), Nicotine Withdrawal (292.0) and Nicotine-Related Disorder Not Otherwise Specified (292.9); Opioid-Related Disorders such as Opioid Dependence (304.00), Opioid Abuse (305.50), Opioid Intoxication (292.89), Opioid Withdrawal (292.0), Opioid Intoxication Delirium, Opioid-Induced Psychotic Disorder, Opioid-Induced Mood
Disorder, Opioid-Induced Sexual Dysfunction, Opioid-Induced Sleep Disorder and Opioid-Related Disorder Not Otherwise Specified (292.9); Phencyclidine (or Phencyclidine-Like)-Related Disorders such as Phencyclidine Dependence (304.60), Phencyclidine Abuse (305.90), Phencyclidine Intoxication (292.89), Phencyclidine Intoxication Delirium, Phencyclidine-Induced Psychotic Disorder, Phencyclidine-Induced Mood Disorder, Phencyclidine-Induced Anxiety Disorder and Phencyclidine-Related Disorder Not Otherwise Specified (292.9); Sedative-, Hypnotic-, or Anxiolytic-Related Disorders such as Sedative, Hypnotic, or Anxiolytic Dependence (304.10), Sedative, Hypnotic, or Anxiolytic Abuse (305.40), Sedative, Hypnotic, or Anxiolytic Intoxication (292.89), Sedative, Hypnotic, or Anxiolytic Withdrawal (292.0), Sedative, Hypnotic, or Anxiolytic Intoxication Delirium, Sedative, Hypnotic, or Anxiolytic Withdrawal Delirium, Sedative-, Hypnotic-, or Anxiolytic-Persisting Dementia, Sedative-, Hypnotic-, or Anxiolytic-Persisting Amnestic Disorder, Sedative-, Hypnotic-, or Anxiolytic-Induced Psychotic Disorder, Sedative-, Hypnotic-, or Anxiolytic-Induced Mood Disorder, Sedative-, Hypnotic-, or Anxiolytic-Induced Anxiety Disorder Sedative-, Hypnotic-, or Anxiolytic-Induced Sexual Dysfunction, Sedative-, Hypnotic-, or Anxiolytic-Induced Sleep Disorder and Sedative-, Hypnotic-, or Anxiolytic-Related Disorder Not Otherwise Specified (292.9); Polysubstance-Related Disorder such as Polysubstance Dependence (304.80); and Other (or Unknown) Substance-Related Disorders such as Anabolic Steroids, Nitrate Inhalants and Nitrous Oxide:

Sleep disorders including primary sleep disorders such as Dyssomnias such as Primary Insomnia (307.42), Primary Hypersomnia (307.44), Narcolepsy (347), Breathing-Related Sleep Disorders (780.59), Circadian Rhythm Sleep Disorder (307.45) and Dyssomnia Not Otherwise Specified (307.47); primary sleep disorders such as Parasomnias such as Nightmare Disorder (307.47), Sleep Terror Disorder (307.46), Sleepwalking Disorder (307.46) and Parasomnia Not Otherwise Specified (307.47); Sleep Disorders Related to Another Mental Disorder such as Insomnia Related to Another Mental Disorder (307.42) and Hypersomnia Related to Another Mental Disorder (307.44); Sleep Disorder Due to a General Medical Condition, in particular sleep disturbances associated with such diseases as neurological disorders, neuropathic pain, restless leg syndrome, heart and lung diseases; and Substance-Induced Sleep Disorder including the subtypes Insomnia Type, Hypersomnia Type, Parasomnia Type and Mixed Type; sleep apnea and jet-lag syndrome:

Autism Spectrum Disorders including Autistic Disorder (299.00), Asperger's Disorder (299.80), Rett's Disorder (299.80), Childhood Disintegrative Disorder (299.10) and Pervasive Disorder Not Otherwise Specified (299.80, including Atypical Autism).

Attention-Deficit/Hyperactivity Disorder including the subtypes Attention-Deficit /Hyperactivity Disorder Combined Type (314.01), Attention-Deficit /Hyperactivity Disorder Predominantly Inattentive Type (314.00), Attention-Deficit /Hyperactivity Disorder
Hyperactive-Impulse Type (314.01) and Attention-Deficit /Hyperactivity Disorder Not Otherwise Specified (314.9); Hyperkinetic Disorder; Disruptive Behaviour Disorders such as Conduct Disorder including the subtypes childhood-onset type (321.81), Adolescent-Onset Type (312.82) and Unspecified Onset (312.89), Oppositional Defiant Disorder (313.81) and Disruptive Behaviour Disorder Not Otherwise Specified; and Tic Disorders such as Tourette's Disorder (307.23):

Personality Disorders including the subtypes Paranoid Personality Disorder (301.0), Schizoid Personality Disorder (301.20), Schizotypal Personality Disorder (301.22), Antisocial Personality Disorder (301.7), Borderline Personality Disorder (301.83), Histrionic Personality Disorder (301.50), Narcissistic Personality Disorder (301.81), Avoidant Personality Disorder (301.82), Dependent Personality Disorder (301.6), Obsessive-Compulsive Personality Disorder (301.4) and Personality Disorder Not Otherwise Specified (301.9):

Enhancement of cognition including the treatment of cognition impairment in other diseases such as schizophrenia, bipolar disorder, depression, other psychiatric disorders and psychotic conditions associated with cognitive impairment, e.g. Alzheimer's disease:

Sexual dysfunctions including Sexual Desire Disorders such as Hypoactive Sexual Desire Disorder (302.71), and Sexual Aversion Disorder (302.79); sexual arousal disorders such as Female Sexual Arousal Disorder (302.72) and Male Erectile Disorder (302.72); orgasmic disorders such as Female Orgasmic Disorder (302.73), Male Orgasmic Disorder (302.74) and Premature Ejaculation (302.75); sexual pain disorder such as Dyspareunia (302.76) and Vaginismus (306.51); Sexual Dysfunction Not Otherwise Specified (302.70); paraphilias such as Exhibitionism (302.4), Fetishism (302.81), Frotteurism (302.89), Pedophilia (302.2), Sexual Masochism (302.83), Sexual Sadism (302.84), Transvestic Fetishism (302.3), Voyeurism (302.82) and Paraphilia Not Otherwise Specified (302.9); gender identity disorders such as Gender Identity Disorder in Children (302.6) and Gender Identity Disorder in Adolescents or Adults (302.85); and Sexual Disorder Not Otherwise Specified (302.9).

Treatment of all of the various forms and sub-forms of the disorders mentioned herein are contemplated as part of the present invention.

Within the context of the present invention, the term "cognitive impairment" includes for example the treatment of impairment of cognitive functions including attention, orientation, learning disorders, memory (i.e. memory disorders, amnesia, amnesic disorders, transient global amnesia syndrome and age-associated memory impairment) and language function; cognitive impairment as a result of stroke, Alzheimer's disease, Huntington's disease, Pick disease, Aids-related dementia or other dementia states such as Multiinfarct
dementia, alcoholic dementia, hypotiroidism-related dementia, and dementia associated
to other degenerative disorders such as cerebellar atrophy and amyotrophic lateral
sclerosis; other acute or sub-acute conditions that may cause cognitive decline such as
delirium or depression (pseudodementia states) trauma, head trauma, age related
cognitive decline, stroke, neurodegeneration, drug-induced states, neurotoxic agents, mild
cognitive impairment, age related cognitive impairment, autism related cognitive
impairment, Down’s syndrome, cognitive deficit related to psychosis, and post-
electroconvulsive treatment related cognitive disorders; and dyskinetic disorders such as
Parkinson’s disease, neuroleptic-induced parkinsonism, and tardive dyskinesias.

The compounds of the invention may be used in combination with the following agents to
treat or prevent psychotic disorders: i) antipsychotics (such as olanzapine, risperidone,
clozapine, ziprazidone and talnetant); ii) drugs for extrapyramidal side effects, for example
anticholinergics (such as benztrpine, biperiden, procyclidine and trihexyphenidyl),
antihistamines (such as diphenhydramine) and dopaminergics (such as amantadine); iii)
antidepressants; iv) anxiolytics; and v) cognitive enhancers for example cholinesterase
inhibitors (such as tacrine, donepezil, rivastigmine and galantamine).

The compounds of the invention may be used in combination with antidepressants to treat
or prevent depression and mood disorders.

The compounds of the invention may be used in combination with the following agents to
treat or prevent bipolar disease: i) mood stabilisers; ii) antipsychotics; and iii)
antidepressants.

The compounds of the invention may be used in combination with the following agents to
treat or prevent anxiety disorders: i) anxiolytics; and ii) antidepressants.

The compounds of the invention may be used in combination with the following agents to
improve nicotine withdrawal and reduce nicotine craving: i) nicotine replacement therapy
for example a sublingual formulation of nicotine beta-cyclodextrin and nicotine patches;
and ii) bupropion.

The compounds of the invention may be used in combination with the following agents to
improve alcohol withdrawal and reduce alcohol craving: i) NMDA receptor antagonists for
example acamprosate; ii) GABA receptor agonists for example tetrabamate; and iii)
Opioid receptor antagonists for example naltrexone.

The compounds of the invention may be used in combination with the following agents to
improve opiate withdrawal and reduce opiate craving: i) opioid mu receptor
agonist/opioid kappa receptor antagonist for example buprenorphine; ii) opioid receptor
antagonists for example naltrexone; and N) vasodilatory antihypertensives for example lofexidine.

The compounds of the invention may be used in combination with the following agents to treat or prevent sleeping disorders: i) benzodiazepines for example temazepam, lormetazepam, estazolam and triazolam; ii) non-benzodiazepine hypnotics for example Zolpidem, zopiclone, zaleplon and indiplon; iii) barbiturates for example aprobital, butabarbital, pentobarbital, secobarbital and phenobarbital; iv) antidepressants; v) other sedative-hypnotics for example chloral hydrate and clormethiazole.

The compounds of the invention may be used in combination with the following agents to treat anorexia: i) appetite stimulants for example cyproheptidine; ii) antidepressants; iii) antipsychotics; iv) zinc; and v) premenstral agents for example pyridoxine and progesterones.

The compounds of the invention may be used in combination with the following agents to treat or prevent bulimia: i) antidepressants; ii) opioid receptor antagonists; iii) antiemetics for example ondansetron; iv) testosterone receptor antagonists for example flutamide; v) mood stabilisers; vi) zinc; and vii) premenstral agents.

The compounds of the invention may be used in combination with the following agents to treat or prevent autism: i) antipsychotics; ii) antidepressants; iii) anxiolytics; and iv) stimulants for example methylphenidate, amphetamine formulations and pemoline.

The compounds of the invention may be used in combination with the following agents to treat or prevent Attention Deficit Hyperactivity Disorder: i) stimulants for example methylphenidate, amphetamine formulations and pemoline; and ii) non-stimulants for example norepinephrine reuptake inhibitors (such as atomoxetine), alpha 2 adrenoceptor agonists (such as clonidine), antidepressants, modafinil, and cholinesterase inhibitors (such as galantamine and donepezil).

The compounds of the invention may be used in combination with the following agents to treat personality disorders: i) antipsychotics; ii) antidepressants; iii) mood stabilisers; and iv) anxiolytics.

The compounds of the invention may be used in combination with the following agents to treat or prevent male sexual dysfunction: i) phosphodiesterase V inhibitors, for example vardenafil and sildenafil; ii) dopamine agonists/dopamine transport inhibitors for example apomorphine and bupropion; iii) alpha adrenoceptor antagonists for example phentolamine; iv) prostaglandin agonists for example alprostadil; v) testosterone agonists such as testosterone; vi) serotonin transport inhibitors for example serotonin reuptake...
inhibitors; v) noradrenaline transport inhibitors for example reboxetine and vii) 5-HT1A agonists, for example fibanserine.

The compounds of the invention may be used in combination with the same agents specified for male sexual dysfunction to treat or prevent female sexual dysfunction, and in addition an estrogen agonist such as estradiol.

Antipsychotic drugs include Typical Antipsychotics (for example chlorpromazine, thioridazine, mesoridazine, fluphenazine, perphenazine, prochlorperazine, trifluoperazine, thiothixine, haloperidol, molindone and loxapine); and Atypical Antipsychotics (for example clozapine, olanzapine, risperidone, quetiapine, aripiprazole, ziprasidone, amisulpride, ziprazidone and talnetant).

Antidepressant drugs include serotonin reuptake inhibitors (such as citalopram, escitalopram, fluoxetine, paroxetine and sertraline); dual serotonin/noradrenaline reuptake inhibitors (such as venlafaxine, duloxetine and milnacipran); Noradrenaline reuptake inhibitors (such as reboxetine); tricyclic antidepressants (such as amitriptyline, clomipramine, imipramine, maprotiline, nortriptyline and trimipramine); monoamine oxidase inhibitors (such as isocarboxazide, moclobemide, phenelzine and tranylcypromine); and others (such as bupropion, mianserin, mirtazapine, nefazodone and trazodone).

Mood stabiliser drugs include lithium, sodium valproate/valproic acid/divalproex, carbamazepine, lamotrigine, gabapentin, topiramate and tiagabine.

Anxiolytics include benzodiazepines such as alprazolam and lorazepam.

The invention is illustrated by the Examples described below.

Starting materials, reagents and solvents were obtained from commercial suppliers and used without further purification unless otherwise stated. Flash chromatography was carried out using pre-packed Isolute Flash™ or Biotage™ silica-gel columns as the stationary phase and analytical grade solvents as the eluent. Catch and release purification was carried out using SCX (strong cation exchanger) cartridges, consisting of bonded-phase silica with sulfonic acid functional groups. Mass directed preparative HPLC was carried out using a 19 mm x 100 mm or 30 mm x 100 mm, 5 µm, reversed phase Waters Atlantis column as the stationary phase and a gradient from water + 0.1% formic acid to acetonitrile + 0.1% formic acid as the eluent. The eluent was monitored by a Waters 996 photodiode array and a Micromass ZQ mass spectrometer. All yields reported are of purified, isolated material. NMR spectra were obtained at 298K, at the frequency stated using either a Bruker™ DPX400 or an Oxford Instruments™ 250 MHz machine and run as a dilute solution of CDCl₃ unless otherwise stated. All NMR spectra
were reference to tetramethylsilane (TMS $\delta_H 0$, $\delta_c 0$). All coupling constants are reported in hertz (Hz), and multiplicities are labelled s (singlet), bs, (broad singlet), d (doublet), t (triplet), q (quartet), dd (doublet of doublets), dt (doublet of triplets) and m (multiplet).

LC/MS (Liquid Chromatography / Mass Spectrometry) data were obtained using an Agilent™ 1100 HPLC system with a 4.6 mm x 50 mm, 3 µm, reversed phase Waters Atlantis™ column as the stationary phase. A gradient elution from 97% water + 0.05% formic acid / 3% acetonitrile + 0.05% formic acid to 97% acetonitrile + 0.05% formic acid over 3 minutes plus a further minute continuing this mixture at a flow rate of 1.5 mL/min was used as the eluent. Retention time is reported as minutes (with percentage intensity for DA / ELSD for the relevant peak). Spectroscopic monitoring was performed using an Agilent™ 1100 diode array (DA) detector or a Sedex™ evaporative light scattering detector (ELSD). Total ion current traces were obtained for electrospray positive and negative ionisation (ES+/ES-) and atmospheric pressure chemical positive and negative ionisation (AP+/AP-).

**Intermediates**

**Intermediate 1:**

**C/s-N-[2-(phenylmethyl)cyclopentyl]-2-propanesulfonamide**

C/s-2-(phenylmethyl)cyclopentylamine (545mg, 3.11mmol) was suspended in dry dichloromethane (5ml) and cooled to 0°C in an ice/methanol bath. 1,8-diazabicyclo[5.4.0]undec-7-ene (945mg, 6.22mmol) was added, followed by the dropwise addition of isopropylsulfonyl chloride (887mg, 6.22mmol) with stirring under an atmosphere of argon. The reaction mix was allowed to warm up to room temperature and stirred for 4h. The reaction mix was then partitioned between dichloromethane (30ml) and 1N hydrochloric acid (30ml). The organic layer was separated, dried over sodium sulphate and reduced to minimum volume under reduced pressure to give a yellow oil. The crude product was chromatographed on a 10g isolute silica sep-pak® column eluting from 0-20% ethyl acetate in 40-60°C petroleum ether to give the **title compound** as an oil (870mg, 100%).

Mass Spectrum (API-): Found 280 (MH-). C-15H23NO2S requires 281.

$^1$H-NMR (400MHz, CDCl$_3$): 1.37 (6H, m), 1.56-1.78 (5H, m), 2.02 (1H, m), 2.23 (1H, m), 2.45 (1H, m), 2.97 (1H, m), 3.14 (1H, m), 3.86 (1H, m), 4.44 (1H, m), 7.19 (3H, m), 7.27 (2H, m).
Intermediate 2

*Clis-N*{-2-[(4-iodophenyl)methyl]cyclopentyl}-2-propanesulfonamide

![Chemical Structure](image)

C/s-\(N\)\{-[2-(phenylmethyl)cyclopentyl]-2-propanesulfonamide\} (700mg, 2.49mmol) was dissolved in glacial acetic acid (7.5ml) and then treated with concentrated sulfuric acid (0.25ml) followed by water (0.75ml) with stirring. This mixture was then treated with periodic acid (131 mg, 0.57mmol) then iodine (271 mg, 1.07mmol), and the whole mixture was stirred at 60\(^\circ\)C for 16h. The reaction mixture was allowed to cool to room temperature and then partitioned between ethyl acetate (30ml) and 10\% aqueous sodium metabisulfite solution (25ml). The organic layer was separated and dried over sodium sulphate and evaporated under reduced pressure to give an oil. The crude product was chromatographed on a 20g isolute silica sep-pak \(\text{\textregistered}\) column eluting from 0-20\% ethyl acetate in 40-60\(^\circ\)C petroleum ether to give the *title compound* as an oil (71 1mg, 70\%).

Mass Spectrum (API-): Found 406 (MH\(^{-}\)). 
\(C_{15}H_{22}INO_{2}S\) requires 407.

\(^1\)H-NMR (400MHz, CDCl\(_3\)): 1.39 (6H, m), 1.51-1.77 (5H, m), 2.03 (1H, m), 2.18 (1H, m), 2.37 (1H, m), 2.93 (1H, m), 3.15 (1H, m), 3.86 (1H, m), 4.00 (1H, m), 6.94 (2H, d, J=8Hz), 7.59 (2H, m).

Intermediate 3

C/s-\(N\)\{-2-(phenylmethyl)cyclopentyl\}ethanesulfonamide

![Chemical Structure](image)

The *title compound* was prepared from c/s-2-(phenylmethyl)cyclopentylamine in a similar manner to Intermediate 1.

Mass Spectrum (API-): Found 266 (MH\(^{-}\)). \(C_{14}H_{21}NO_{2}S\) requires 267.

\(^1\)H-NMR (400MHz, CDCl\(_3\)): 1.35 (3H, m), 1.60-1.83 (5H, m), 2.02 (1H, m), 2.27 (1H, m), 2.47 (1H, m), 2.93 (1H, m), 2.99 (2H, m), 3.82 (1H, m), 4.22 (1H, m), 7.18 (3H, m), 7.28 (2H, m).

Intermediate 4

C/s-\(N\)\{-2-[(4-iodophenyl)methyl]cyclopentyl\}ethaneanesulfonamide
The title compound was prepared from Cis-N-[2-(phenylmethyl)cyclopentyl]ethanesulfonamide in a similar manner to Intermediate 2.

Mass Spectrum (API-): Found 392 (MH-). C-14H20INO2S requires 393.

$^1$H-NMR (400MHz, CDCl$_3$): 1.37 (3H, t, J=8Hz), 1.56-1.78 (5H, m), 2.02 (1H, m), 2.20 (1H, m), 2.40 (1H, m), 2.90 (1H, m), 3.02 (2H, m), 3.83 (1H, m), 4.09 (1H, m), 6.94 (2H, d, J=8Hz), 7.59 (2H, m).

Example 1

C/s-W-I^-^S'-KmethylsulfonylJaminol^-biphenyly^-methylJcyclopentyl^-propanesulfonamide

A mixture of c/s-N-[2-[(4-iodophenyl)methyl]cyclopentyl]-2-propanesulfonamide (70mg, 0.17mmol), 3-methanesulphonamidophenylboronic acid (41 mg, 0.19mmol) and cesium carbonate (81 mg, 0.25mmol) in a 3:1 mixture of 1,4-dioxane:water (5ml) was degassed with argon for 10mins. To this solution was added triphenylphosphine (9mg, 0.034mmol) and palladium (II) acetate (2.2mg, 0.01mmol), and the whole mixture was stirred at 80°C for 16h. The reaction mixture was allowed to cool to room temperature and partitioned between ethyl acetate (6ml) and water (8ml). The organic layer was removed, dried over sodium sulfate and evaporated to dryness under reduced pressure. The crude product was purified using mass directed auto-prep to give the title compound as an oil (43mg, 56%).

Mass Spectrum (API-): Found 449 (MH-). C22H30N2O4S2 requires 450.

$^1$H-NMR (400MHz, CDCl$_3$): 1.39 (6H, m), 1.53-1.79 (5H, m), 2.03 (1H, m), 2.27 (1H, m), 2.47 (1H, m), 2.98 (1H, m), 3.04 (3H, s), 3.15 (1H, m), 3.89 (1H, m), 4.10 (1H, m), 7.17 (2H, m), 7.26 (3H, m), 7.41 (2H, m), 7.49 (2H, m).

Example 2
C/sWV^-flSXmethylsulfonylJ^-biphenyllylmethy^cyclopentyl)^-propanesulfonamide

The title compound was prepared from c/s-N^-{2-[(4-iodophenyl)methyl]cyclopentyl}-2-propanesulfonamide in a similar manner to Example 1.

Mass Spectrum (API-): Found 434 (MH-). C22H29NO4S2 requires 435.

\[^1\text{H-NMR}\ (400\text{MHz, CDCl}_3): 1.39\ (6\text{H, m}), 1.54-1.78\ (5\text{H, m}), 2.03\ (1\text{H, m}), 2.27\ (1\text{H, m}), 2.47\ (1\text{H, m}), 3.01\ (1\text{H, m}), 3.10\ (3\text{H, s}), 3.15\ (1\text{H, m}), 3.88\ (1\text{H, m}), 4.09\ (1\text{H, m}), 7.19\ (2\text{H, m}), 7.30\ (2\text{H, m}), 7.54\ (1\text{H, m}), 7.63\ (1\text{H, m}), 7.88\ (1\text{H, m}), 8.15\ (1\text{H, m}).

Example 3

*Ciisperamides*

*Cis-N^-{2-[(4-(3-thienyl)phenyl)methyl]cyclopentyl}-2-propanesulfonamide*

The title compound was prepared from c/s-N^-{2-[(4-iodophenyl)methyl]cyclopentyl}-2-propanesulfonamide in a similar manner to Example 1.

Mass Spectrum (API-): Found 362 (MH-). C19H25NO2S2 requires 363.

\[^1\text{H-NMR}\ (400\text{MHz, CDCl}_3): 1.39\ (6\text{H, m}), 1.48-1.80\ (5\text{H, m}), 2.03\ (1\text{H, m}), 2.27\ (1\text{H, m}), 2.45\ (1\text{H, m}), 2.99\ (1\text{H, m}), 3.16\ (1\text{H, m}), 3.88\ (1\text{H, m}), 4.04\ (1\text{H, m}), 7.22\ (2\text{H, d, J=8Hz}), 7.38\ (2\text{H, m}), 7.42\ (1\text{H, m}), 7.52\ (2\text{H, m}).

Example 4

*Cis-N^-{2-[^\*'-cyano^-biphenyllyl]methyl]cyclopentyl}^-propanesulfonamide*

The title compound was prepared from c/s-N^-{2-[(4-iodophenyl)methyl]cyclopentyl}-2-propanesulfonamide in a similar manner to Example 1.

Mass Spectrum (API-): Found 381 (MH-). C22H26N2O2S requires 382.
$^1$H-NMR (400MHz, CDCl$_3$): 1.39 (6H, m), 1.54-1.80 (5H, m), 2.03 (1H, m), 2.28 (1H, m), 2.49 (1H, m), 3.05 (1H, m), 3.17 (1H, m), 3.90 (1H, m), 4.01 (1H, m), 7.31 (2H, d, J=8Hz), 7.52 (2H, d, J=8Hz), 7.69 (4H, m).

5 Example 5

**Cis-N-[-2-[(4-iodophenyl)methyl]cyclopentyl]-2-propanesulfonamide**

The title compound was prepared as described in intermediate II.


$^1$H-NMR (400MHz, CDCl$_3$): 1.39 (6H, m), 1.51-1.77 (5H, m), 2.03 (1H, m), 2.18 (1H, m), 2.37 (1H, m), 2.93 (1H, m), 3.15 (1H, m), 3.86 (1H, m), 4.00 (1H, m), 6.94 (2H, d, J=8Hz), 7.59 (2H, m).

15 Example 6

**C/s-Λ-[-2-[(4-iodophenyl)methyl]cyclopentyl]ethanesulfonamide**

The title compound was prepared from Cis-N-[-2-(phenylmethyl)cyclopentyl]ethanesulfonamide as described for intermediate IV.

20 Mass Spectrum (API-): Found 392 (MH-). C14H20INO2S requires 393.

$^1$H-NMR (400MHz, CDCl$_3$): 1.37 (3H, t, J=8Hz), 1.56-1.78 (5H, m), 2.02 (1H, m), 2.20 (1H, m), 2.40 (1H, m), 2.90 (1H, m), 3.02 (2H, m), 3.83 (1H, m), 4.09 (1H, m), 6.94 (2H, d, J=8Hz), 7.59 (2H, m).

25 Example 7

**Cis-N-[-2-[^'-fluoro^-biphenylyljmethyllcyclopentyl^-propanesulfonamide**

A mixture of c/s-Λ-[-2-[(4-iodophenyl)methyl]cyclopentyl]-2-propanesulfonamide (70mg, 0.17mmol), 2-fluorophenylboronic acid (27mg, 0.19mmol) and cesium carbonate (81 mg, 0.25mmol) in a 3:1 mixture of 1,4-dioxane:water (5ml) was degassed with argon for
IOmins. To this solution was added triphenylphosphine (9mg, 0.034mmol) and palladium (II) acetate (2.2mg, 0.01mmol), and the whole mixture was stirred at 80°C for 16h. The reaction mixture was allowed to cool to room temperature and partitioned between ethyl acetate (6ml) and water (8ml). The organic layer was removed, dried over sodium sulfate and evaporated to dryness under reduced pressure. The crude product was purified using mass directed auto-prep to give the title compound as an oil (20mg, 31%).


1H-NMR (400MHz, CDCl3): 1.38 (6H, m), 1.56-1.79 (5H, m), 2.03 (1H, m), 2.29 (1H, m), 2.49 (1H, m), 3.01 (1H, m), 3.15 (1H, m), 3.90 (1H, m), 4.00 (1H, m), 7.17 (3H, m), 7.29 (2H, m), 7.44 (3H, m).

Biological Assays.
The ability of the compounds of the invention to potentiate AMPA receptor-mediated response were determined a) by using fluorescent calcium-indicator dyes such as FLUO4 and b) by measuring glutamate-evoked current recorded from human GluR2 flip unedited HEK293 cells.

a) Calcium Influx Fluorescence Assay

384 well plates were prepared containing confluent monolayer of HEK 293 cells either stably expressing or transiently transfected with human GluR2 flip (unedited) AMPA receptor subunit. These cells form functional homotetrameric AMPA receptors. The tissue culture medium in the wells were discarded and the wells each washed three times with standard buffer (80 µl) for the stable cell line (145 mM NaCl, 5 mM KCl, 1 mM MgCl2, 2 mM CaCl2, 20 mM N-[2-hydroxyethyl]-piperazine-N-[2-ethanesulfonic acid (HEPES), 5.5 mM glucose, pH 7.3) or with a Na-free buffer for the transient transfected cells (145 mM N-methyl-glucamine instead of NaCl). The plates were then incubated for 60 minutes in the dark with 2 µM FLUO4-AM dye (20 µl) (Molecular Probes, Netherlands) at room temperature to allow cell uptake of the FLUO-4AM, which was then converted to FLUO-4 by intracellular esterases which is unable to leave the cell. After incubation each well was washed three times with buffer (80 µl) (30 µl of buffer remained in each well after washing).

Compounds of the invention (or the reference compound, cyclothiazide) were dissolved in dimethylsulfoxide (DMSO) at a stock concentration of 10 mM. These solutions were further diluted with DMSO using a Biomek FX (Beckman Coulter) in a 384 compound plate. Each dilution (1 µl) was transferred to another compound plate and buffer (50 µl) was added. An agonist stimulus (glutamate) plate was prepared by dissolving sodium glutamate in water to give a concentration of 100 mM. This solution was diluted with buffer to give a final concentration of 500 µM and dispensed into another 384-well plate (50 µl/well) using a Multidrop (Thermolabsystems).
The cell plate was then transferred into a fluorescence imaging plate based reader [such as the FLIPR384 (Molecular Devices)]. A baseline fluorescence reading was taken over a 10 to 240 second period, and then 10 µL from each plate containing a compound of the invention made up in standard buffer solution (in a concentration range from 100 µM to 10 pM) was added (to give a final concentration in the range 30 µM to 3 pM). The fluorescence was read over 5 minute period. 500 µM glutamate solution (10µL) was added (to give a final concentration of 100 µM). The fluorescence was then read over a 4 minute period. The activities of the compounds of the invention and reference compounds were determined by measuring peak fluorescence after the last addition. The activity was also expressed relative to the fluorescence increase induced by cyclothiazide at their maximum response (i.e. greater than 30 µM).

The assay described above was believed to have an effective limit of detection of a pEC$_{50}$ in the region of 3.5-4.0 due to the limitations of compound solubility. The pEC$_{50}$ result was generally considered to be accurate +/- 0.3. Accordingly, a compound exhibiting a pEC$_{50}$ value within this range from such an assay may indeed have a reasonable affinity for the receptor, but equally it may also have a lower affinity, including a considerably lower affinity.

All examples were screened using Assay a). Using Assay a) Examples 1 to 5 gave a PEC50 equal to or greater than 4.4 and demonstrated an activity of at least 25% that of cyclothiazide (at their maximal responses).

b) Whole cell voltage-clamp electrophysiology Assay

The ability of the compounds of the invention to potentiate AMPA-subtype glutamate receptor-mediated response were determined by measuring AMPA-evoked current recorded from rat cultured hippocampal neurons.

This assay involved the electrophysiological characterisation of AMPA receptor positive modulators using rat cultured hippocampal neurons. The extracellular recording solution contained: 145 mM NaCl, 2.5 mM KCl, 1.2 mM MgCl$_2$, 1.5 mM CaCl$_2$, 10 mM N-[2-hydroxyethyl]-piperazine-N-[2-ethanesulfonic acid (HEPES), 10 mM D-glucose, pH 7.3 with NaOH. The intracellular solution contained : 80 mM CsCl, 80 mM CsF, 10 mM N-[2-hydroxyethyl]-piperazine-N-[2-ethanesulfonic acid (HEPES), 10 mM ethylene glycol-bis(g-aminoethyl ether)-N,N',N',N-tetra-acetic acid (EGTA), 14 mM MgATP, 14 mM DiTris Creatine Phosphate, 50 U/ml Creatine Phosphokinase pH 7.3 with CsOH. Recording electrodes were prepared from glass capillary tubes (Clark Electromedical GC120-F10) pulled into two equal lengths using a Zeitz Instruments DMZ Universal Puller, program 09, resulting in electrodes with a resistance of approximately 3-6 MOhms when measured in extracellular solution. Electrodes were back filled with internal recording solution. Positive pressure was applied to the electrode to prevent mixture of internal and external solutions and assist in formation of high resistance seal when the electrode makes contact with the
cell membrane. Glass coverslip fragment, bearing rat cultured hippocampal neurons, was placed in the recording chamber positioned on the stage of an inverted microscope. A tube at the edge of the chamber was used to apply extracellular solution to the bath. Rapid solution exchange used a fast step perfusion system (Biologic RSC160). Two outlet tubes attached together along their length were positioned close to a chosen cell so that the outflow from only one tube can pass directly over the cell surface. A motorized stepper could re-position the tubes such that the outflow from the second outlet tube flowed over the cell allowing solution exchange at the cell membrane surface to occur within 10-20 ms. Excess bath solution was removed via a tube positioned at the edge of the chamber connected to a vacuum line.

A prospective cell was positioned in the centre of the microscope field of view. Recording electrode was positioned directly above the cell membrane surface. Using fine manipulator control (Luigs and Neumann, SM-6) the electrode was lowered, while monitoring the change in electrode resistance during delivery of a 5 mV depolarizing pulse, until a high resistance seal (gigaseal) was achieved. Whole cell configuration was achieved by removing by suction a small fragment of cell membrane immediately beneath the recording electrode tip. The cell membrane potential was held at -70 mV (voltage-clamped) via the electrode (Axopatch 200B Integrating patch clamp amplifier, pClamp software, Axon Instruments). Test solutions were applied using the fast application system using the following protocol and changes in inward current were recorded and stored for off-line analysis.

1) Control current - exchange from extracellular solution to extracellular solution + 30 µM AMPA (2 s application time, 30 s interval between applications) repeated until measurements were stable.

2) Test current - exchange from extracellular solution + 10 nM of compound of invention to extracellular solution + 10 nM of compound of invention + 30 µM AMPA (2 s application time, 30 s interval between applications) repeated until measurements were stable.

All experiments were performed at ambient temperature (20 to 22 °C).

The activity of a compound of the invention was determined by measuring the area under the curve (during 2 s period of application) for the 30 µM AMPA response in the presence of the compound of the invention and expressing it as % of potentiation of the 30 µM AMPA alone response (30 µM AMPA in the absence of the compound of the invention).
Claims.

1. A compound of formula (I) or a salt thereof:

   ![Chemical Structure](image)

   (I)

   wherein

   $R^1$ is C$_2$-galkyl, haloC$_{1-2}$galkyl, C$_2$-galkenyl, amino, monoC$_{1-4}$alkylamino or
diC$_{1-2}$alkylamino;

   $R^2$, $R^3$, $R^4$, $R^5$, $R^6$, $R^7$, and $R^{10}$, which may be the same or different, are selected from
hydrogen, halogen, C$_2$-galkyl, haloC$_{1-2}$galkyl and C$_{1-4}$alkoxy;

   each $R^8$, which may be the same or different, is C$_1$-galkyl, halogen, haloC$_1$-galkyl, C$_1$-
4alkoxy, haloC$_{1-4}$alkoxy or cyano;

   $p$ is 0, 1 or 2;

   $R^9$ is halo; or phenyl or aromatic heterocyclyl, either of which is optionally substituted by
one or more groups independently selected from the group consisting of: halogen, haloC$_2$-galkyl, C$_2$-
4alkoxy, haloC$_{1-4}$alkoxy, cyano, -(CH$_2$)$_q$ NR$_a$(c=O)R$_b$ SC$_2$R$_c$; -(CH$_2$)$_q$ NR$_a$(c=O)N(R$_b$)$_c$; -(CH$_2$)$_q$(C=O)R$_d$ and
-(CH$_2$)$_q$SO$_2$R$_e$; where $R^a$ and each $R^b$, which may be the same or different, is
hydrogen or C$_1$-galkyl; $R^b$ is C$_1$-galkyl or haloC$_1$-galkyl; $R^d$ is C$_1$-galkyl,
C$_{1-4}$alkoxy or haloC$_{1}$-galkyl; or $R^a$ and $R^b$, $R^a$ and $R^c$, or $R^a$ and $R^d$
together with the interconnecting atoms, may form a 5- or 6-membered ring; and $q$ is
0, 1, or 2.

2. A compound according to claim 1 wherein $R^1$ is C$_1$-g alkyl.

3. A compound according to any preceding claim wherein $R^2$, $R^3$, $R^4$, $R^5$, $R^6$, $R^7$, and
$R^{10}$, which may be the same or different, are hydrogen, halogen or C$_1$-g alkyl.

4. A compound according to any preceding claim wherein $R^2$, $R^3$, $R^4$, $R^5$, $R^6$, $R^7$, and
$R^{10}$, which may be the same or different, are hydrogen, fluorine or methyl.

5. A compound according to any preceding claim wherein, when present, each $R^8$, which
may be the same or different, is C$_1$-g alkyl or halogen.

6. A compound according to any preceding claim wherein $p$ is 0.
7. A compound according to any preceding claim wherein R is a phenyl, pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, thiényl, imidazolyl, pyrroyl, oxazolyl or pyrazolyl, optionally substituted with one or more groups independently selected from those defined in claim 1.

8. A compound according to any preceding claim wherein the compound is of formula (Ia):

```
   R1
   R2
   R3
   R4
   R5
   R6
   R7
   R8
   R9
   R10
   NH
   SO
```

(Ia)

wherein R1, R2, R3, R4, R5, R6, R7, R8, R9 and R10 are as defined in any of claims 1-7.

9. A compound as claimed in any of claims 1-8 or an pharmaceutically acceptable salt thereof.

10. A pharmaceutical composition comprising a compound of as claimed in claim 9 and at least one pharmaceutically acceptable carrier or diluent.

11. A compound as claimed in claims 9 for use in treating or preventing a disease or condition caused by a reduction or imbalance in glutamate receptor function in a mammal.

12. A compound as claimed in claim 11 wherein the disease is schizophrenia or impairment of cognition.

13. Use of a compound as claimed in claim 9 in the manufacture of a medicament for treating or preventing a disease or a condition caused by a reduction or imbalance in glutamate receptor function.

14. Use as claimed in claim 13 wherein the disease is schizophrenia or impairment of cognition.

15. A method of treatment or prevention of a disease or condition caused by a reduction or imbalance in glutamate receptor function in a mammal comprising administering an effective amount of a compound as claimed in claim 9.
16. A method as claimed in claim 15 wherein the disease is schizophrenia or impairment of cognition.
A. CLASSIFICATION OF SUBJECT MATTER

INV. C07C311/08 C07C311/09 C07C317/32 C07D333/20 A61K31/18
A61K31/277 A61K31/381 A61P25/18

B. FIELDS SEARCHED

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

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

EPO-Internal, BEILSTEIN Data, WPI Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

<table>
<thead>
<tr>
<th>Category</th>
<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
<th>Relevant to claim No</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>US 6 639 107 B1 (J.A. AIKINS, ET AL.) 28 October 2003 (2003-10-28) column 3, lines 8-11; claim 1</td>
<td>1-16</td>
</tr>
</tbody>
</table>

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

X See patent family annex

| ‘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 |

Date of the actual completion of the international search: 28 April 2009

Date of mailing of the international search report: 08/05/2009

Name and mailing address of the ISA/

European Patent Office, P B 5818 Patentlaan 2
NL - 2280 HV RI|SWI|k
Tel (+31-70) 340-2040,
Fax (+31-70) 340-3016

Authorized officer:

English, Russel
<table>
<thead>
<tr>
<th>Patent document cited in search report</th>
<th>Publication date</th>
<th>Patent family member(s)</th>
<th>Publication date</th>
</tr>
</thead>
<tbody>
<tr>
<td>US 6639107 B1</td>
<td>28-10-2003</td>
<td>NONE</td>
<td></td>
</tr>
</tbody>
</table>