

(19) World Intellectual Property
Organization
International Bureau



(43) International Publication Date
29 December 2004 (29.12.2004)

PCT

(10) International Publication Number
WO 2004/113301 A1

(51) International Patent Classification⁷: **C07D 215/58**,
209/08, 209/44, 217/06, A61K 31/33, A61P 25/18

(74) Agent: **KONDO, Rie**; GlaxoSmithKline, CIP (CN925.1),
980 Great West Road, Brentford Middlesex TW8 9GS
(GB).

(21) International Application Number:
PCT/EP2004/006593

(81) Designated States (*unless otherwise indicated, for every kind of national protection available*): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(22) International Filing Date: 17 June 2004 (17.06.2004)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
0314479.7 20 June 2003 (20.06.2003) GB

(71) Applicant (*for all designated States except US*): **GLAXO GROUP LIMITED** [GB/GB]; Glaxo Wellcome House, Berkeley Avenue, Greenford Middlesex UB6 0NN (GB).

(72) Inventors; and

(75) Inventors/Applicants (*for US only*): **BRANCH, Clive, Leslie** [GB/GB]; GlaxoSmithKline, New Frontiers Science Park South, Third Avenue, Harlow Essex CM19 5AW (GB). **COULTON, Steven** [GB/GB]; GlaxoSmithKline, New Frontiers Science Park South, Third Avenue, Harlow Essex CM19 5AW (GB). **PORTER, Roderick, Alan** [GB/GB]; GlaxoSmithKline, New Frontiers Science Park South, Third Avenue, Harlow Essex CM19 5AW (GB).

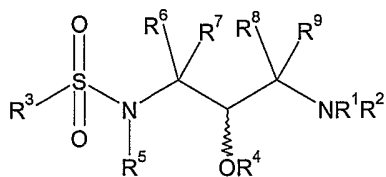
(84) Designated States (*unless otherwise indicated, for every kind of regional protection available*): ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

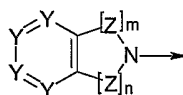
— with international search report

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: GLYT1 TRANSPORTER INHIBITORS AND USES THEREOF IN TREATMENT OF NEUROLOGICAL AND NEUROPSYCHIATRIC DISORDERS



(I)



(a)

N; R⁴ and R⁵ are independently selected from hydrogen, optionally substituted C₁-C₆ alkyl, optionally substituted C₃-C₆cycloalkyl, optionally substituted aryl and optionally substituted arylC₁-C₄ alkyl; and R⁶, R⁷, R⁸ and R⁹ are independently selected from hydrogen, optionally substituted C₁-C₆ alkyl and optionally substituted arylC₁-C₄alkyl, or R⁶ and R⁷ together form an optionally substituted C₃-C₆ cycloalkyl group, or R⁸ and R⁹ together form an optionally substituted C₃-C₆ cycloalkyl group. Methods of preparation and uses of the compounds in medicine for the treatment of a disorder mediated by GlyT1, for example schizophrenia, are also disclosed.

GlyT1 Transporter Inhibitors And Uses Thereof In Treatment Of Neurological And Neuropsychiatric Disorders

5 The present invention relates to glycine transporter inhibiting compounds, their use in the manufacture of medicaments for treating neurological and neuropsychiatric disorders, in particular psychosis, dementia or attention deficit disorder. The invention further comprises processes to make these compounds and pharmaceutical formulations thereof.

10 Synaptic transmission is a complex form of intercellular communication that involves a considerable array of specialised structures in both the pre-and post-synaptic terminal and surrounding glial cells (Kanner and Schuldiner, CRC Critical Reviews in Biochemistry, 22, 1987:1032). Transporters sequester neurotransmitter from the synapse, thereby regulating the concentration of neurotransmitter in the synapse, as
15 well as its duration therein, which together influence the magnitude of synaptic transmission. Further, by preventing the spread of transmitter to neighbouring synapses, transporters maintain the fidelity of synaptic transmission. Last, by sequestering released transmitter into the presynaptic terminal, transporters allow for transmitter reutilisation.

20 Neurotransmitter transport is dependent upon extracellular sodium and the voltage difference across the membrane; under conditions of intense neuronal firing, as, for example, during seizure, transporters can function in reverse, releasing neurotransmitter in a calcium-independent non-exocytotic manner (Atwell *et al.*,
25 Neuron, 11, 1993: 401-407). Pharmacologic modulation of neurotransmitter transporters thus provides a means for modifying synaptic activity, which provides useful therapy for the treatment of neurological and psychiatric disturbances.

30 The amino acid glycine is a major neurotransmitter in the mammalian central nervous system, functioning at both inhibitory and excitatory synapses. By nervous system, both the central and peripheral portions of the nervous system are intended. These distinct functions of glycine are mediated by two different types of receptor, each of which is associated with a different class of glycine transporter. The inhibitory actions of glycine are mediated by glycine receptors that are sensitive to the
35 convulsant alkaloid strychnine, and are thus referred to as "strychnine-sensitive". Such receptors contain an intrinsic chloride channel that is opened upon binding of glycine to the receptor; by increasing chloride conductance, the threshold for firing of an action potential is increased. Strychnine-sensitive glycine receptors are found predominantly in the spinal cord and brainstem, and pharmacological agents that
40 enhance the activation of such receptors will thus increase inhibitory neurotransmission in these regions.

Glycine also functions in excitatory transmission by modulating the actions of glutamate, the major excitatory neurotransmitter in the central nervous system. See Johnson and Ascher, *Nature*, 325, 1987: 529-531; Fletcher *et al.*, *Glycine Transmission*, Otterson and Storm-Mathisen, eds., 1990: 193-219. Specifically, glycine is an obligatory co-agonist at the class of glutamate receptor termed N-methyl-D-aspartate (NMDA) receptor. Activation of NMDA receptors increases sodium and calcium conductance, which depolarises the neuron, thereby increasing the likelihood that it will fire an action potential. NMDA receptors are widely distributed throughout the brain, with a particularly high density in the cerebral cortex and hippocampal formation.

Molecular cloning has revealed the existence in mammalian brains of two classes of glycine transporters, termed GlyT1 and GlyT2. GlyT1 is found predominantly in the forebrain and its distribution corresponds to that of glutaminergic pathways and NMDA receptors (Smith, *et al.*, *Neuron*, 8, 1992: 927-935). Molecular cloning has further revealed the existence of three variants of GlyT1, termed GlyT-1a, GlyT-1b and GlyT-1c (Kim *et al.*, *Molecular Pharmacology*, 45, 1994: 608-617), each of which displays a unique distribution in the brain and peripheral tissues. The variants arise by differential splicing and exon usage, and differ in their N-terminal regions. GlyT2, in contrast, is found predominantly in the brain stem and spinal cord, and its distribution corresponds closely to that of strychnine-sensitive glycine receptors (Liu *et al.*, *J. Biological Chemistry*, 268, 1993: 22802-22808; Jursky and Nelson, *J. Neurochemistry*, 64, 1995 : 1026-1033). Another distinguishing feature of glycine transport mediated by GlyT2 is that it is not inhibited by sarcosine as is the case for glycine transport mediated by GlyT1. These data are consistent with the view that, by regulating the synaptic levels of glycine, GlyT1 and GlyT2 selectively influence the activity of NMDA receptors and strychnine-sensitive glycine receptors, respectively.

NMDA receptors are critically involved in memory and learning (Rison and Staunton, *Neurosci. Biobehav. Rev.*, 19 533-552 (1995); Danysz *et al.*, *Behavioral Pharmacol.*, 6 455-474 (1995)); and, furthermore, decreased function of NMDA-mediated neurotransmission appears to underlie, or contribute to, the symptoms of schizophrenia (Olney and Farber, *Archives General Psychiatry*, 52, 998-1007 (1996). Thus, agents that inhibit GlyT1 and thereby increase glycine activation of NMDA receptors can be used as novel antipsychotics and anti-dementia agents, and to treat other diseases in which cognitive processes are impaired, such as attention deficit disorders and organic brain syndromes. Conversely, over-activation of NMDA receptors has been implicated in a number of disease states, in particular the neuronal death associated with stroke and possibly neurodegenerative diseases, such as Alzheimer's disease, multi-infarct dementia, AIDS dementia, Huntington's disease, Parkinson's disease, amyotrophic lateral sclerosis or other conditions in which neuronal cell death occurs, such as stroke or head trauma. Coyle &

Puttfarcken, Science, 262, 689-695 (1993); Lipton and Rosenberg, New Engl. J. of Medicine, 330, 613-622 (1993); Choi, Neuron, 1, 623-634 (1988). Thus, pharmacological agents that increase the activity of GlyT1 will result in decreased glycine-activation of NMDA receptors, which activity can be used to treat these and related disease states. Similarly, drugs that directly block the glycine site of the NMDA receptors can be used to treat these and related disease states.

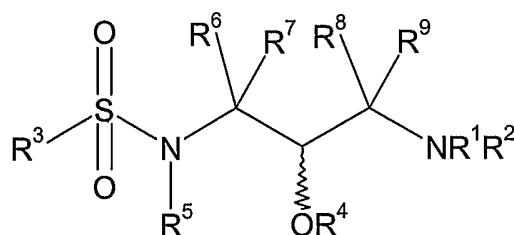
Glycine transport inhibitors are already known in the art, for example as disclosed in published International Applications WO97/45423 (Trophix Pharmaceuticals, Inc.), and WO97/45115 (Trophix Pharmaceuticals Inc.). The classes of compounds disclosed in these applications inhibit glycine transport *via* the GlyT1 or GlyT2 transporters.

In published International Application WO99/34790 (Allelix Neuroscience, Inc.), there is disclosed a class of compounds which also inhibits glycine transport *via* the GlyT1 or GlyT2 transporters, with preferred compounds showing selectivity for the inhibition of glycine transport *via* GlyT2 versus GlyT1.

There still remains the need to identify further compounds that can inhibit GlyT1 transporters, including those that inhibit GlyT1 transporters selectively over GlyT2 transporters.

It has now surprisingly been found that a class of compounds inhibit GlyT1 transporters and are thus useful in the treatment of certain neurological and neuropsychiatric disorders, including schizophrenia.

Thus, in a first aspect, there is provided a compound of formula (I),



(I)

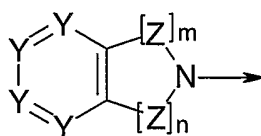
or a salt, solvate or a physiologically functional derivative thereof, wherein:

R¹ and R² is independently selected from hydrogen, optionally substituted C₁₋₆alkyl, optionally substituted C₃₋₆cycloalkyl, optionally substituted aryl, optionally

substituted arylC₁₋₄alkyl and optionally substituted arylC₃₋₆cycloalkyl, wherein R¹ and R² are not both hydrogen, or

R¹ and R², together with the nitrogen atom to which they are attached, are linked to form an optionally substituted 4-, 5-, 6- or 7-membered saturated ring, wherein one or more of the carbon atoms is optionally replaced by a heteroatom independently selected from N, O and S;

R³ is an optionally substituted group of formula (a):



(a)

wherein

m and n are independently 0, 1, 2 or 3 and m+n is 2, 3 or 4;

each Z is independently -CH₂-, -NH-, -O- or -S-; and

each Y is independently CH or N;

R⁴ and R⁵ are independently selected from hydrogen, optionally substituted C₁-C₆ alkyl, optionally substituted C₃-C₆ cycloalkyl, optionally substituted aryl and optionally substituted arylC₁-C₄ alkyl; and

R⁶, R⁷, R⁸ and R⁹ are independently selected from hydrogen, optionally substituted C₁-C₆ alkyl and optionally substituted arylC₁-C₄ alkyl, or R⁶ and R⁷ together form an optionally substituted C₃-C₆ cycloalkyl group, or R⁸ and R⁹ together form an optionally substituted C₃-C₆ cycloalkyl group.

As used herein, the terms "Cx-y" and "Cx-Cy" are equivalent. Thus, "C₁₋₆alkyl" is the same as "C₁-C₆ alkyl".

As used herein, the term "C₁-C₆ alkyl" refers to a straight or branched chain hydrocarbon which contains at least 1, and at most 6, carbon atoms. Examples of "C₁-C₆ alkyl" groups useful in the present invention include, but are not limited to, methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, t-butyl, n-pentyl, n-hexyl.

In a like manner, the term "C₁-C₄ alkyl" refers to a straight or branched chain hydrocarbon which contains at least 1, and at most 4, carbon atoms. Examples of "C₁-C₄ alkyl" groups useful in the present invention include, but are not limited to, methyl, ethyl, n-propyl, i-propyl, n-butyl, i-propyl and t-butyl.

As used herein, the term "C₃-C₆ cycloalkyl" refers to a non-aromatic cyclic hydrocarbon ring having from three to six carbon atoms. Exemplary "C₃-C₆ cycloalkyl" groups include cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl.

- 5 As used herein, the term "C₃-C₆ cycloalkylC₁-C₄ alkyl" refers to a C₃-C₆ cycloalkyl group, as hereinbefore defined, attached through a C₁-C₄ alkylene linker, wherein C₁-C₄ alkylene is as defined herein. Examples of "C₃-C₆ cycloalkylC₁-C₄ alkyl" include, but are not limited to, cyclohexylmethyl.
- 10 As used herein, the term "aryl" refers to a 5- to 7- membered monocyclic aromatic ring or a 6- to 11- membered bicyclic aromatic ring, wherein one or more of the carbon atoms is optionally replaced by a heteroatom independently selected from N, O and S. Examples of monocyclic aryl groups include: phenyl, pyrrolyl, pyrrolinyl, imidazolyl, pyrazolyl, pyrazolinyl, isothiazolyl, thiazolyl, isoxazolyl, furazanyl, oxazolyl, furyl, thienyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, azepinyl and pyranyl.
- 15

- As used herein, the term "bicyclic aromatic ring" includes bicyclic ring systems in which both rings are aromatic, as well as bicyclic ring systems in which one of the rings is partially or fully saturated. Examples of bicyclic aryl groups in which both rings are aromatic include: naphthyl, indenyl, indolyl, isoindolyl, indazolyl, benzimidazolyl, benzoxazolyl, benzothienyl, benzothiazolyl, benzofuranyl, naphthridinyl, quinolyl, quinoxalyl, quinazolinyl and isoquinolyl. Examples of bicyclic aryl groups in which one of the rings is partially or fully saturated includes dihydrobenzofuranyl, indanyl, tetrahydronaphthyl, indolinyl, isoindolinyl, tetrahydroisoquinolyl, tetrahydroquinolyl, benzoxazinyl and benzoazepinyl.
- 20
- 25

- As used herein, the term "aryl C₁-C₄ alkyl" refers to an aryl group, as hereinbefore defined, attached through a C₁-C₄ alkylene linker, wherein C₁-C₄ alkylene is as defined herein. Examples of "aryl C₁-C₄ alkyl" include, but are not limited to, benzyl, phenethyl, pyridylmethyl and phenylpropyl.
- 30

- As used herein, the terms "C₁-C₂ alkylene", "C₁-C₃ alkylene" and "C₁-C₄ alkylene" refer to a straight or branched chain divalent hydrocarbon radical, which contains at least 1, and at most 2, 3 or 4, carbon atoms respectively. Examples of "C₁-C₂ alkylene", "C₁-C₃ alkylene" and "C₁-C₄ alkylene" groups useful in the present invention include methylene, ethylene, n-propylene and n-butylene.
- 35

- As used herein, the term "C₂ alkenylene" refers to a divalent hydrocarbon radical with a double bond, which contains 2 carbon atoms.
- 40

As used herein, the term "C₂ alkynylene" refers to a divalent hydrocarbon radical with a triple bond, which contains 2 carbon atoms.

As used herein, the term "hal" is an abbreviation for "halogen" and refers to fluorine,
5 chlorine, bromine, or iodine.

As used herein, the term "optionally" means that the subsequently described event(s) may or may not occur, and includes both event(s) which occur, and event(s) that do not occur.

10

As used herein, the term "substituted" refers to substitution with the named substituent or substituents, multiple degrees of substitution by independently chosen substituents being allowed unless otherwise stated.

15 As used herein, the term "salt" refers to any salt of a compound according to the present invention prepared from an inorganic or organic acid or base, quaternary ammonium salts and internally formed salts. Physiologically acceptable salts are particularly suitable for medical applications because of their greater aqueous solubility relative to the parent compounds. Such salts must clearly have a
20 physiologically acceptable anion or cation. Suitably physiologically acceptable salts of the compounds of the present invention include acid addition salts formed with inorganic acids such as hydrochloric, hydrobromic, hydroiodic, phosphoric, metaphosphoric, nitric and sulfuric acids, and with organic acids, such as tartaric, acetic, trifluoroacetic, citric, malic, lactic, fumaric, benzoic, formic, propionic, glycolic,
25 gluconic, maleic, succinic, camphorsulfuric, isothionic, mucic, gentisic, isonicotinic, saccharic, glucuronic, furoic, glutamic, ascorbic, anthranilic, salicylic, phenylacetic, mandelic, embonic (pamoic), methanesulfonic, ethanesulfonic, pantothenic, stearic, sulfinilic, alginic, galacturonic and arylsulfonic, for example benzenesulfonic and p-toluenesulfonic, acids; base addition salts formed with alkali metals and alkaline
30 earth metals and organic bases such as N,N-dibenzylethylenediamine, chloroprocaine, choline, diethanolamine, ethylenediamine, meglumine (N-methylglucamine), lysine and procaine; and internally formed salts. Salts having a non-physiologically acceptable anion or cation are within the scope of the invention as useful intermediates for the preparation of physiologically acceptable salts and/or
35 for use in non-therapeutic, for example, *in vitro*, situations.

As used herein, the term "solvate" refers to a complex of variable stoichiometry formed by a solute (in this invention, a compound of formula (I) or formula (Ia), or a salt or physiologically functional derivative thereof) and a solvent. Such solvents for
40 the purpose of the invention may not interfere with the biological activity of the solute. Examples of suitable solvents include, but are not limited to, water, methanol, ethanol and acetic acid. Preferably the solvent used is a pharmaceutically

acceptable solvent. Examples of suitable pharmaceutically acceptable solvents include water, ethanol and acetic acid. Most preferably the solvent used is water.

As used herein, the term "physiologically functional derivative" refers to any pharmaceutically acceptable derivative of a compound of the present invention, for example, an ester or an amide, which upon administration to a mammal is capable of providing (directly or indirectly) a compound of the present invention or an active metabolite thereof. Such derivatives are clear to those skilled in the art, without undue experimentation, and with reference to the teaching of Burger's Medicinal Chemistry And Drug Discovery, 5th Edition, Vol 1: Principles and Practice, which is incorporated herein by reference to the extent that it teaches physiologically functional derivatives.

Suitable optional substituents for R¹, R², R³, R⁴, R⁵, R⁶, R⁷, R⁸ and R⁹, and for the optionally substituted 4-, 5-, 6- or 7-membered saturated ring formed by R¹ and R², together with the nitrogen atom to which they are attached, and for the optionally substituted C₃-C₆ cycloalkyl group formed by R⁶ and R⁷, and for the optionally substituted C₃-C₆ cycloalkyl group formed by R⁸ and R⁹, include one or more groups selected from:

halogen, hydroxy, oxo, cyano, nitro, C₁₋₆alkyl, C₁₋₄alkoxy, haloC₁₋₄alkyl, haloC₁₋₄alkoxy, arylC₁₋₄alkoxy, C₁₋₄alkylthio, hydroxyC₁₋₄alkyl, C₁₋₄alkoxyC₁₋₄alkyl, C₃₋₆cycloalkyl, C₃₋₆cycloalkylC₁₋₄alkoxy, C₁₋₄alkanoyl, C₁₋₄alkoxycarbonyl, C₁₋₄alkylsulfonyl, C₁₋₄alkylsulfonyloxy, C₁₋₄alkylsulfonylC₁₋₄alkyl, arylsulfonyl, arylsulfonyloxy, arylsulfonylC₁₋₄alkyl, C₁₋₄alkylsulfonamido, C₁₋₄alkylamido, C₁₋₄alkylsulfonamidoC₁₋₄alkyl, C₁₋₄alkylamidoC₁₋₄alkyl, arylsulfonamido, arylcarboxamido, arylsulfonamidoC₁₋₄alkyl, arylcarboxamidoC₁₋₄alkyl, aroyl, aroylC₁₋₄alkyl, arylC₁₋₄alkanoyl, C₁₋₄acyl, aryl, arylC₁₋₄alkyl, C₁₋₄alkylaminoC₁₋₄alkyl, a group R³⁰R³¹N-, R³⁰OCO(CH₂)_r, R³⁰CON(R³¹)(CH₂)_r, R³⁰R³¹NCO(CH₂)_r, R³⁰R³¹NSO₂(CH₂)_r or R³⁰SO₂NR³¹(CH₂)_r (where each of R³⁰ and R³¹ independently represents a hydrogen atom or a C₁₋₄alkyl group or where appropriate R³⁰R³¹ forms part of a C₃₋₆azacycloalkane or C₃₋₆(2-oxo)azacycloalkane ring and r represents zero or an integer from 1 to 4), a group R³⁰R³¹N(CH₂)_n- or R³⁰R³¹N(CH₂)_nO- (wherein n represents an integer from 1 to 4); wherein when the substituent is R³⁰R³¹N(CH₂)_n- or R³⁰R³¹N(CH₂)_nO, R³⁰ with at least one CH₂ of the (CH₂)_n portion of the group may also form a C₃₋₆azacycloalkane and R³¹ may represent hydrogen, a C₁₋₄alkyl group or with the nitrogen to which it is attached, may form a second C₃₋₆azacycloalkane fused to the first C₃₋₆azacycloalkane.

Furthermore, the optionally substituted 4-, 5-, 6- or 7-membered saturated ring formed by R¹ and R² may be additionally optionally bridged by a C₁–C₃ alkylene group; and the optionally substituted 4-, 5-, 6- or 7-membered saturated ring formed by R¹ and R² may be additionally optionally fused to a C₅–C₇ alicyclic or 5- or 6-membered aromatic or heteroaromatic ring optionally substituted by one or more groups independently selected from C₁–C₆ alkyl and C₃–C₆ cycloalkyl.

Where there is more than one substituent, the substituents may be different or the same. If substituent(s) is/are present, preferably the number of substituent(s) is 1, 2, 3 or 4.

Suitably, R³ is an N-linked 9-, 10- or 11- membered bicyclic moiety wherein the ring containing the linking nitrogen atom is saturated, the bicyclic moiety being optionally substituted at any available position by one or more substituents as defined above. In one embodiment, R³ is substituted by one or more groups selected from hydrogen, hal, C₁–C₆ alkyl, C₁–C₆ alkoxy, -CF₃, -CN and C₃–C₆ cycloalkyl. Suitably R³ is selected from: optionally substituted indolinyl, isoindolinyl, tetrahydroisoquinolinyl, tetrahydroquinolyl and benzazepinyl.

In one embodiment, R¹ and R² are independently selected from optionally substituted C₁–C₆ alkyl, preferably C₃–C₆ alkyl.

In another embodiment, R¹ and R² together with the nitrogen atom to which they are attached are linked to form a 4-, 5-, 6- or 7-membered heterocyclic ring, wherein the sole heteroatom is the nitrogen atom to which R¹ and R² are attached, said ring being optionally substituted as hereinbefore described, and said ring being further optionally fused to a C₅–C₇ alicyclic or 5- or 6-membered aromatic or heteroaromatic ring as hereinbefore described.

In another embodiment, R¹ and R² together with the nitrogen atom to which they are attached are linked to form a 5- or 6-membered ring, wherein one or more of the carbon atoms is optionally replaced by a heteroatom independently selected from N, O and S, said ring being optionally substituted as hereinbefore described, and said ring being further optionally fused to a C₅–C₇ alicyclic or 5- or 6-membered aromatic or heteroaromatic ring as hereinbefore described.

In another embodiment, R¹ and R² together with the nitrogen atom to which they are attached are linked to form a 5- or 6-membered heterocyclic ring, wherein the sole heteroatom is the nitrogen atom to which R¹ and R² are attached, said ring being optionally substituted as hereinbefore described, preferably by one or more groups independently selected from optionally substituted C₁–C₆ alkyl and optionally

substituted C₃–C₆ cycloalkyl, more preferably by one or more groups independently selected from C₁–C₄ alkyl, most preferably methyl, ethyl or isopropyl.

5 Suitably, the 4-, 5-, 6- or 7-membered saturated ring formed by R¹ and R² together with the nitrogen atom to which they are linked is selected from the group comprising: azetidine, azepine, pyrrolidine, imidazolidine, piperidine, morpholine, thiomorpholine, piperazine.

10 In another embodiment, R¹ and R² together with the nitrogen atom to which they are attached are linked to form a pyrrolidinyl ring, said ring being optionally substituted by one or more groups independently selected from optionally substituted C₁–C₄ alkyl, preferably methyl, ethyl or isopropyl. Preferably, the pyrrolidinyl ring formed by R¹ and R² together with the nitrogen atom to which they are attached is substituted by one or more C₁–C₄ alkyl groups, preferably methyl, ethyl or isopropyl groups,
15 preferably at the 2- and/or 5-positions, more preferably at the 2-position.

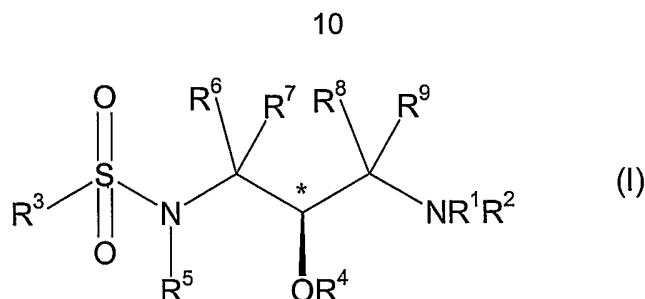
In another embodiment, R¹ and R² together with the nitrogen atom to which they are attached are linked to form a piperidinyl ring, said ring being optionally substituted by one or more groups independently selected from optionally substituted C₁–C₄ alkyl,
20 preferably methyl or ethyl. Preferably, the piperidinyl ring formed by R¹ and R² together with the nitrogen atom to which they are attached is substituted by one or more methyl or ethyl groups, preferably at the 2- and 6-positions. More preferably, the piperidinyl ring formed by R¹ and R² together with the nitrogen atom to which they are attached is substituted by two methyl groups, preferably at the 2- and 6-
25 positions.

In another embodiment, R⁴ is hydrogen or C₁–C₆ alkyl, preferably hydrogen.

30 In another embodiment, R⁵ is selected from hydrogen, C₁–C₆ alkyl, aryl and benzyl, optionally substituted by one or more groups independently selected from hal, C₁–C₆ alkyl, hydroxy and C₁–₆alkoxy. Preferably, R⁵ is hydrogen.

In another embodiment, R⁶, R⁷, R⁸ and R⁹ are independently selected from hydrogen and C₁–C₆ alkyl, preferably hydrogen.

35 Preferably, the compound of formula (I) as hereinbefore described has the following stereochemical configuration:



It will be understood by the skilled artisan that the stereochemical configuration at the chiral centre marked with a * will be assigned the Cahn-Ingold-Prelog notation of (R).

5

Examples of compounds of the invention include:

- *N*-{(2*R*)-3-[(2*R*,6*S*)-2,6-dimethyl-1-piperidiny]-2-hydroxypropyl}-3,4-dihydro-1(2*H*)-quinolinesulfonamide
- 10 • *N*-{(2*R*)-3-[(2*R*,6*S*)-2,6-dimethyl-1-piperidiny]-2-hydroxypropyl}-2,3-dihydro-1*H*-indole-1-sulfonamide
- *N*-{(2*R*)-3-[(2*R*,6*S*)-2,6-Dimethyl-1-piperidiny]-2-hydroxypropyl}-1,3-dihydro-2*H*-isoindole-2-sulfonamide
- *N*-{(2*R*)-3-[(2*R*,6*S*)-2,6-Dimethyl-1-piperidiny]-2-hydroxypropyl}-3,4-dihydro-2(1*H*)-isoquinolinesulfonamide

15

and salts, solvates and physiologically functional derivatives thereof.

The compounds of formula (I) have the ability to crystallise in more than one form, a characteristic, which is known as polymorphism, and it is understood that such polymorphic forms ("polymorphs") are within the scope of formula (I). Polymorphism generally can occur as a response to changes in temperature or pressure or both and can also result from variations in the crystallisation process. Polymorphs can be distinguished by various physical characteristics known in the art such as x-ray diffraction patterns, solubility, and melting point.

25

Certain of the compounds described herein may exist in stereoisomeric forms (i.e. they may contain one or more asymmetric carbon atoms or may exhibit *cis-trans* isomerism). The individual stereoisomers (enantiomers and diastereoisomers) and mixtures of these are included within the scope of the present invention. Likewise, it is understood that compounds of formula (I) may exist in tautomeric forms other than that shown in the formula and these are also included within the scope of the present invention.

30

As referred to above, individual enantiomers of compounds of formula (I) may be prepared and an indication of the preferred stereochemistry for such enantiomers has been given. In a preferred embodiment, an optically pure enantiomer is desired. The term "optically pure enantiomer" means that the compound contains greater than

35

about 90 % of the desired isomer by weight, preferably greater than about 95 % of the desired isomer by weight, and most preferably greater than about 99 % of the desired isomer by weight, said weight percent based upon the total weight of the isomer(s) of the compound.

5

The compounds of this invention may be made by a variety of methods, including standard chemistry. Any previously defined variable will continue to have the previously defined meaning unless otherwise indicated. Illustrative general synthetic methods are set out below and then specific compounds of the invention are prepared in the working Examples.

10

Compounds of general formula (I) may be prepared by methods disclosed in the documents hereinbefore referred to and by methods known in the art of organic synthesis as set forth in part by the following synthesis schemes. It is also recognised that in all of the schemes described below, it is well understood that protecting groups for sensitive or reactive groups are employed where necessary in accordance with general principles of chemistry. Protecting groups are manipulated according to standard methods of organic synthesis (T. W. Greene and P. G. M. Wuts (1991) Protecting Groups in Organic Synthesis, John Wiley & Sons). These groups are removed at a convenient stage of the compound synthesis using methods that are readily apparent to those skilled in the art. The selection of processes as well as the reaction conditions and order of their execution shall be consistent with the preparation of compounds of formula (I). Those skilled in the art will recognise if a stereocentre exists in compounds of formula (I). Accordingly, the present invention includes both possible stereoisomers and includes not only racemic compounds but the individual enantiomers as well. Where the stereochemistry is indicated as being variable at certain positions, a mixture of stereoisomers may be obtained, this mixture having been separated where indicated. Stereoisomers may be separated by high-performance liquid chromatography or other appropriate means. When a compound is desired as a single enantiomer, it may be obtained by stereospecific synthesis or by resolution of the final product or any convenient intermediate. Resolution of the final product, an intermediate, or a starting material may be effected by any suitable method known in the art. See, for example, Stereochemistry of Organic Compounds by E. L. Eliel, S. H. Wilen, and L. N. Mander (Wiley-Interscience, 1994).

15

20

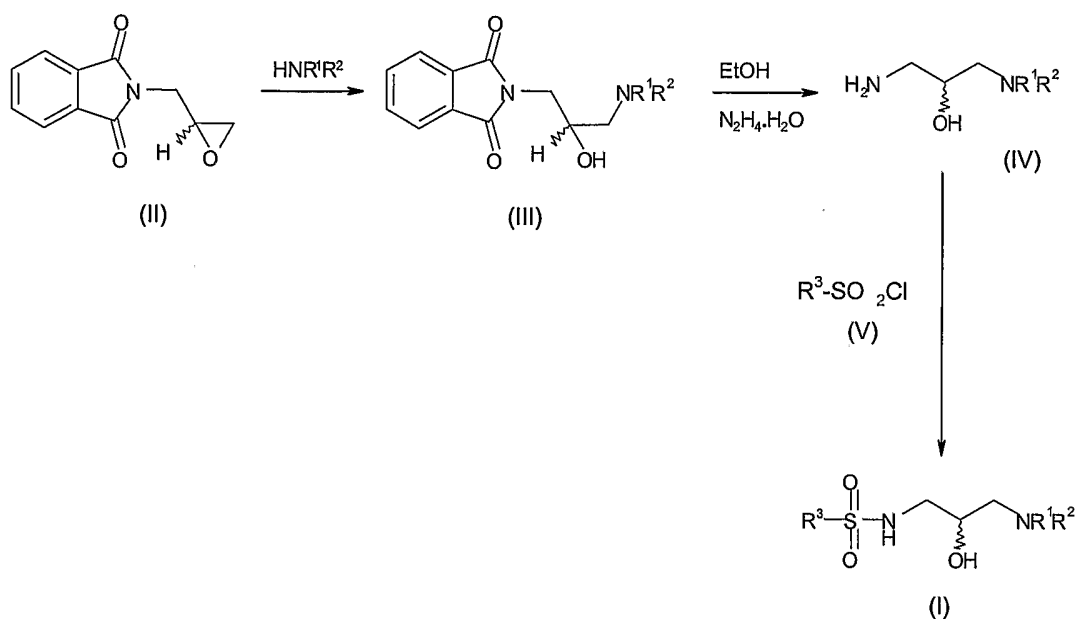
25

30

35

Typical reaction routes for the preparation of a compound of formula (I) as hereinbefore defined, wherein R⁵, R⁶, R⁷, R⁸ and R⁹ are hydrogen, are shown in the scheme below.

12



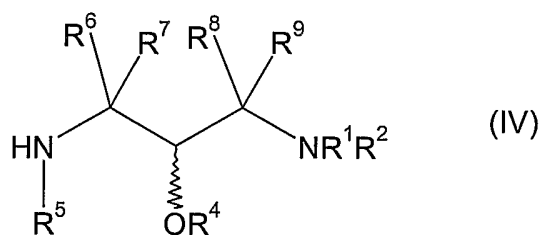
- 5 In the above scheme, the compounds of formula (I) may be prepared using methodology similar to that described by Gutcait A. *et al.*, *Tetrahedron Asymmetry*, 1996, 7(6), 1641-1648.

10 Intermediates of type (V) can be made by methods known in the art. For example, sulfamic acid salts as described by L.F.Audrieth and M. Sveda, *J. Org. Chem.*, **9**, 89 (1944) and sulfamoyl chlorides as reported by J. A. Kloek and K. L. Leschinsky *J. Org. Chem.*, **41**, 25 (1976) and refs. therein.

15 As indicated above, the above scheme can be adapted to prepare compounds wherein R⁴, R⁵, R⁶, R⁷, R⁸ and R⁹ are other than hydrogen.

Thus, in a further aspect of the invention, there is provided a process for the preparation of the compound of formula (I) as hereinbefore defined by reacting a compound of formula (IV)

20



wherein R^1 , R^2 , R^4 , R^5 , R^6 , R^7 , R^8 and R^9 are as hereinbefore defined, with a compound of formula (V):



5

wherein R^3 is as hereinbefore defined and L is a suitable leaving group, such as, for example, a halogen, preferably chlorine;

and thereafter optionally:

- 10
- removing any protecting groups and/or
 - converting a compound of formula (I) into another compound of formula (I) and/or
 - forming a pharmaceutically acceptable salt.

15 Compounds of formula (I) can be converted into further compounds of formula (I) using standard techniques. For example, and by way of illustration rather than limitation, possible conversion reactions include acylation with an appropriate acylating agent such as acetyl chloride, alkylation using an appropriate alkylating reagent such as methyl iodide, and sulfonylation using a sulfonylating agent such as methanesulfonic anhydride.

20

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

25 The compounds of the present invention inhibit the GlyT1 transporter. The compounds may selectively inhibit the GlyT1 transporter over the GlyT2 transporter.

Such compounds would be suitable for the treatment of certain neurological and neuropsychiatric disorders. As used herein, the terms "treatment" and "treating" refer to the alleviation and/or cure of established symptoms as well as prophylaxis.

30

The affinity of the compounds of the present invention for the GlyT1 transporter may be measured by the following assay:

35 HEK293 cells expressing the Glycine (Type 1) transporter were grown in cell medium (DMEM/NUT mix F12) containing 2 mM L-Glutamine, 0.8 mg/mL G418 and 10% heat inactivated fetal calf serum (Gibco BRL) at 37°C in 5% CO₂. Cells grown to 70-80% confluency in T175 flasks were harvested and resuspended at 1.6×10^6 cells/ml in assay buffer [NaCl (140 mM), KCl (5.4 mM), CaCl₂ (1.8 mM), MgSO₄ (0.8 mM), HEPES (20 mM), glucose (5 mM) and alanine (5 mM), pH 7.4]. An equal volume of
40 LeadseekerTM SPA beads (12.5mg/ml suspended in assay buffer) was added to the cells and 25mL of the cell/bead suspension transferred to each well of a 384-well white solid bottom plate (20,000 cells/well) that contained 14mL of assay buffer.

Compounds were prepared as 10mM stocks in DMSO. Two-fold serial dilutions of the compounds were made in DMSO from a top concentration of 5mM. 1mL of compound at each concentration was added to the assay plate using 384-well parallel dispensing. Substrate (10mL) was added to each well [1:40 dilution of [³H]-glycine in assay buffer containing 5mM glycine). Final DMSO concentration = 2%.
5 Data was collected using a PerkinElmer Viewlux as 5 minute exposures. IC₅₀ values were determined using Grafit.

10 The example compounds below were found to have a pIC₅₀ at the GlyT1 transporter of between 5.4 and 7.1.

Accordingly, in a further aspect of the invention, there is provided a compound of formula (I) as hereinbefore described and salts, solvates and physiologically functional derivatives thereof for use in therapy.

15 In another aspect of the invention, there is provided a compound of formula (I) as hereinbefore described and salts, solvates and physiologically functional derivatives thereof for use in the treatment of a disorder mediated by GlyT1.

20 As used herein, the term "a disorder mediated by GlyT1" refers to a disorder that may be treated by the administration of a medicament that alters the activity of the GlyT1 transporter. As hereinbefore described, the action of GlyT1 transporters affects the local concentration of glycine around NMDA receptors. As a certain amount of glycine is needed for the efficient functioning of NMDA receptors, any
25 change to that local concentration can affect NMDA-mediated neurotransmission. As hereinbefore described, changes in NMDA-mediated neurotransmission have been implicated in certain neuropsychiatric disorders such as dementia, depression and psychoses, for example schizophrenia, and learning and memory disorders, for example attention deficit disorders and autism. Thus, alterations in the activity of the
30 GlyT1 transporter are expected to influence such disorders.

The disorders mediated by GlyT1 referred to herein include neurological and neuropsychiatric disorders, including psychoses such as schizophrenia, dementia and other forms of impaired cognition such as attention deficit disorders and organic
35 brain syndromes. Other neuropsychiatric disorders include drug-induced (phencyclidine, ketamine and other dissociative anesthetics, amphetamine and other psychostimulants and cocaine) psychosis, psychosis associated with affective disorders, brief reactive psychosis, schizoaffective psychosis, and psychosis NOS, "schizophrenia-spectrum" disorders such as schizoid or schizotypal personality
40 disorders, or illness associated with psychosis (such as major depression, manic depressive (bipolar) disorder, Alzheimer's disease and post-traumatic stress

syndrome), and NMDA receptor-related disorders such as autism, depression, benign forgetfulness, childhood learning disorders and closed head injury.

5 In another aspect of the invention, there is provided a method of treating a mammal, including a human, suffering from or susceptible to a disorder mediated by GlyT1 which comprises administering an effective amount of a GlyT1 inhibiting compound of formula (I) as hereinbefore defined or a salt, solvate or a physiologically functional derivative thereof.

10 In another aspect of the invention, there is provided use of a compound of formula (I) as hereinbefore defined or a salt, solvate or a physiologically functional derivative thereof, in the preparation of a medicament for the treatment of a disorder mediated by GlyT1.

15 Preferably, the disorders mediated by GlyT1 to be treated by the use or method as hereinbefore described are psychoses, including schizophrenia, dementia and attention deficit disorders, particularly schizophrenia.

20 As used herein, the term "effective amount" means that amount of a drug or pharmaceutical agent that will elicit the biological or medical response of a tissue, system, animal or human that is being sought, for instance, by a researcher or clinician.

25 Compounds for use according to the invention may be administered as the raw material but the active ingredients are preferably provided in the form of pharmaceutical compositions.

30 Accordingly, in a further aspect of the invention, there is provided a pharmaceutical composition comprising a compound of formula (I) as hereinbefore described or a salt, solvate or a physiologically functional derivative thereof, and at least one pharmaceutically acceptable carrier, diluent or excipient.

35 These pharmaceutical compositions may be used in the treatment of clinical conditions for which a GlyT1 inhibitor is indicated such as, for example, schizophrenia. The carrier must be pharmaceutically acceptable to the recipient and must be compatible with, i.e. not have a deleterious effect upon, the other ingredients in the composition. The carrier may be a solid or a liquid and is preferably formulated with at least one compound of formula (I) as hereinbefore described as a unit dose formulation. If desired, other physiologically active ingredients may also be
40 incorporated in the pharmaceutical compositions of the invention.

It will be appreciated by those skilled in the art that the compounds according to the invention may advantageously be used in conjunction with one or more other therapeutic agents, for instance, different antidepressant agents such as 5HT3 antagonists, serotonin agonists, NK-1 antagonists, selective serotonin reuptake inhibitors (SSRI), noradrenaline re-uptake inhibitors (SNRI), tricyclic antidepressants, dopaminergic antidepressants, H3 antagonists, 5HT1A antagonists, 5HT1B antagonists, 5HT1D antagonists, D1 agonists, M1 agonists and/or anticonvulsant agents, as well as atypical antipsychotic drugs and cognitive enhancers.

5 Suitable 5HT3 antagonists which may be used in combination of the compounds of the inventions include for example ondansetron, granisetron, metoclopramide. Suitable serotonin agonists which may be used in combination with the compounds of the invention include sumatriptan, rauwolscine, yohimbine, metoclopramide.

15 Suitable SSRIs which may be used in combination with the compounds of the invention include fluoxetine, citalopram, femoxetine, fluvoxamine, paroxetine, indalpine, sertraline, zimeldine.

Suitable SNRIs which may be used in combination with the compounds of the invention include venlafaxine and reboxetine.

25 Suitable tricyclic antidepressants which may be used in combination with a compound of the invention include imipramine, amitriptyline, chlormipramine and nortriptyline.

Suitable dopaminergic antidepressants which may be used in combination with a compound of the invention include bupropion and amineptine.

30 Suitable anticonvulsant agents which may be used in combination of the compounds of the invention include for example divalproex, carbamazepine and diazepam.

Suitable atypical antipsychotic drugs which which may be used in combination of the compounds of the invention include for example risperidone, olanzapine, ziprasidone, aripiprazole and clozapine.

35 It will be appreciated that the compounds of the combination or composition may be administered simultaneously (either in the same or different pharmaceutical formulations), separately or sequentially.

40 Possible formulations include those suitable for oral, sub-lingual, buccal, parenteral (for example, subcutaneous, intramuscular, or intravenous), rectal, topical and intranasal administration and in forms suitable for administration by inhalation or

insufflation (either through the mouth or nose). The most suitable means of administration for a particular patient will depend on the nature and severity of the conditions being treated and on the nature of the active compound, but, where possible, oral administration is preferred.

5

Formulations suitable for oral administration may be provided as discrete units, such as tablets, capsules, cachets, or lozenges, each containing a predetermined amount of the active compound; as powders or granules; as solutions or suspensions in aqueous or non-aqueous liquids; or as oil-in-water or water-in-oil emulsions.

10

Formulations suitable for sublingual or buccal administration include lozenges comprising the active compound and, typically, a flavoured base, such as sugar and acacia or tragacanth and pastilles comprising the active compound in an inert base, such as gelatin and glycerin or sucrose and acacia.

15

Formulations suitable for parenteral administration typically comprise sterile aqueous solutions containing a predetermined concentration of the active compound; the solution is preferably isotonic with the blood of the intended recipient. Although such solutions are preferably administered intravenously, they may also be administered by subcutaneous or intramuscular injection.

20

Formulations suitable for rectal administration are preferably provided as unit-dose suppositories comprising the active ingredient and one or more solid carriers forming the suppository base, for example, cocoa butter.

25

Formulations suitable for topical or intranasal application include ointments, creams, lotions, pastes, gels, sprays, aerosols and oils. Suitable carriers for such formulations include petroleum jelly, lanolin, polyethylene glycols, alcohols, and combinations thereof.

30

The formulations of the invention may be prepared by any suitable method, typically by uniformly and intimately admixing the active compound(s) with liquids or finely divided solid carriers, or both, in the required proportions and then, if necessary, shaping the resulting mixture into the desired shape.

35

For example, a tablet may be prepared by compressing an intimate mixture comprising a powder or granules of the active ingredient and one or more optional ingredients, such as a binder, lubricant, inert diluent, or surface active dispersing agent, or by moulding an intimate mixture of powdered active ingredient and inert liquid diluent.

40

Aqueous solutions for parenteral administration are typically prepared by dissolving the active compound in sufficient water to give the desired concentration and then rendering the resulting solution sterile and isotonic.

- 5 It will be appreciated that the precise dose administered will depend on the age and condition of the patient and the frequency and route of administration and will be at the ultimate discretion of the attendant physician. The compound may be administered in single or divided doses and may be administered one or more times, for example 1 to 4 times per day.

10

- A proposed dose of the active ingredient for use according to the invention for oral, sub-lingual, parenteral, buccal, rectal, intranasal or topical administration to a human (of approximately 70 kg bodyweight) for the treatment of neurological and neuropsychiatric disorders mediated by a GlyT1 inhibitor, including schizophrenia, may be about 1 to about 1000 mg, preferably about 5 to about 500 mg, more preferably about 10 to about 100 mg of the active ingredient per unit dose which could be administered, for example, 1 to 4 times per day.

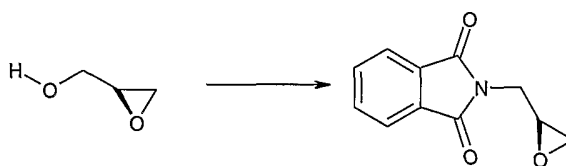
15

The invention is further illustrated by the following non-limiting examples.

20 Examples

The following descriptions set out the syntheses of intermediates particularly useful in the synthesis of compounds of formula (I).

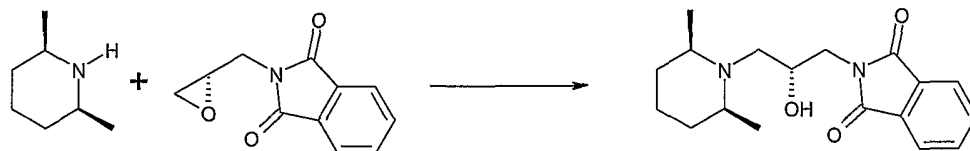
Description 1: 2-Oxiranylmethyl-isoindole-1,3-dione (D1)



- 25 To a stirred solution of phthalimide (10.36g) in THF (350ml) was added triphenylphosphine (18.46g) and (S)-glycidol (5.4ml). This solution was cooled using an external ice bath for the dropwise addition of diethylazodicarboxylate (11.1ml). The reaction mixture was stirred at room temperature overnight. The reaction mixture was then concentrated, and stirred in diethyl ether for 5h. White precipitate was filtered and liquor was evaporated. The residual yellow oil was chromatographed over silica gel, eluting with ethyl acetate/hexane (1:1). Title compound was obtained as a white solid (13g, 91%). Mass Spectrum (Electrospray LC/MS): Found 204 (MH⁺). C₁₁H₉NO₃ requires 203.

30

Description 2 :2-[(R)-3-[(2R,6S)-Dimethylpiperidin-1-yl]-2-hydroxy-propyl]-isoindole-1,3-dione (D2)



- 2,6-Dimethylpiperidine (0.67ml) and 2-oxiranylmethylisoindole-1,3-dione (D1) (1.0g) were heated together under argon at 90°C overnight. After cooling to room temperature the crude mixture was chromatographed over silica gel, eluting with methanol-chloroform (1:9). Title compound was obtained as a white solid (1.07g, 68%). Mass Spectrum (Electrospray): Found 317 (MH⁺). C₁₈H₂₄N₂O₃ requires 316.

Description 3: (S)-1-Amino-3-[(2R,6S)-dimethylpiperidin-1-yl]-propan-2-ol (D3)



- 2-[(R)-3-[(2R,6S)-Dimethylpiperidin-1-yl]-2-hydroxy-propyl]-isoindole-1,3-dione (D2) (0.96g) was stirred in ethanol (60ml) with hydrazine monohydrate (0.74ml) overnight. White precipitate was removed by filtration and liquor concentrated. Re-evaporation from chloroform afforded the title compound (0.56g, 99%) which was used without further purification. Mass Spectrum (Electrospray LC/MS): Found 187 (MH⁺). C₁₀H₂₂N₂O requires 186.

Description 4: Sodium 3,4-dihydro-1(2H)-quinolinesulfonate (D4)



- To 1,2,3,4-tetrahydroquinoline (19.96g) in dichloromethane (100ml) was added chlorosulphonic acid (5.83g) in dichloromethane (3.3ml) at 0°C over 1h. After a further 0.25h. the reaction mixture was evaporated and sodium carbonate (6.4g) in water (55ml) added. The mixture was extracted with diethyl ether (x4) and the aqueous phase evaporated to a white solid. After drying in vacuo for 24h. the resulting solid was extracted with ethanol and the extracts evaporated to give the title product (10g, 85%). Mass Spectrum (Electrospray LC/MS): Found 212 (M-Na⁺). C₉H₁₀NO₃SNa requires 235.

Description 5: 3,4-Dihydro-1(2H)-quinolinesulfonyl chloride (D5)

5

To sodium 3,4-dihydro-1(2H)-quinolinesulfonate (D4) (1g) in anhydrous toluene under argon was added phosphorus pentachloride (0.87g) and the mixture heated at 100°C for 18h. The resulting mixture was cooled in ice, filtered and evaporated to afford the title product as a gum, which was used without further purification.

10

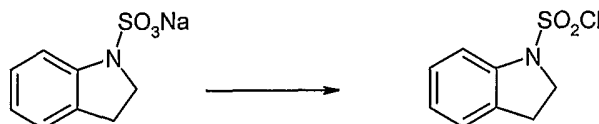
Description 6: Sodium 2,3-dihydro-1H-indole-1-sulfonate (D6)

To indoline (1.98g) and triethylamine (4.59ml) in dichloromethane (30ml) was added chlorosulphonic acid (1.94g) in dichloromethane (1.1ml) at 0°C over 0.5h. After a further 0.8h. the reaction mixture was evaporated and sodium carbonate (2.13g) in water (20ml) added. The mixture was extracted with diethyl ether (x4) and the aqueous phase evaporated. After drying in vacuo for 24h. the resulting solid was extracted with ethanol and the extracts evaporated to give the title product (3.2g, 86%). Mass Spectrum (Electrospray LC/MS): Found 198 (M-Na⁺). C₈H₈NO₃Na requires 221.

20

Description 7: 2,3-Dihydro-1H-indole-1-sulfonyl chloride (D7)

25



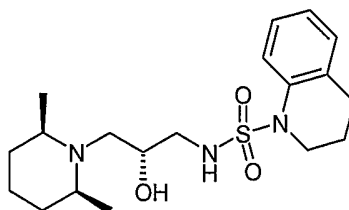
To sodium 2,3-dihydro-1H-indole-1-sulfonate (D6) (1g) in anhydrous toluene under argon was added phosphorus pentachloride (0.94g) and the mixture heated at 100°C for 18h. The resulting mixture was cooled in ice, filtered and evaporated to afford the title product as an oil, which was used without further purification.

30

Example 1: N-[(2R)-3-[(2R,6S)-2,6-dimethyl-1-piperidiny]-2-hydroxypropyl]-3,4-dihydro-1(2H)-quinolinesulfonamide

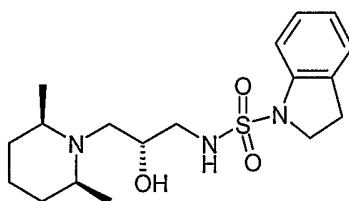
35

21



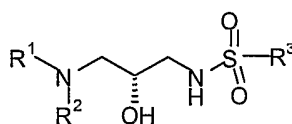
To (S)-1-amino-3-[(2R,6S)-dimethylpiperidin-1-yl]-propan-2-ol (D3) (0.14g) in dichloromethane (4ml) was added triethylamine (0.23ml) followed at ambient temperature by 3,4-dihydro-1(2H)-quinolinesulfonyl chloride (D5) (0.17g). The mixture was stirred for 18h. washed with saturated aqueous sodium hydrogencarbonate and the organic phase loaded onto a pre-packed silica gel cartridge. Gradient elution with ethyl acetate to 10%methanol/ethyl acetate followed by 10%methanol/ethyl acetate to 10%methanol/ethyl acetate containing 2% ammonia afforded the title product (0.065g, 23%). Mass Spectrum (Electrospray LC/MS): Found 382 (MH⁺). C₁₉H₃₁N₃O₃S requires 381.

Example 2: N-[(2R)-3-[(2R,6S)-2,6-dimethyl-1-piperidinyl]-2-hydroxypropyl]-2,3-dihydro-1H-indole-1-sulfonamide



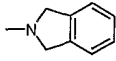
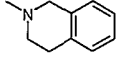
The title product (0.064g, 25%) was obtained as a gum from (S)-1-amino-3-[(2R,6S)-dimethylpiperidin-1-yl]-propan-2-ol (D3) (0.13g) and 2,3-dihydro-1H-indole-1-sulfonyl chloride (D7) (0.15g) using a similar procedure to that described in Example 1. Mass Spectrum (Electrospray LC/MS): Found 368 (MH⁺). C₁₈H₂₉N₃O₃S requires 367.

Examples 3 and 4 were synthesised using methods similar to those described in the above descriptions and examples.



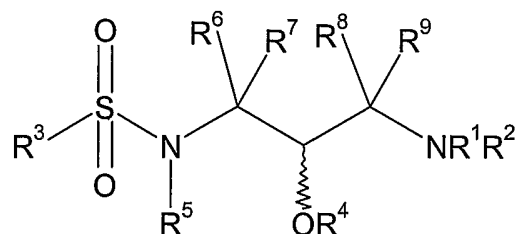
(I)

Example	Compound name	R ¹ R ² N-	-R ³	Mass Spectrum (Electrospray LC/MS) API ⁺

3	<i>N</i> -{[(2 <i>R</i>)-3-[(2 <i>R</i> ,6 <i>S</i>)-2,6-Dimethyl-1-piperidinyl]-2-hydroxypropyl]-1,3-dihydro-2 <i>H</i> -isoindole-2-sulfonamide			Found 368 (MH ⁺). C ₁₈ H ₂₉ N ₃ O ₃ S requires 367
4	<i>N</i> -{[(2 <i>R</i>)-3-[(2 <i>R</i> ,6 <i>S</i>)-2,6-Dimethyl-1-piperidinyl]-2-hydroxypropyl]-3,4-dihydro-2(1 <i>H</i>)-isoquinolinesulfonamide			Found 382 (MH ⁺). C ₁₉ H ₃₁ N ₃ O ₃ S requires 381

Claims

1. A compound of formula (I),

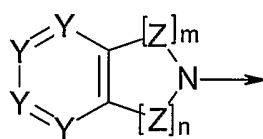


(I)

or a salt, solvate or a physiologically functional derivative thereof, wherein:

R^1 and R^2 is independently selected from hydrogen, optionally substituted C_{1-6} alkyl, optionally substituted C_{3-6} cycloalkyl, optionally substituted aryl, optionally substituted aryl C_{1-4} alkyl and optionally substituted aryl C_{3-6} cycloalkyl, wherein R^1 and R^2 are not both hydrogen, or R^1 and R^2 , together with the nitrogen atom to which they are attached, are linked to form an optionally substituted 4-, 5-, 6- or 7-membered saturated ring, wherein one or more of the carbon atoms is optionally replaced by a heteroatom independently selected from N, O and S;

R^3 is an optionally substituted group of formula (a):



(a)

wherein

m and n are independently 0, 1, 2 or 3 and $m+n$ is 2, 3 or 4;

each Z is independently $-CH_2-$, $-NH-$, $-O-$ or $-S-$; and

each Y is independently CH or N;

R^4 and R^5 are independently selected from hydrogen, optionally substituted C_{1-6} alkyl, optionally substituted C_{3-6} cycloalkyl, optionally substituted aryl and optionally substituted aryl C_{1-4} alkyl; and

R^6 , R^7 , R^8 and R^9 are independently selected from hydrogen, optionally substituted C_{1-6} alkyl and optionally substituted aryl C_{1-4} alkyl, or R^6 and R^7 together form an

optionally substituted C₃–C₆ cycloalkyl group, or R⁸ and R⁹ together form an optionally substituted C₃–C₆ cycloalkyl group.

2. A compound as claimed in claim 1, wherein R¹, R², R³, R⁴, R⁵, R⁶, R⁷, R⁸, R⁹, the 4-, 5-, 6- or 7-membered saturated ring formed by R¹ and R² together with the nitrogen atom to which they are attached, the C₃–C₆ cycloalkyl group formed by R⁶ and R⁷, and/or the C₃–C₆ cycloalkyl group formed by R⁸ and R⁹, are substituted by 1, 2, 3 or 4 substituents selected from:

halogen, hydroxy, oxo, cyano, nitro, C₁–₆alkyl, C₁–₄alkoxy, haloC₁–₄alkyl, haloC₁–₄alkoxy, arylC₁–₄alkoxy, C₁–₄alkylthio, hydroxyC₁–₄alkyl, C₁–₄alkoxyC₁–₄alkyl, C₃–₆cycloalkyl, C₃–₆cycloalkylC₁–₄alkoxy, C₁–₄alkanoyl, C₁–₄alkoxycarbonyl, C₁–₄alkylsulfonyl, C₁–₄alkylsulfonyloxy, C₁–₄alkylsulfonylC₁–₄alkyl, arylsulfonyl, arylsulfonyloxy, arylsulfonylC₁–₄alkyl, C₁–₄alkylsulfonamido, C₁–₄alkylamido, C₁–₄alkylsulfonamidoC₁–₄alkyl, C₁–₄alkylamidoC₁–₄alkyl, arylsulfonamido, arylcarboxamido, arylsulfonamidoC₁–₄alkyl, arylcarboxamidoC₁–₄alkyl, aroyl, aroylC₁–₄alkyl, arylC₁–₄alkanoyl, C₁–₄acyl, aryl, arylC₁–₄alkyl, C₁–₄alkylaminoC₁–₄alkyl, a group R³⁰R³¹N-, R³⁰OCO(CH₂)_r, R³⁰CON(R³¹)(CH₂)_r, R³⁰R³¹NCO(CH₂)_r, R³⁰R³¹NSO₂(CH₂)_r or R³⁰SO₂NR³¹(CH₂)_r (where each of R³⁰ and R³¹ independently represents a hydrogen atom or a C₁–₄alkyl group or where appropriate R³⁰R³¹ forms part of a C₃–₆azacycloalkane or C₃–₆(2-oxo)azacycloalkane ring and r represents zero or an integer from 1 to 4), a group R³⁰R³¹N(CH₂)_n- or R³⁰R³¹N(CH₂)_nO- (wherein n represents an integer from 1 to 4); wherein when the substituent is R³⁰R³¹N(CH₂)_n- or R³⁰R³¹N(CH₂)_nO, R³⁰ with at least one CH₂ of the (CH₂)_n portion of the group may also form a C₃–₆azacycloalkane and R³¹ may represent hydrogen, a C₁–₄alkyl group or with the nitrogen to which it is attached, may form a second C₃–₆azacycloalkane fused to the first C₃–₆azacycloalkane; furthermore, the optionally substituted 4-, 5-, 6- or 7-membered saturated ring formed by R¹ and R² may be additionally optionally bridged by a C₁–₃ alkylene group; and the optionally substituted 4-, 5-, 6- or 7-membered saturated ring formed by R¹ and R² may be additionally optionally fused to a C₅–₇ alicyclic or 5- or 6-membered aromatic or heteroaromatic ring optionally substituted by one or more groups independently selected from C₁–₆ alkyl and C₃–₆ cycloalkyl.

3. A compound as claimed in claim 1 or claim 2, wherein R³ is an N-linked 9-, 10- or 11- membered bicyclic moiety wherein the ring containing the linking nitrogen atom is saturated, the bicyclic moiety being optionally substituted by one or more groups selected from hydrogen, hal, C₁–₆ alkyl, C₁–₆ alkoxy, -CF₃, -CN and C₃–₆ cycloalkyl.

4. A compound as claimed in claim 3, wherein R^3 is selected from: optionally substituted indoliny, isoindoliny, tetrahydroisoquinoliny, tetrahydroquinolyl and benzazepiny.
5. A compound as claimed in any of claims 1-4, wherein R^1 and R^2 are independently selected from optionally substituted C_1-C_6 alkyl, preferably C_3-C_6 alkyl.
6. A compound as claimed in any of claims 1-4, wherein R^1 and R^2 together with the nitrogen atom to which they are attached are linked to form an optionally substituted 4-, 5-, 6- or 7-membered heterocyclic ring, wherein the sole heteroatom is the nitrogen atom to which R^1 and R^2 are attached, said ring being further optionally fused to a C_5-C_7 alicyclic or 5- or 6-membered aromatic or heteroaromatic ring.
7. A compound as claimed in any of claims 1-4, wherein R^1 and R^2 together with the nitrogen atom to which they are attached are linked to form an optionally substituted 5- or 6-membered ring, wherein one or more of the carbon atoms is optionally replaced by a heteroatom independently selected from N, O and S, said ring being further optionally fused to a C_5-C_7 alicyclic or 5- or 6-membered aromatic or heteroaromatic ring.
8. A compound as claimed in any of claims 1-4, wherein R^1 and R^2 together with the nitrogen atom to which they are attached are linked to form 5- or 6-membered heterocyclic ring, wherein the sole heteroatom is the nitrogen atom to which R^1 and R^2 are attached, optionally substituted by one or more groups independently selected from optionally substituted C_1-C_6 alkyl and optionally substituted C_3-C_6 cycloalkyl, more preferably by one or more groups independently selected from C_1-C_4 alkyl, most preferably methyl, ethyl or isopropyl.
9. A compound as claimed in any of claims 1-4, wherein the 4-, 5-, 6- or 7-membered saturated ring formed by R^1 and R^2 together with the nitrogen atom to which they are linked is selected from the group comprising: azetidine, azepine, pyrrolidine, imidazolidine, piperidine, morpholine, thiomorpholine, piperazine.
10. A compound as claimed in any of claims 1-4, wherein R^1 and R^2 together with the nitrogen atom to which they are attached are linked to form a pyrrolidiny ring optionally substituted by one or more groups independently selected from optionally substituted C_1-C_4 alkyl, preferably methyl, ethyl or isopropyl.
11. A compound as claimed in claim 10, wherein the pyrrolidiny ring formed by R^1 and R^2 together with the nitrogen atom to which they are attached is substituted by

one or more C₁–C₄ alkyl groups, preferably methyl, ethyl or isopropyl groups, preferably at the 2- and/or 5-positions, more preferably at the 2-position.

12. A compound as claimed in any of claims 1-4, wherein R¹ and R² together with the nitrogen atom to which they are attached are linked to form a piperidinyl ring optionally substituted by one or more groups independently selected from optionally substituted C₁–C₄ alkyl, preferably methyl or ethyl.

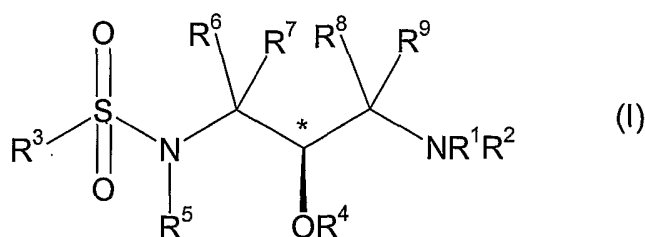
13. A compound as claimed in claim 12, wherein the piperidinyl ring formed by R¹ and R² together with the nitrogen atom to which they are attached is substituted by one or more methyl or ethyl groups, preferably at the 2- and 6-positions.

14. A compound as claimed in claim 1-13, wherein R⁴ is hydrogen or C₁–C₆ alkyl.

15. A compound as claimed in claim 1-14, wherein R⁵ is selected from hydrogen, C₁–C₆ alkyl, aryl and benzyl, optionally substituted by one or more groups independently selected from hal, C₁–C₆ alkyl, hydroxy and C₁–₆alkoxy.

16. A compound as claimed in claim 1-15, wherein R⁶, R⁷, R⁸ and R⁹ are independently selected from hydrogen and C₁–C₆ alkyl.

17. A compound as claimed in claim 1-16 which has the following stereochemical configuration:



25

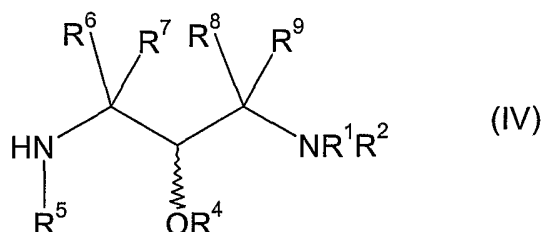
18. A compound as claimed in claim 1, which is:

- *N*-{(2*R*)-3-[(2*R*,6*S*)-2,6-dimethyl-1-piperidinyl]-2-hydroxypropyl}-3,4-dihydro-1(2*H*)-quinolinesulfonamide
 - *N*-{(2*R*)-3-[(2*R*,6*S*)-2,6-dimethyl-1-piperidinyl]-2-hydroxypropyl}-2,3-dihydro-1*H*-indole-1-sulfonamide
 - *N*-{(2*R*)-3-[(2*R*,6*S*)-2,6-Dimethyl-1-piperidinyl]-2-hydroxypropyl}-1,3-dihydro-2*H*-isoindole-2-sulfonamide
 - *N*-{(2*R*)-3-[(2*R*,6*S*)-2,6-Dimethyl-1-piperidinyl]-2-hydroxypropyl}-3,4-dihydro-2(1*H*)-isoquinolinesulfonamide
- or a salt, solvate or a physiologically functional derivative thereof.

30

35

19. A process for the preparation of a compound as defined in any of claims 1-8, by reacting a compound of formula (IV)



wherein R^1 , R^2 , R^4 , R^5 , R^6 , R^7 , R^8 and R^9 are as defined in any of claims 1-18, with a compound of formula (V):



wherein R^3 is as defined in any of claims 1-18, and L is a suitable leaving group, such as, for example, a halogen, preferably chlorine;

and thereafter optionally:

- removing any protecting groups and/or
- converting a compound of formula (I) into another compound of formula (I) and/or
- forming a pharmaceutically acceptable salt.

20. A compound as claimed in any of claims 1-18 for use in therapy.

21. A compound as claimed in any of claims 1-18 for use in the treatment of a disorder mediated by GlyT1.

22. A compound as claimed in any of claims 1-18 for use in the treatment of psychosis, including schizophrenia, dementia or attention deficit disorder.

23. A method of treating a mammal, including a human, suffering from or susceptible to a disorder mediated by GlyT1 which comprises administering an effective amount of a compound as defined in any of claims 1-18.

24. A method as claimed in claim 23, wherein the disorder is psychosis, including schizophrenia, dementia or attention deficit disorder.

25. Use of a compound as defined in any of claims 1-18 in the preparation of a medicament for the treatment of a disorder mediated by GlyT1.

26. Use as claimed in claim 25, wherein the disorder is psychosis, including schizophrenia, dementia or attention deficit disorder.
27. A pharmaceutical composition comprising a compound as defined in any of claims 1-18, and at least one pharmaceutically acceptable carrier, diluent or excipient.
- 5

INTERNATIONAL SEARCH REPORT

International Application No.

PCT/EP2004/006593

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07D215/58 C07D209/08 C07D209/44 C07D217/06 A61K31/33
A61P25/18

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D A61K A61P

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, WPI Data, CHEM ABS Data, BEILSTEIN Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,A	WO 03/055478 A (COULTON STEVEN ; JOINER GRAHAM J (GB); HADLEY MICHAEL STEWART (GB); HE) 10 July 2003 (2003-07-10) abstract examples claims	1-27
A	EP 0 076 072 A (BEECHAM WUELFING GMBH & CO KG) 6 April 1983 (1983-04-06) examples claims	1-27
A	WO 02/22581 A (ALI SYED M ; BRUNDEN KURT R (US); GLIATECH INC (US); JIANG JACK B (US)) 21 March 2002 (2002-03-21) abstract examples claims	1-27



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.

* & * document member of the same patent family

Date of the actual completion of the international search

29 September 2004

Date of mailing of the international search report

06/10/2004

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Stix-Malaun, E

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP2004/006593

Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

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

Although claims 23,24 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

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

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP2004/006593

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
WO 03055478	A	10-07-2003	EP 1455777 A1 WO 03055478 A1	15-09-2004 10-07-2003
EP 0076072	A	06-04-1983	AU 8862282 A CA 1173443 A1 DE 3276313 D1 EP 0076072 A2 ES 8308843 A1 JP 58065267 A US 4485108 A ZA 8206953 A	31-03-1983 28-08-1984 19-06-1987 06-04-1983 16-12-1983 18-04-1983 27-11-1984 27-07-1983
WO 0222581	A	21-03-2002	AU 9078601 A CA 2422044 A1 EP 1324986 A1 JP 2004518628 T WO 0222581 A1 US 2004034069 A1 US 2002082283 A1	26-03-2002 21-03-2002 09-07-2003 24-06-2004 21-03-2002 19-02-2004 27-06-2002