(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
16 November 2006 (16.11.2006)

PCT

(10) International Publication Number
WO 2006/120544 A1

(51) International Patent Classification:
C07C 229/34 (2006.01) *A61P 29/02* (2006.01)
A61K 31/195 (2006.01)

(21) International Application Number:
PCT/IB2006/001209

(22) International Filing Date: 24 April 2006 (24.04.2006)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/678,523 6 May 2005 (06.05.2005) US

(71) Applicant *(for all designated States except US)*: **PFIZER LIMITED** [GB/GB]; Ramsgate Road, Sandwich, Kent CT13 9NJ (GB).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: **CRAWFORD, Terry, Dale** [US/US]; Pfizer Global Research and Development, Ann Arbor Laboratories, 2800 Plymouth Road, Ann Arbor, MI 48105 (US). **RAWSON, David, James** [GB/GB]; Pfizer Global Research and Development, Ramsgate Road, Sandwich, Kent CT13 9NJ (GB). **THORPE, Andrew, John** [GB/US]; Pfizer Global Research and Development, Ann Arbor Laboratories, 2800 Plymouth Road, Ann Arbor, MI 48105 (US).

(74) Agents: **DROUIN, Stéphane** et al.; Pfizer Research and Development, Ramsgate Road, Sandwich, Kent CT13 9NJ (GB).

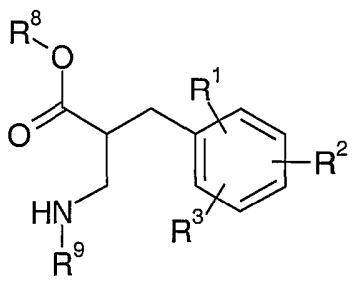
(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LC,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

(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, IS, IT, LT, LU, LV, 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*
— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*

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: β-AMINO ACID DERIVATIVES



(I)

(57) Abstract: The present invention relates to a compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof, wherein R^1, R^2, R^3, R^8 and R^9 are as defined herein, as well as to compositions containing such a compound and the uses of such a compound. Compounds of formula (I) are especially useful in the treatment of pain.

WO 2006/120544 A1

β-Amino Acid Derivatives

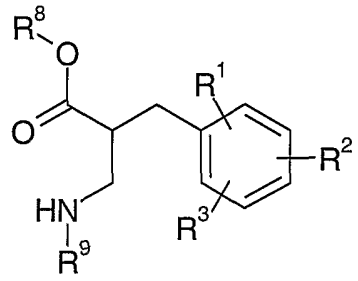
This invention relates to β-amino acid derivatives derivatives. More particularly, this invention relates to α-arylmethyl-β-amino acid derivatives and to processes for the preparation of, intermediates used in the preparation of, compositions containing and the uses of such derivatives.

The compounds of the present invention are alpha-2-delta (α2δ) receptor ligands (also known as alpha-2-delta ligands) and as such are useful in the treatment of a number of different diseases. An alpha-2-delta receptor ligand is a molecule which binds to any sub-type of the human calcium channel alpha-2-delta subunit. The calcium channel alpha-2-delta subunit comprises a number of sub-types which have been described in the literature (e.g. type 1, *J. Biol. Chem.*, 1996, **271**(10), 5768-76; types 2 and 3, *J. Membr. Biol.*, 2001, **184**(1), 35-43 and *Mol. Pharmacol.*, 2001, **59**(5), 1243-1248, 2001; and type 4, *Mol. Pharmacol.*, 2002, **62**(3), 485-496). Alpha-2-delta receptor ligands are also sometimes known as GABA analogues.

Among known alpha-2-delta ligands are marketed drugs such as gabapentin (sold under the trade mark Neurontin) and pregabalin (sold under the trade mark Lyrica). Gabapentin is an anti-convulsant which is marketed for the treatment of epilepsy. Pregabalin is marketed for the treatment of neuropathic pain.

There is always a need to provide new drugs, which potentially have improved properties (e.g. greater potency, greater selectivity, better absorption from the gastrointestinal tract, greater metabolic stability and more favourable pharmacokinetic properties). Other potential advantages include greater or lesser penetration of the blood brain barrier, according to the disease targeted, lower toxicity and a decreased incidence of side-effects.

The invention therefore provides, as embodiment A, a compound of formula (I):



(I)

or a pharmaceutically acceptable salt or solvate thereof, wherein

R^1 and R^2 are each independently H, cyano, halo or -X-Y-R^4, or R^1 and R^2, taken together with two adjacent carbon atoms to which they are attached, form a fused 5- or 6-membered, saturated, partially unsaturated or aromatic ring optionally containing one or two nitrogen, oxygen or sulphur hereroatoms, said ring being optionally substituted by one ore more groups selected from cyano, halo and -X-Y-R^4;

-X- is a direct bond, C_1-C_6 alkylene, C_3-C_8 cycloalkylene, C_2-C_6 alkenylene or C_2-C_6 alkynylene, said C_1-C_6 alkylene, C_3-C_8 cycloalkylene, C_2-C_6 alkenylene and C_2-C_6 alkynylene being optionally substituted by one or more halo (preferably fluoro) groups;

-Y- is a direct bond, -O-, -S-, -SO-, -SO_2-, -NR^5-, -CO-, -OCO-, -C(O)O-, -NR^5CO-, -C(O)NR^5-, -NR^5SO_2- or -SO_2NR^5-;

R^3 is H, cyano, halo, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy or C_3-C_8 cycloalkyl, said C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy and C_3-C_8 cycloalkyl being optionally substituted by one or more halo (preferably fluoro) groups;

R^4 is C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_8 cycloalkyl, aryl, Het^1 or Het^2, said C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_8 cycloalkyl being optionally substituted by one or more halo (preferably fluoro) groups;

R^5 is H, C_1-C_6 alkyl or C_3-C_8 cycloalkyl;

Het^1 is a 3- to 8-membered, saturated or partially unsaturated heterocyclic group comprising one or two ring members selected from $-NR^6-$, -O-, -S-, -SO- and $-SO_2-$ said heterocyclic group being optionally substituted on a ring carbon atom by one or more substituents selected from oxo, halo, $-R^5$ or $-OR^5$ and optionally benzo-fused, said benzo-fused portion being optionally substituted by one or more substituents selected from halo, C_1-C_6 alkyl, C_3-C_8 cycloalkyl, C_1-C_6 alkoxy and cyano;

R^6 is H, C_1-C_6 alkyl, C_3-C_8 cycloalkyl, $-COR^7$, $-SO_2R^7$ or a bond to the group which is substituted with Het^1;

R^7 is C_1-C_6 alkyl or C_3-C_8 cycloalkyl;

Het^2 is a 5-membered aromatic heterocyclic group comprising either (a) 1 to 4 nitrogen atoms, (b) one oxygen or one sulphur atom or (c) 1 oxygen atom or 1 sulphur atom and 1 or 2 nitrogen atoms or a 6-membered aromatic heterocyclic group comprising 1 or 2 nitrogen atoms, said 5- or 6-membered heterocyclic group being optionally substituted by one or more substituents selected from halo, $-NR^5R^5$, C_1-C_6 alkyl, C_3-C_8 cycloalkyl, C_1-C_6 alkoxy and cyano;

aryl is phenyl or naphthyl optionally substituted by one or more substituents selected from halo, $-NR^5R^5$, C_1-C_6 alkyl, C_3-C_8 cycloalkyl, C_1-C_6 alkoxy and cyano; and

R^8 and R^9 are each independently H or a group which is converted to H following administration of the compound to a mammal;

with the proviso that the compound of formula (I) is not one of the following specific compounds:

3-amino-2-(naphthalen-1-ylmethyl)propionic acid;
3-amino-2-(3,8-dimethoxynaphthalen-1-ylmethyl)propionic acid;
3-amino-2-(3,4-dichlorobenzyl)propionic acid;

3-amino-2-(4-dimethylaminobenzyl)propionic acid;
3-amino-2-(benzo[1,3]dioxol-5-ylmethyl)propionic acid;
3-amino-2-benzylpropanoic acid;
3-amino-2-(2,6-dichlorobenzyl)propanoic acid;
3-amino-2-(4-methylbenzyl)propanoic acid;
3-amino-2-(4-chlorobenzyl)propanoic acid;
3-amino-2-(4-hydroxybenzyl)propanoic acid;
3-amino-2-(4-methoxybenzyl)propanoic acid
3-amino-2-(4-tert-butyloxybenzyl)propanoic acid; or
3-amino-2-(2,4,6-trimethylbenzyl)propanoic acid.

In the above definitions, halo means fluoro, chloro or bromo and is preferably fluoro or chloro. Alkyl, alkenyl, alkynyl, alkylene, alkenylene, alkynylene and alkoxy groups containing the requisite number of carbon atoms can be unbranched or branched chain. Examples of alkyl include methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, sec-butyl and t-butyl. Examples of alkenyl include ethenyl, propen-1-yl, propen-2-yl, propen-3-yl, but-1-en-1-yl, but-1-en-2-yl, but-1-en-3-yl, but-1-en-4-yl, but-2-en-1-yl and but-2-en-2-yl. Examples of alkynyl include ethynyl, propyn-3-yl, but-1-yn-1-yl, but-1-yn-3-yl, but-1-yn-4-yl and but-2-yn-1-yl. Examples of alkoxy include methoxy, ethoxy, n-propoxy, i-propoxy, n-butoxy, i-butoxy, sec-butoxy and t-butoxy. Examples of alkylene include methylene, 1,1-ethylene, 1,2-ethylene, 1,1-propylene, 1,2-propylene, 1,3-propylene and 2,2-propylene. Examples of alkenylene include 1,1-ethenylene, 1,2-ethenylene, 1,1-propenylene, 1,2-propenylene and 1,3-propenylene. Examples of alkynylene include 1,2-ethynylene, 1,3-propynylene and 3,3-propynylene. Examples of cycloalkyl include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl.

In formula (I), the R^1, R^2 and R^3 groups may be attached to any of the five free positions on the phenyl ring. Where Y is -O-, -S-, -NR^5-, -C(O)O-, -C(O)NR^5-, or -SO_2NR^5- and R^4 is Het^1 or Het^2, the Het^1 or Het^2 group may not be attached to the Y group through a ring heteroatom.

Specific examples of Het^1 are oxiranyl, aziridinyl, oxetanyl, azetidinyl, tetrahydrofuranyl, pyrrolidinyl, tetrahydropyranyl, piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl, azepanyl, oxapanyl, oxazepanyl and diazepanyl (optionally substituted as specified above).

Specific examples of Het^2 are thienyl, furanyl, pyrrolyl, pyrazolyl, imidazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, triazolyl, oxadiazolyl, thiadiazolyl, tetrazolyl, pyridyl, pyrimidinyl, pyrazinyl and pyridazinyl (optionally substituted as specified above).

In the following embodiments B to D, the definitions given in embodiment A apply unless otherwise indicated.

In embodiment B, the invention provides a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, wherein:

(a) R^8 is H, C_1-C_6 alkyl, aryl, indanyl or (C_1-C_6 alkyl)OC(O)O(C_1-C_6 alkyl);and

(b) R^9 is H, –CO(C_1-C_6 alkyl), -CO(aryl), or a natural α-amino acid joined through its carboxy group; or

(c) R^8 and R^9 are both H.

In embodiment C, the invention provides a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, wherein R^8 and R^9 are as defined above in embodiment A or embodiment B and R^3 is H.

In embodiment D the invention provides a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, wherein R^8 and R^9 are as defined above in embodiment A or embodiment B, R^3 is as defined above in embodiment A or embodiment C and R^1 and R^2 are independently either:

(a) H, halo or -X-Y-R^4; or

(b) H, halo or -Y-R^4; or

(c) H, halo, -R^4, -OR^4 or -SR^4; or

(d) H, halo, C_1-C_6 alkyl, aryl, -O(C_1-C_6 alkyl) or -S(C_1-C_6 alkyl), each of said C_1-C_6 alkyl groups being optionally substituted by one or more halo groups; or

(e) H, chloro, bromo, -OCF_3, -SCH_3, butyl or fluorophenyl; or

(f) H, chloro, bromo, -OCF_3, -SCH_3, 2-methylpropyl or 4-fluorophenyl.

Specific preferred compounds according to the invention are:

(2*S*)-3-amino-2-(3-chlorobenzyl)propanoic acid;
(2*S*)-3-amino-2-(2,5-dichlorobenzyl)propanoic acid;
(2*S*)-3-amino-2-(3-trifluoromethyloxy)propanoic acid;
(2*S*)-3-Amino-2-(3-isobutylbenzyl)propanoic acid;
(2*S*)-3-amino-2-(3,5-dichlorobenzyl)propanoic acid;
(2*S*)-3-Amino-2-(3-methylthiobenzyl)propanoic acid;
(2*S*)-3-Amino-2-(3-bromobenzyl)propanoic acid; and
(2*S*)-3-Amino-2-((2-(4-fluorophenyl)phenyl)methyl)propanoic acid;

and pharmaceutically acceptable salts and solvates thereof, particularly (2*S*)-3-amino-2-(3-chlorobenzyl)propanoic acid and the pharmaceutically acceptable salts and solvates thereof (most especially the hydrochloride salt).

Pharmaceutically acceptable salts of a compound of formula (I) include the acid addition and base salts thereof.

Suitable acid addition salts are formed from acids which form non-toxic salts. Examples include the acetate, aspartate, benzoate, besylate, bicarbonate/carbonate, bisulphate/sulphate, borate, camsylate, citrate, edisylate, esylate, formate, fumarate, gluceptate, gluconate, glucuronate, hexafluorophosphate, hibenzate, hydrochloride/chloride, hydrobromide/bromide, hydroiodide/iodide, isethionate, lactate, malate, maleate, malonate, mesylate, methylsulphate, naphthylate, 2-napsylate, nicotinate, nitrate, orotate, oxalate, palmitate, pamoate, phosphate/hydrogen phosphate/dihydrogen phosphate, saccharate, stearate, succinate, tartrate, tosylate and trifluoroacetate salts.

Suitable base salts are formed from bases which form non-toxic salts. Examples include the aluminium, arginine, benzathine, calcium, choline, diethylamine,

diolamine, glycine, lysine, magnesium, meglumine, olamine, potassium, sodium, tromethamine and zinc salts.

Hemisalts of acids and bases may also be formed, for example, hemisulphate and hemicalcium salts.

For a review on suitable salts, see Handbook of Pharmaceutical Salts: Properties, Selection, and Use by Stahl and Wermuth (Wiley-VCH, Weinheim, Germany, 2002).

Pharmaceutically acceptable salts of a compound of formula (I) may be prepared by one or more of three methods:

(i) by reacting the compound of formula (I) with the desired acid or base;

(ii) by removing an acid- or base-labile protecting group from a suitable precursor of the compound of formula (I) or by ring-opening a suitable cyclic precursor, for example, a lactone or lactam, using the desired acid or base; or

(iii) by converting one salt of the compound of formula (I) to another by reaction with an appropriate acid or base or by means of a suitable ion exchange column.

All three reactions are typically carried out in solution. The resulting salt may precipitate out and be collected by filtration or may be recovered by evaporation of the solvent. The degree of ionisation in the resulting salt may vary from completely ionised to almost non-ionised.

A compound of formula (I) may exist in both unsolvated and solvated forms. The term 'solvate' is used herein to describe a molecular complex comprising the compound of formula (I) and a stoichiometric amount of one or more pharmaceutically acceptable solvent molecules, for example, ethanol. The term 'hydrate' is employed when said solvent is water.

Included within the scope of the invention are complexes such as clathrates, drug-host inclusion complexes wherein, in contrast to the aforementioned solvates, the drug and host are present in stoichiometric or non-stoichiometric amounts. Also included are complexes of the drug containing two or more organic and/or inorganic components which may be in stoichiometric or non-stoichiometric amounts. The resulting complexes may be ionised, partially ionised, or non-ionised. For a review of such complexes, see J. Pharm. Sci., 64 (8), 1269-1288, by Haleblian (August 1975).

Hereinafter, all references to a compound of formula (I) include references to salts, solvates and complexes thereof and to solvates and complexes of salts thereof.

A compound of formula (I), as hereinbefore defined, may exist in one or more crystalline (polymorphic) or isomeric forms (including optical, geometric and tautomeric isomers), in an isotopically labelled form or as a prodrug. All such crystalline/isomeric forms and prodrugs are within the scope of the present invention and are further described below. All references to a compound of formula (I) should be interpreted accordingly.

Compounds of the formula (I) wherein R^8 and/or R^9 is a group which is converted to H following administration of the compound to a mammal (preferably a human) are known as prodrugs. Thus, these derivatives, which may have little or no pharmacological activity themselves can, when administered into or onto the body, be converted into compounds of formula (I) wherein R^8 and R^9 are both H, such compounds having the desired activity as alpha-2-delta ligands. Such prodrugs can be converted, for example, by hydrolytic cleavage.

Typically, R^8 is an alkyl group, preferably a C_1-C_6 alkyl group. Specific examples of suitable alkyl groups are ethyl, isopropyl and *n*-butyl. Alternatively, R^8 can be an aryl group (wherein aryl is as defined above), such as phenyl, or an indanyl group. In other suitable embodiments R^8 can be an alkylocycarbonyloxyalkyl group, such as $-CH_2OC(O)O^tBu$, $-CH(CH_3)OC(O)OEt$ or

$CH(CH_3)OC(O)O^iPr$ (see *Journal of Pharmcology and Experimental Therapeutics*, 311, 1, 324-335) or a cyclic carbonate linked via a methylene group.

Typically, R^9 is an amide-forming group such as $-CO(C_1-C_6$ alkyl) or -CO(aryl) (wherein aryl is as defined above). Specific examples are methylcarbonyl, isopropylcarbonyl and phenylcarbonyl. Alternatively, R^9 may be an α-amino acid residue joined through its carboxyl group to form an amide. The naturally occurring amino acids, particularly glycine, alanine and valine are preferred.

Whether or not a particular compound will act as a prodrug and be hydrolytically cleaved to the active compound in vivo may be accurately assessed using a number of *in vitro* tests and *in vivo* animal models. Prodrug hydrolysis can be characterised *in vitro* using a range of tissue fractions including simple homogenates and microsomes: see, for example, *Journal of Pharmacology and Experimental Therapeutics*, 294, 2, 580-587; *Life Sci.*, 62, 14, 1231-124; *International Journal of Pharmaceutics*, 166, 1, 45-53; and *Toxicol. Lett.*, 82-83, 439-445. Rat liver microsome homogenates are particularly useful in this regard. *In vivo* assays can also be used to investigate prodrug properties. Intravenous and oral pharmacokinetics with both the active principle and the prodrug provides information about the relative bioavailability of the prodrug, the ability of the body to hydrolyse the prodrug and the rate of hydrolysis to the active species (see *Antimicrob. Agents. Chemother.* 42, 3, 647-653). A proposed screening strategy for assaying prodrugs has been given in a recent review (Current Drug Metabolism, 2003, vol 4, no. 6, p 483).

Further information on the use of prodrugs may be found in Pro-drugs as Novel Delivery Systems, Vol. 14, ACS Symposium Series (T. Higuchi and W. Stella) and Bioreversible Carriers in Drug Design, Pergamon Press, 1987 (ed. E. B. Roche, American Pharmaceutical Association).

Prodrugs of compounds of the formula (I) other than those involving R^8 and R^9 groups are also within the scope of the invention and can, for example, be produced by replacing appropriate functionalities present in the compounds of

formula (I) with certain moieties known to those skilled in the art as 'pro-moieties' as described, for example, in Design of Prodrugs by H. Bundgaard (Elsevier, 1985).

Some examples of other prodrugs in accordance with the invention include:

(i) where the compound of formula (I) contains an alcohol functionality (-OH), an ether thereof, for example, a compound wherein the hydrogen of the alcohol functionality of the compound of formula (I) is replaced by (C_1-C_6)alkanoyloxymethyl; and

(ii) where the compound of formula (I) contains a primary or secondary amino functionality (-NH_2 or -NHR where R ≠ H), an amide thereof, for example, a compound wherein, as the case may be, one or both hydrogens of the amino functionality of the compound of formula (I) is/are replaced by (C_1-C_{10})alkanoyl.

Further examples of replacement groups in accordance with the foregoing examples and examples of other prodrug types may be found in the aforementioned references.

Moreover, certain compounds of formula (I) may themselves act as prodrugs of other compounds of formula (I).

Also included within the scope of the invention are metabolites of compounds of formula (I), that is, compounds formed *in vivo* upon administration of the drug. Some examples of metabolites in accordance with the invention include

(i) where the compound of formula (I) contains a methyl group, an hydroxymethyl derivative thereof (-CH_3 -> -CH_2OH):

(ii) where the compound of formula (I) contains an alkoxy group, an hydroxy derivative thereof (-OR -> -OH);

(iii) where the compound of formula (I) contains a tertiary amino group, a secondary amino derivative thereof ($-NR^1R^2$ -> $-NHR^1$ or $-NHR^2$);

(iv) where the compound of formula (I) contains a secondary amino group, a primary derivative thereof ($-NHR^1$ -> $-NH_2$);

(v) where the compound of formula (I) contains a phenyl moiety, a phenol derivative thereof (-Ph -> -PhOH); and

(vi) where the compound of formula (I) contains a carboxamide group, a carboxylic acid derivative thereof ($-CONH_2$ -> COOH).

Compounds of formula (I) containing one or more asymmetric carbon atoms can exist as two or more stereoisomers. Where a compound of formula (I) contains an alkenyl or alkenylene group, geometric *cis*/*trans* (or Z/E) isomers are possible. Where structural isomers are interconvertible *via* a low energy barrier, tautomeric isomerism ('tautomerism') can occur. This can take the form of proton tautomerism in compounds of formula (I) containing, for example, an imino, keto, or oxime group, or so-called valence tautomerism in compounds which contain an aromatic moiety. It follows that a single compound may exhibit more than one type of isomerism.

Included within the scope of the present invention are all stereoisomers, geometric isomers and tautomeric forms of the compounds of formula (I), including compounds exhibiting more than one type of isomerism, and mixtures of one or more thereof. Also included are acid addition or base salts wherein the counterion is optically active, for example, *d*-lactate or *l*-lysine, or racemic, for example, *dl*-tartrate or *dl*-arginine.

Cis/*trans* isomers may be separated by conventional techniques well known to those skilled in the art, for example, chromatography and fractional crystallisation.

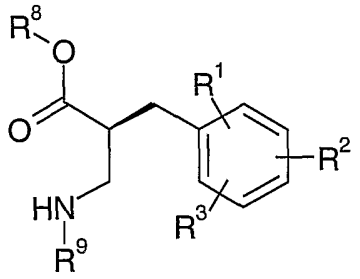
Conventional techniques for the preparation/isolation of individual enantiomers include chiral synthesis from a suitable optically pure precursor or resolution of the racemate (or the racemate of a salt or derivative) using, for example, chiral high pressure liquid chromatography (HPLC).

Alternatively, the racemate (or a racemic precursor) may be reacted with a suitable optically active compound, for example, an alcohol, or, in the case where the compound of formula (I) contains an acidic or basic moiety, a base or acid such as 1-phenylethylamine or tartaric acid. The resulting diastereomeric mixture may be separated by chromatography and/or fractional crystallization and one or both of the diastereoisomers converted to the corresponding pure enantiomer(s) by means well known to a skilled person.

Chiral compounds of the invention (and chiral precursors thereof) may be obtained in enantiomerically-enriched form using chromatography, typically HPLC, on an asymmetric resin with a mobile phase consisting of a hydrocarbon, typically heptane or hexane, containing from 0 to 50% by volume of isopropanol, typically from 2% to 20%, and from 0 to 5% by volume of an alkylamine, typically 0.1% diethylamine. Concentration of the eluate affords the enriched mixture.

Stereoisomeric conglomerates may be separated by conventional techniques known to those skilled in the art - see, for example, Stereochemistry of Organic Compounds by E. L. Eliel and S. H. Wilen (Wiley, New York, 1994).

A preferred compound of formula (I) is a compound according to any of embodiments A-D above wherein the stereochemistry at the carbon atom alpha to the carboxylic acid is in the S configuration, i.e. a compound of formula (Ia).



(Ia)

The present invention includes all pharmaceutically acceptable isotopically-labelled compounds of formula (I) wherein one or more atoms are replaced by atoms having the same atomic number, but an atomic mass or mass number different from the atomic mass or mass number which predominates in nature.

Examples of isotopes suitable for inclusion in the compounds of the invention include isotopes of hydrogen, such as ^{2}H and ^{3}H, carbon, such as ^{11}C, ^{13}C and ^{14}C, chlorine, such as ^{36}Cl, fluorine, such as ^{18}F, iodine, such as ^{123}I and ^{125}I, nitrogen, such as ^{13}N and ^{15}N, oxygen, such as ^{15}O, ^{17}O and ^{18}O, phosphorus, such as ^{32}P, and sulphur, such as ^{35}S.

Certain isotopically-labelled compounds of formula (I), for example, those incorporating a radioactive isotope, are useful in drug and/or substrate tissue distribution studies. The radioactive isotopes tritium, *i.e.* ^{3}H, and carbon-14, *i.e.* ^{14}C, are particularly useful for this purpose in view of their ease of incorporation and ready means of detection.

Substitution with heavier isotopes such as deuterium, *i.e.* ^{2}H, may afford certain therapeutic advantages resulting from greater metabolic stability, for example, increased *in vivo* half-life or reduced dosage requirements, and hence may be preferred in some circumstances.

Substitution with positron emitting isotopes, such as ^{11}C, ^{18}F, ^{15}O and ^{13}N, can be useful in Positron Emission Topography (PET) studies for examining substrate receptor occupancy.

Isotopically-labeled compounds of formula (I) can generally be prepared by conventional techniques known to those skilled in the art or by processes analogous to those described in the accompanying Examples and Preparations using an appropriate isotopically-labeled reagent in place of the non-labeled reagent previously employed.

Pharmaceutically acceptable solvates in accordance with the invention include those wherein the solvent of crystallization may be isotopically substituted, *e.g.* D_2O, d_6-acetone, d_6-DMSO.

The compounds of formula (I), being alpha-2-delta receptor ligands, are potentially useful in the treatment of a wide range of disorders. The treatment of pain, particularly neuropathic, is a preferred use.

Physiological pain is an important protective mechanism designed to warn of danger from potentially injurious stimuli from the external environment. The system operates through a specific set of primary sensory neurones and is activated by noxious stimuli *via* peripheral transducing mechanisms (see Millan, 1999, Prog. Neurobiol., 57, 1-164 for a review). These sensory fibres are known as nociceptors and are characteristically small diameter axons with slow conduction velocities. Nociceptors encode the intensity, duration and quality of noxious stimulus and by virtue of their topographically organised projection to the spinal cord, the location of the stimulus. The nociceptors are found on nociceptive nerve fibres of which there are two main types, A-delta fibres (myelinated) and C fibres (non-myelinated). The activity generated by nociceptor input is transferred, after complex processing in the dorsal horn, either directly, or via brain stem relay nuclei, to the ventrobasal thalamus and then on to the cortex, where the sensation of pain is generated.

Pain may generally be classified as acute or chronic. Acute pain begins suddenly and is short-lived (usually in twelve weeks or less). It is usually associated with a specific cause such as a specific injury and is often sharp and severe. It is the kind of pain that can occur after specific injuries resulting from surgery, dental work, a strain or a sprain. Acute pain does not generally result in any persistent

psychological response. In contrast, chronic pain is long-term pain, typically persisting for more than three months and leading to significant psychological and emotional problems. Common examples of chronic pain are neuropathic pain (e.g. painful diabetic neuropathy, postherpetic neuralgia), carpal tunnel syndrome, back pain, headache, cancer pain, arthritic pain and chronic post-surgical pain.

When a substantial injury occurs to body tissue, *via* disease or trauma, the characteristics of nociceptor activation are altered and there is sensitisation in the periphery, locally around the injury and centrally where the nociceptors terminate. These effects lead to a heightened sensation of pain. In acute pain these mechanisms can be useful, in promoting protective behaviours which may better enable repair processes to take place. The normal expectation would be that sensitivity returns to normal once the injury has healed. However, in many chronic pain states, the hypersensitivity far outlasts the healing process and is often due to nervous system injury. This injury often leads to abnormalities in sensory nerve fibres associated with maladaptation and aberrant activity (Woolf & Salter, 2000, Science, 288, 1765-1768).

Clinical pain is present when discomfort and abnormal sensitivity feature among the patient's symptoms. Patients tend to be quite heterogeneous and may present with various pain symptoms. Such symptoms include: 1) spontaneous pain which may be dull, burning, or stabbing; 2) exaggerated pain responses to noxious stimuli (hyperalgesia); and 3) pain produced by normally innocuous stimuli (allodynia - Meyer et al., 1994, Textbook of Pain, 13-44). Although patients suffering from various forms of acute and chronic pain may have similar symptoms, the underlying mechanisms may be different and may, therefore, require different treatment strategies. Pain can also therefore be divided into a number of different subtypes according to differing pathophysiology, including nociceptive, inflammatory and neuropathic pain.

Nociceptive pain is induced by tissue injury or by intense stimuli with the potential to cause injury. Pain afferents are activated by transduction of stimuli by nociceptors at the site of injury and activate neurons in the spinal cord at the

level of their termination. This is then relayed up the spinal tracts to the brain where pain is perceived (Meyer et al., 1994, Textbook of Pain, 13-44). The activation of nociceptors activates two types of afferent nerve fibres. Myelinated A-delta fibres transmit rapidly and are responsible for sharp and stabbing pain sensations, whilst unmyelinated C fibres transmit at a slower rate and convey a dull or aching pain. Moderate to severe acute nociceptive pain is a prominent feature of pain from central nervous system trauma, strains/sprains, burns, myocardial infarction and acute pancreatitis, post-operative pain (pain following any type of surgical procedure), posttraumatic pain, renal colic, cancer pain and back pain. Cancer pain may be chronic pain such as tumour related pain (e.g. bone pain, headache, facial pain or visceral pain) or pain associated with cancer therapy (e.g. postchemotherapy syndrome, chronic postsurgical pain syndrome or post radiation syndrome). Cancer pain may also occur in response to chemotherapy, immunotherapy, hormonal therapy or radiotherapy. Back pain may be due to herniated or ruptured intervertabral discs or abnormalities of the lumber facet joints, sacroiliac joints, paraspinal muscles or the posterior longitudinal ligament. Back pain may resolve naturally but in some patients, where it lasts over 12 weeks, it becomes a chronic condition which can be particularly debilitating.

Neuropathic pain is currently defined as pain initiated or caused by a primary lesion or dysfunction in the nervous system. Nerve damage can be caused by trauma and disease and thus the term 'neuropathic pain' encompasses many disorders with diverse aetiologies. These include, but are not limited to, peripheral neuropathy, diabetic neuropathy, post herpetic neuralgia, trigeminal neuralgia, back pain, cancer neuropathy, HIV neuropathy, phantom limb pain, carpal tunnel syndrome, central post-stroke pain and pain associated with chronic alcoholism, hypothyroidism, uremia, multiple sclerosis, spinal cord injury, Parkinson's disease, epilepsy and vitamin deficiency. Neuropathic pain is pathological as it has no protective role. It is often present well after the original cause has dissipated, commonly lasting for years, significantly decreasing a patient's quality of life (Woolf and Mannion, 1999, Lancet, 353, 1959-1964). The symptoms of neuropathic pain are difficult to treat, as they are often heterogeneous even between patients with the same disease (Woolf &

Decosterd, 1999, Pain Supp., 6, S141-S147; Woolf and Mannion, 1999, Lancet, 353, 1959-1964). They include spontaneous pain, which can be continuous, and paroxysmal or abnormal evoked pain, such as hyperalgesia (increased sensitivity to a noxious stimulus) and allodynia (sensitivity to a normally innocuous stimulus).

The inflammatory process is a complex series of biochemical and cellular events, activated in response to tissue injury or the presence of foreign substances, which results in swelling and pain (Levine and Taiwo, 1994, Textbook of Pain, 45-56). Arthritic pain is the most common inflammatory pain. Rheumatoid disease is one of the commonest chronic inflammatory conditions in developed countries and rheumatoid arthritis is a common cause of disability. The exact aetiology of rheumatoid arthritis is unknown, but current hypotheses suggest that both genetic and microbiological factors may be important (Grennan & Jayson, 1994, Textbook of Pain, 397-407). It has been estimated that almost 16 million Americans have symptomatic osteoarthritis (OA) or degenerative joint disease, most of whom are over 60 years of age, and this is expected to increase to 40 million as the age of the population increases, making this a public health problem of enormous magnitude (Houge & Mersfelder, 2002, Ann Pharmacother., 36, 679-686; McCarthy et al., 1994, Textbook of Pain, 387-395). Most patients with osteoarthritis seek medical attention because of the associated pain. Arthritis has a significant impact on psychosocial and physical function and is known to be the leading cause of disability in later life. Ankylosing spondylitis is also a rheumatic disease that causes arthritis of the spine and sacroiliac joints. It varies from intermittent episodes of back pain that occur throughout life to a severe chronic disease that attacks the spine, peripheral joints and other body organs.

Another type of inflammatory pain is visceral pain which includes pain associated with inflammatory bowel disease (IBD). Visceral pain is pain associated with the viscera, which encompass the organs of the abdominal cavity. These organs include the sex organs, spleen and part of the digestive system. Pain associated with the viscera can be divided into digestive visceral pain and non-digestive visceral pain. Commonly encountered gastrointestinal (GI) disorders that cause

pain include functional bowel disorder (FBD) and inflammatory bowel disease (IBD). These GI disorders include a wide range of disease states that are currently only moderately controlled, including, in respect of FBD, gastro-esophageal reflux, dyspepsia, irritable bowel syndrome (IBS) and functional abdominal pain syndrome (FAPS), and, in respect of IBD, Crohn's disease, ileitis and ulcerative colitis, all of which regularly produce visceral pain. Other types of visceral pain include the pain associated with dysmenorrhea, cystitis and pancreatitis and pelvic pain.

It should be noted that some types of pain have multiple aetiologies and thus can be classified in more than one area, e.g. back pain and cancer pain have both nociceptive and neuropathic components.

Other types of pain include:

- pain resulting from musculo-skeletal disorders, including myalgia, fibromyalgia, spondylitis, sero-negative (non-rheumatoid) arthropathies, non-articular rheumatism, dystrophinopathy, glycogenolysis, polymyositis and pyomyositis;
- heart and vascular pain, including pain caused by angina, myocardical infarction, mitral stenosis, pericarditis, Raynaud's phenomenon, scleredoma and skeletal muscle ischemia;
- head pain, such as migraine (including migraine with aura and migraine without aura), cluster headache, tension-type headache mixed headache and headache associated with vascular disorders; and
- orofacial pain, including dental pain, otic pain, burning mouth syndrome and temporomandibular myofascial pain.

The compounds of formula (I) are potentially useful in the treatment of all kinds of pain but are particularly useful in the treatment of neuropathic pain.

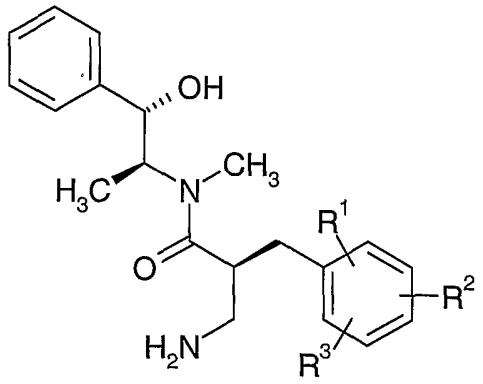
Apart from pain, the compounds of formula (I) are also potentially useful in the treatment of any disease or condition which is treatable using an alpha-2-delta ligand. Such conditions include epilepsy, gastrointestinal disorders, premature

ejaculation, burning mouth syndrome, bladder disorders (such as over active bladder), faintness attacks, fibromyalgia, hypokinesia, cranial disorders, hot flashes, essential tremor, chemical dependencies and addictions, withdrawal symptoms associated with dependencies or addictions, addictive behaviours, spasticity, arthritis, inflammatory disorders (e.g. rheumatoid arthritis, osteoarthritis, psoriasis), diuresis, premenstrual syndrome, premenstrual dysphoric disorder, tinnitus, gastric damage, Down's syndrome, demyelinating diseases (e.g. multiple sclerosis and amylolateral sclerosis), cerebral vascular disorders due to acute or chronic cerebrovascular damage (e.g. cerebral infarction, subarachnoid haemorrhage or cerebral oedema), head trauma, spinal cord trauma and neuronal damage that occurs, for instance, during stroke, in cardiac bypass surgery, in incidents of intracranial hemorrhage, in perinatal asphyxia, in cardiac arrest and in status epilepticus. Alpha-2-delta ligands may also be useful in the treatment of delirium, dementia and amnestic and other cognitive or neurodegenerative disorders (e.g. Parkinson's disease, Huntington's disease, Alzheimer's disease, senile dementia, memory disorder, vascular dementia). They may be useful in the treatment of movement disorders such as akinesias, dyskinesias, spasticities, Tourette's syndrome, Scott syndrome, palsys, akinetic-rigid syndrome and extra-pyramidal movement disorders. They may also be useful in the treatment of sleep disorders, mood disorders, depression, depressive disorders, bipolar disorders, anxiety disorders, panic, borderline personality disorder, schizophrenia, psychotic disorders, behavioural disturbances associated with mental retardation, autistic disorder and conduct disorders.

All of the compounds of formula (I) can be prepared by conventional routes such as by the procedures described in the general methods presented below or by the specific methods described in the Examples section and the Preparations section, or by similar methods thereto. The present invention also encompasses any one or more of these processes for preparing the compounds of formula (I), in addition to any novel intermediates used therein.

In the following general methods, R^1, R^2, R^3, R^8 and R^9 are as previously defined for a compound of formula (I) unless otherwise stated.

A compound of formula (Ia), wherein R^8 and R^9 are H, may be prepared by the hydrolysis of a compound of formula (II)

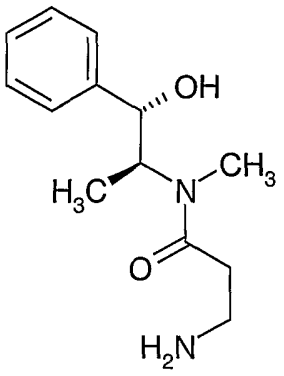


(II)

wherein R^1, R^2 and R^3 are as defined above.

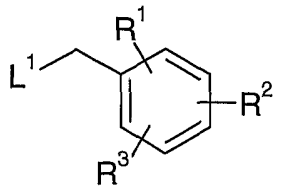
The reaction may be achieved under neutral conditions or with basic or acidic catalysis, most typically under neutral conditions. The reaction is typically performed in water, optionally in the presence of a co-solvent (e.g. 1,4-dioxane or tetrahydrofuran), at elevated temperature for about 4 days. Preferably a solution of the compound of formula (II) in a 1:1 (by volume) mixture of water and 1,4-dioxane is heated under at reflux for 4 days.

A compound of formula (II) may be prepared by the alkylation of a compound of formula (III)



(III)

with a compound of formula

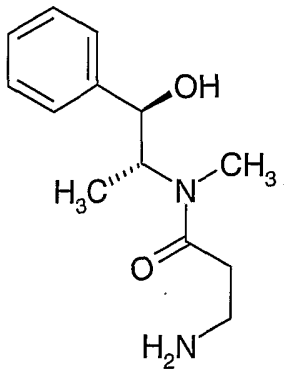


(IV)

wherein R^1, R^2 and R^3 are as defined above and L^1 is a suitable leaving group. L^1 is typically a bromide or trifluoromethanesulphonate (triflate) group, preferably a bromide group. The compound of formula (III) is de-protonated using a suitable base, and the resulting anion is quenched by the addition of a compound of formula (IV). In a typical procedure, a solution of a compound of formula (III) in a suitable solvent (such as tetrahydrofuran or ether) is treated with a strong base (such as lithium diisopropylamide or lithium hexamethyldisilazide), optionally in the presence of an additive (such as lithium chloride), at low temperature (e.g. between -10° and 0°C) for about 1 hour and the resulting anion is then quenched with the compound of formula (IV). Preferably a solution of the compound of formula (III) in tetrahydrofuran is treated with 3.2 equivalents of lithium hexamethyldisilazide and 4 equivalents of lithium chloride at a temperature of between -5° and 0°C for about 1 hour, followed by the addition of 1 equivalent of the compound of formula (IV) at 0°C.

A compound of formula (III) may be prepared using the methods described in *Organic Letters*, 2000, **2**(22), 3527-3529. Compounds of formula (IV) are either commercially available or may be prepared from commercially available starting materials using standard chemical transformations well known to the skilled person, e.g. the treatment of a corresponding alcohol with hydrogen bromide (see 'Comprehensive Organic Transformations' by Richard Larock (1999, VCH Publishers Inc.) for details of such standard transformations).

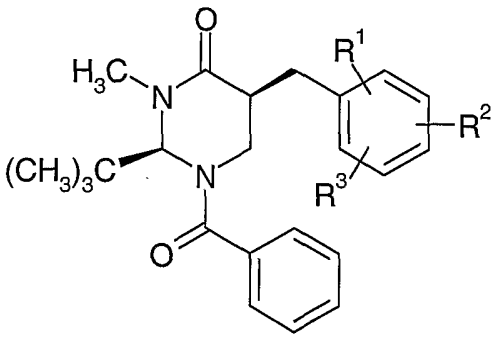
Compounds of formula (I) having the alternative (R) stereochemistry can of course be easily prepared by using a compound of formula



(IIIa)

instead of a compound of formula (III). Compounds of formula (I) wherein R^8 and/or R^9 are not H may be prepared from compounds of formula (I) wherein R^8 and/or R^9 are H by simple chemical transformations well known to the skilled man. Suitable conditions for such amide and ester forming reactions may be found in Comprehensive Organic Transformations referenced above.

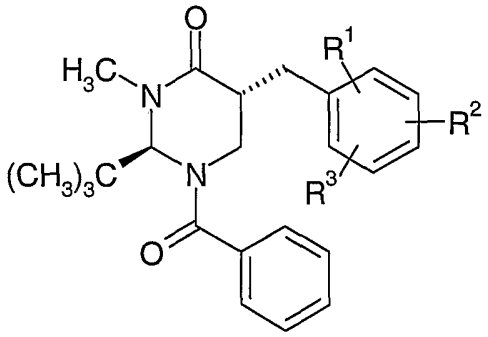
Compounds of formula (Ia) wherein R^8 and R^9 are H may alternatively be prepared by hydrolysis of a compound of formula (V)



(V)

wherein R^1, R^2 and R^3 are as defined above. This reaction may be achieved with basic or acidic catalysis, acidic catalysis being preferred. In a typical procedure, a compound of formula (V) in a mixture of water and a mineral acid (e.g. hydrochloric acid or sulphuric acid), optionally in the presence of an organic co-solvent such as tetrahydrofuran, is heated for about 24 hours. In a preferred procedure, a solution of a compound of formula (V) in 6M hydrochloric acid is heated under reflux for about 24 hours.

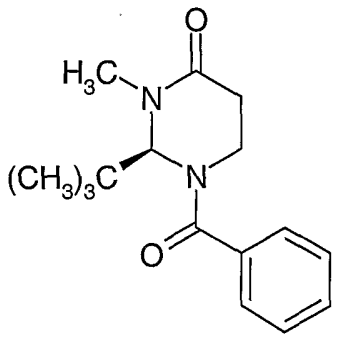
Compounds of formula (V) may be prepared by epimerisation of a compound of formula (VI)



(VI)

wherein R^1, R^2 and R^3 are as defined above. The epimerisation is accomplished by treating a compound of formula (VI) with suitable base, and quenching the resulting anion with aqueous acid. In a typical procedure, a solution of a compound of formula (VI) in a suitable solvent (e.g. tetrahydrofuran or ether) is treated with a strong base (e.g. lithium diisopropylamide, lithium hexamethyldisilazide or sodium hexamethyldisilazide) at very low temperature, for example between about -78° and -60°C, for about 3 hours, and the resulting anion is quenched (e.g. with aqueous ammonium chloride). In a preferred procedure a solution of the compound of formula (VI) in tetrahydrofuran is treated with 1.3 equivalents of lithium diisopropylamide at between -78° and -60°C for 3 hours and aqueous ammonium chloride is added.

Compounds of formula (VI) may be prepared by the alkylation of a compound of formula

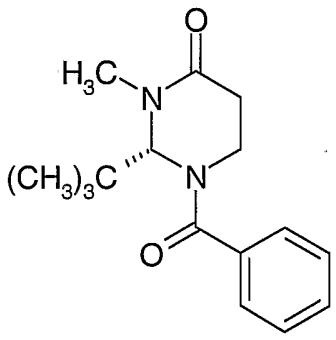


(VII)

with a compound of formula (IV), as defined above. The compound of formula (VII) is de-protonated using a suitable base, and the resulting anion is quenched by addition of the compound of formula (IV). In a typical procedure, a solution of a compound of formula (VII) in a suitable solvent (such as tetrahydrofuran or ether) is treated with a strong base (such as lithium diisopropylamide or lithium hexamethyldisilazide), at low temperature (e.g. at about -78°C) for about 1 hour and the resulting anion is then quenched with the compound of formula (IV). Preferably, a solution of the compound of formula (VII) in tetrahydrofuran is treated with 1.2 equivalents of lithium diisopropylamide at a temperature of about -78°C for about 80 minutes, followed by the addition of 1.2 equivalents of the compound of formula (IV) at -78°C, warming slowly to room temperature.

A compound of formula (VII) may be prepared by the method of Juaristi *et al* in *Tetrahedron Asymmetry*, 1996, 2233-2246.

Compounds of formula (I) having the alternative (R) stereochemistry can of course be easily prepared by using a compound of formula (VIIa)



(VIIa)

instead of a compound of formula (VII) and applying the same methods as described above. A compound of formula (VIIa) may also be prepared using the method of Juaristi *et al* in *Tetrahedron Asymmetry*, 1996, 2233-2246. Alternatively, compounds of formula (I) having the alternative (R) stereochemistry may be prepared directly from a compound of formula (VI) applying the hydrolysis described above in relation to a compound of formula (V). Equally, compounds of formula (Ia) may be prepared by a sequence of alkylation and hydrolysis performed on a compound of formula (VIIa).

Compounds of formula (I) may also be prepared using methods analogous to those described in WO-A-03/082807 and the references therein or by the method of Lavielle *et al* in *European Journal of Organic Chemistry* 2000, **1**, 83-89.

Compounds of formula (I) can also be prepared by using the reactions described above to construct a compound wherein R^1, R^2, R^3, R^8 or R^9 are partially formed or protected and then completing the synthesis by functional group manipulation. Suitable protecting groups are described in 'Protective Groups in Organic Synthesis' by Theodora Greene and Peter Wuts (third edition, 1999, John Wiley and Sons). Suitable functional group transformations are described in 'Comprehensive Organic Transformations' by Richard Larock (1999, VCH Publishers Inc.).

Compounds of formula (I) may be administered as crystalline or amorphous products. They may be obtained, for example, as solid plugs, powders, or films by methods such as precipitation, crystallization, freeze drying, spray drying, or evaporative drying. Microwave or radio frequency drying may be used for this purpose.

They may be administered alone or in combination with one or more other compounds of formula (I) or in combination with one or more other drugs (or as any combination thereof). Generally, they will be administered as a formulation in association with one or more pharmaceutically acceptable excipients. The term 'excipient' is used herein to describe any ingredient other than a compound of formula (I). The choice of excipient will to a large extent depend on factors such as the particular mode of administration, the effect of the excipient on solubility and stability, and the nature of the dosage form.

Pharmaceutical compositions suitable for the delivery of compounds of formula (I) and methods for their preparation will be readily apparent to those skilled in the art. Such compositions and methods for their preparation may be found, for example, in Remington's Pharmaceutical Sciences, 19th Edition (Mack Publishing Company, 1995).

A compound of formula (I) may be administered orally. Oral administration may involve swallowing, so that the compound enters the gastrointestinal tract, or buccal or sublingual administration may be employed by which the compound enters the blood stream directly from the mouth.

Formulations suitable for oral administration include solid formulations such as tablets, capsules containing particulates, liquids, powders, lozenges (including liquid-filled lozenges), chews, multi- and nano-particulates, gels, solid solutions, liposomes, films, ovules, sprays and liquid formulations.

Liquid formulations include suspensions, solutions, syrups and elixirs. Such formulations may be employed as fillers in soft or hard capsules and typically comprise a carrier, for example, water, ethanol, polyethylene glycol, propylene glycol, methylcellulose or a suitable oil, and one or more emulsifying agents and/or suspending agents. Liquid formulations may also be prepared by the reconstitution of a solid, for example, from a sachet.

A compound of formula (I) may also be used in fast-dissolving, fast-disintegrating dosage forms such as those described in Expert Opinion in Therapeutic Patents, 11 (6), 981-986, by Liang and Chen (2001).

For tablet dosage forms, depending on dose, a compound of formula (I) may make up from 1 weight % to 80 weight % of the dosage form, more typically from 5 weight % to 60 weight % of the dosage form. In addition to the compound of formula (I), tablets generally contain a disintegrant. Examples of disintegrants include sodium starch glycolate, sodium carboxymethyl cellulose, calcium carboxymethyl cellulose, croscarmellose sodium, crospovidone, polyvinylpyrrolidone, methyl cellulose, microcrystalline cellulose, lower alkyl-substituted hydroxypropyl cellulose, starch, pregelatinised starch and sodium alginate. Generally, the disintegrant will comprise from 1 weight % to 25 weight %, preferably from 5 weight % to 20 weight % of the dosage form.

Binders are generally used to impart cohesive qualities to a tablet formulation. Suitable binders include microcrystalline cellulose, gelatin, sugars, polyethylene glycol, natural and synthetic gums, polyvinylpyrrolidone, pregelatinised starch, hydroxypropyl cellulose and hydroxypropyl methylcellulose. Tablets may also contain diluents, such as lactose (as, for example, the monohydrate, spray-dried monohydrate or anhydrous form), mannitol, xylitol, dextrose, sucrose, sorbitol, microcrystalline cellulose, starch and dibasic calcium phosphate dihydrate.

Tablets may also optionally comprise surface active agents, such as sodium lauryl sulfate and polysorbate 80, and glidants such as silicon dioxide and talc. When present, surface active agents may comprise from 0.2 weight % to 5 weight % of the tablet, and glidants may comprise from 0.2 weight % to 1 weight % of the tablet.

Tablets also generally contain lubricants such as magnesium stearate, calcium stearate, zinc stearate, sodium stearyl fumarate, and mixtures of magnesium stearate with sodium lauryl sulphate. Lubricants generally comprise from 0.25 weight % to 10 weight %, preferably from 0.5 weight % to 3 weight % of the tablet.

Other possible ingredients include anti-oxidants, colourants, flavouring agents, preservatives and taste-masking agents.

Exemplary tablets contain up to about 80% of a compound of formula (I), from about 10 weight % to about 90 weight % binder, from about 0 weight % to about 85 weight % diluent, from about 2 weight % to about 10 weight % disintegrant, and from about 0.25 weight % to about 10 weight % lubricant.

Tablet blends may be compressed directly or by roller to form tablets. Tablet blends or portions of blends may alternatively be wet-, dry-, or melt-granulated, melt congealed, or extruded before tabletting. The final formulation may comprise one or more layers and may be coated or uncoated; it may even be encapsulated.

The formulation of tablets is discussed in Pharmaceutical Dosage Forms: Tablets, Vol. 1, by H. Lieberman and L. Lachman (Marcel Dekker, New York, 1980).

Consumable oral films for human or veterinary use are typically pliable water-soluble or water-swellable thin film dosage forms which may be rapidly dissolving or mucoadhesive and typically comprise a compound of formula (I), a film-forming polymer, a binder, a solvent, a humectant, a plasticiser, a stabiliser or emulsifier, a viscosity-modifying agent and a solvent. Some components of the formulation may perform more than one function.

A compound of formula (I) for use in a film may be water-soluble or insoluble. A water-soluble compound typically comprises from 1 weight % to 80 weight %, more typically from 20 weight % to 50 weight %, of the solutes. Less soluble compounds may comprise a greater proportion of the composition, typically up to 88 weight % of the solutes. Alternatively, a compound of formula (I) may be used in the form of multiparticulate beads.

The film-forming polymer may be selected from natural polysaccharides, proteins, or synthetic hydrocolloids and is typically present in the range 0.01 to 99 weight %, more typically in the range 30 to 80 weight %.

Other possible ingredients in such a film include anti-oxidants, colorants, flavourings, flavour enhancers, preservatives, salivary stimulating agents, cooling agents, co-solvents (including oils), emollients, bulking agents, anti-foaming agents, surfactants and taste-masking agents.

Films in accordance with the invention are typically prepared by evaporative drying of thin aqueous films coated onto a peelable backing support or paper. This may be done in a drying oven or tunnel, typically a combined coater dryer, or by freeze-drying or vacuuming.

Solid formulations for oral administration may be formulated to be immediate and/or modified release. Modified release formulations include delayed, sustained, pulsed, controlled, targeted and programmed release formulations.

Suitable modified release formulations for the purposes of the invention are described in US Patent No. 6,106,864. Details of other suitable release technologies such as high energy dispersions and osmotic and coated particles are to be found in Pharmaceutical Technology On-line, 25(2), 1-14, by Verma *et al* (2001). The use of chewing gum to achieve controlled release is described in WO 00/35298.

A compound of formula (I) may also be administered directly into the blood stream, into muscle, or into an internal organ. Suitable routes for such parenteral administration include intravenous, intraarterial, intraperitoneal, intrathecal, intraventricular, intraurethral, intrasternal, intracranial, intramuscular and subcutaneous delivery. Suitable means for parenteral administration include needle (including microneedle) injectors, needle-free injectors and infusion techniques.

Parenteral formulations are typically aqueous solutions which may contain excipients such as salts, carbohydrates and buffering agents (preferably at a pH of from 3 to 9), but, for some applications, they may be more suitably formulated as a sterile non-aqueous solution or as a dried form to be used in conjunction with a suitable vehicle such as sterile, pyrogen-free water.

The preparation of parenteral formulations under sterile conditions, for example, by lyophilisation, may readily be accomplished using standard pharmaceutical techniques well known to those skilled in the art.

The solubility of a compound of formula (I) used in the preparation of a parenteral formulation may be increased by the use of appropriate formulation techniques, such as the incorporation of solubility-enhancing agents.

Formulations for parenteral administration may be formulated to be immediate and/or modified release. Modified release formulations include delayed, sustained, pulsed, controlled, targeted and programmed release formulations. Thus, a compound of formula (I) may be formulated as a solid, semi-solid, or thixotropic liquid for administration as an implanted depot providing modified release of the active compound. Examples of such formulations include drug-coated stents and poly(*dl*-lactic-coglycolic)acid (PGLA) microspheres.

A compound of formula (I) may also be administered topically to the skin or mucosa, i.e. dermally or transdermally. Typical formulations for this purpose include gels, hydrogels, lotions, solutions, creams, ointments, dusting powders, dressings, foams, films, skin patches, wafers, implants, sponges, fibres, bandages and microemulsions. Liposomes may also be used. Typical carriers include alcohol, water, mineral oil, liquid petrolatum, white petrolatum, glycerin, polyethylene glycol and propylene glycol. Penetration enhancers may be incorporated - see, for example, J. Pharm. Sci., 88 (10), 955-958, by Finnin and Morgan (October 1999).

Other means of topical administration include delivery by electroporation, iontophoresis, phonophoresis, sonophoresis and microneedle or needle-free (*e.g.* Powderject™, Bioject™, *etc.*) injection.

Formulations for topical administration may be formulated to be immediate and/or modified release. Modified release formulations include delayed, sustained, pulsed, controlled, targeted and programmed release formulations.

A compound of formula (I) can also be administered intranasally or by inhalation, typically in the form of a dry powder (either alone, as a mixture, for example, in a dry blend with lactose, or as a mixed component particle, for example, mixed with phospholipids, such as phosphatidylcholine) from a dry powder inhaler or as an aerosol spray from a pressurised container, pump, spray, atomiser (preferably an atomiser using electrohydrodynamics to produce a fine mist), or nebuliser, with or without the use of a suitable propellant, such as 1,1,1,2-tetrafluoroethane or

1,1,1,2,3,3,3-heptafluoropropane. For intranasal use, the powder may comprise a bioadhesive agent, for example, chitosan or cyclodextrin.

The pressurised container, pump, spray, atomizer, or nebuliser contains a solution or suspension of a compound of formula (I) comprising, for example, ethanol, aqueous ethanol, or a suitable alternative agent for dispersing, solubilising, or extending release of the active, a propellant(s) as solvent and an optional surfactant, such as sorbitan trioleate, oleic acid, or an oligolactic acid.

Prior to use in a dry powder or suspension formulation, a drug product is micronised to a size suitable for delivery by inhalation (typically less than 5 microns). This may be achieved by any appropriate comminuting method, such as spiral jet milling, fluid bed jet milling, supercritical fluid processing to form nanoparticles, high pressure homogenisation, or spray drying.

Capsules (made, for example, from gelatin or hydroxypropylmethylcellulose), blisters and cartridges for use in an inhaler or insufflator may be formulated to contain a powder mix of a compound of formula (I), a suitable powder base such as lactose or starch and a performance modifier such as *l*-leucine, mannitol, or magnesium stearate. The lactose may be anhydrous or in the form of the monohydrate, preferably the latter. Other suitable excipients include dextran, glucose, maltose, sorbitol, xylitol, fructose, sucrose and trehalose.

A suitable solution formulation for use in an atomiser using electrohydrodynamics to produce a fine mist may contain from 1µg to 20mg of a compound of formula (I) per actuation and the actuation volume may vary from 1µl to 100µl. A typical formulation may comprise a compound of formula (I), propylene glycol, sterile water, ethanol and sodium chloride. Alternative solvents which may be used instead of propylene glycol include glycerol and polyethylene glycol.

Suitable flavours, such as menthol and levomenthol, or sweeteners, such as saccharin or saccharin sodium, may be added to those formulations intended for inhaled/intranasal administration.

Formulations for inhaled/intranasal administration may be formulated to be immediate and/or modified release using, for example, PGLA. Modified release formulations include delayed, sustained, pulsed, controlled, targeted and programmed release formulations.

In the case of dry powder inhalers and aerosols, the dosage unit is determined by means of a valve which delivers a metered amount. Units in accordance with the invention are typically arranged to administer a metered dose or "puff". The overall daily dose will be administered in a single dose or, more usually, as divided doses throughout the day.

A compound of formula (I) may be administered rectally or vaginally, e.g. in the form of a suppository, pessary, or enema. Cocoa butter is a traditional suppository base, but various alternatives may be used as appropriate.

Formulations for rectal/vaginal administration may be formulated to be immediate and/or modified release. Modified release formulations include delayed, sustained, pulsed, controlled, targeted and programmed release formulations.

A compound of formula (I) may also be administered directly to the eye or ear, typically in the form of drops of a micronised suspension or solution in isotonic, pH-adjusted, sterile saline. Other formulations suitable for ocular and aural administration include ointments, biodegradable (*e.g.* absorbable gel sponges, collagen) and non-biodegradable (*e.g.* silicone) implants, wafers, lenses and particulate or vesicular systems, such as niosomes or liposomes. A polymer such as crossed-linked polyacrylic acid, polyvinylalcohol, hyaluronic acid, a cellulosic polymer, for example, hydroxypropylmethylcellulose, hydroxyethylcellulose, or methyl cellulose, or a heteropolysaccharide polymer, for example, gelan gum, may be incorporated together with a preservative, such as benzalkonium chloride. Such formulations may also be delivered by iontophoresis.

Formulations for ocular/aural administration may be formulated to be immediate and/or modified release. Modified release formulations include delayed, sustained, pulsed, controlled, targeted, or programmed release formulations.

A compound of formula (I) may be combined with a soluble macromolecular entitiy, such as a cyclodextrin or a suitable derivative thereof or a polyethylene glycol-containing polymer, in order to improve its solubility, dissolution rate, taste-masking, bioavailability and/or stability in any of the aforementioned modes of administration.

Drug-cyclodextrin complexes, for example, are found to be generally useful for most dosage forms and administration routes. Both inclusion and non-inclusion complexes may be used. As an alternative to direct complexation with the drug, the cyclodextrin may be used as an auxiliary additive, i.e. as a carrier, diluent, or solubiliser. Most commonly used for these purposes are alpha-, beta- and gamma-cyclodextrins, examples of which may be found in International Patent Applications Nos. WO-A-91/11172, WO-A-94/02518 and WO-A-98/55148.

For administration to human patients, the total daily dose of a compound of formula (I) is typically in the range of from 1 mg to 1000 mg (preferably between 10mg and 500mg) depending, of course, on the mode of administration and the potency of the selected compound. The total daily dose may be administered in single or divided doses and may, at the physician's discretion, fall outside of the typical range given herein.

These dosages are based on an average human subject having a weight of about 60kg to 70kg. The physician will readily be able to determine doses for subjects whose weight falls outside this range, such as infants and the elderly.

For the avoidance of doubt, references herein to "treatment" include references to curative, palliative and prophylactic treatment.

The biological activity of the alpha-2-delta ligands of the invention may be measured in a radioligand binding assay using [^{3}H]gabapentin and the $\alpha_2\delta$ subunit derived from porcine brain tissue based on the method given in *J. Biol. Chem.*, 1996, **271**(10), 5768-5776). This assay is reproduced below.

[^{3}H]Gabapentin binding assay

Preparation of brain membranes

All solutions were maintained at 4°C throughout. Pig brain cortex (up to 50 g) (fresh or frozen) was homogenised in 10 volumes of Buffer A (0.32 M Sucrose/1 mM EDTA/1 mM EGTA/10 mM Hepes/KOH, pH 7.4) by six strokes of a glass/teflon homogeniser at 600 r.p.m. After removal of the 1000 *g* x 10 minute pellet, the supernatant was centrifuged at 40,000 *g* for 20 minutes and the resulting pellet was resuspended in 10 volumes of Buffer B (1 mM EDTA/1 mM EGTA/10 mM Hepes/KOH, pH 7.4). Following 30 minutes of continuous stirring, membranes were pelleted as above twice more by centrifugation with Buffer B, before a final re-suspension in approximately 3 volumes of storage buffer (1.25 mM EDTA/1.25 mM EGTA/25% Glycerol/12.5 mM Hepes/KOH, pH 7.4) to give a concentration of about 3 milligrams of protein per millilitre. Aliquots were stored at -80°C until required.

Binding assay protocol:

Binding of [^{3}H]gabapentin to pig cerebral cortex membranes was carried out at 22°C in 10 mM Hepes/KOH, pH 7.4 for 60 minutes. Non-specific binding (nsb) was defined as the binding obtained in the presence of 10μM pregabalin. An assay volume of 250μl was employed, comprising 200μl of membranes, 25μl test compound/buffer/nsb, 25μl [^{3}H]gabapentin (final assay concentration ~10nM). Separation of unbound radioligand was effected by rapid filtration under vacuum through cold 50 mM Tris/HCl, pH 7.4-dipped GF/B unifilter plates, using 2 x 1ml of cold 50 mM Tris/HCl, pH 7.4. Plates were left to dry before addition of 50μl/well microscint-40 and the amount of radioactivity bound determined using a TopCount scintillation counter. Results may be expressed as an IC_{50} in terms of μM or nM.

All the Examples described below were tested in this alpha-2-delta assay and were found to have a binding affinity (IC_{50}) of 1 μM or less. For instance, (2*S*)-3-

amino-2-(3-chlorobenzyl)propanoic acid hydrochloride (Example 1) had a binding affinity of 0.020 μM.

An alpha-2-delta receptor ligand may be usefully combined with another pharmacologically active compound, or with two or more other pharmacologically active compounds, particularly in the treatment of pain. For example, an alpha-2-delta receptor ligand, particularly a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, as defined above, may be administered simultaneously, sequentially or separately in combination with one or more agents selected from:

- an opioid analgesic, e.g. morphine, heroin, hydromorphone, oxymorphone, levorphanol, levallorphan, methadone, meperidine, fentanyl, cocaine, codeine, dihydrocodeine, oxycodone, hydrocodone, propoxyphene, nalmefene, nalorphine, naloxone, naltrexone, buprenorphine, butorphanol, nalbuphine or pentazocine;
- a nonsteroidal antiinflammatory drug (NSAID), e.g. aspirin, diclofenac, diflusinal, etodolac, fenbufen, fenoprofen, flufenisal, flurbiprofen, ibuprofen, indomethacin, ketoprofen, ketorolac, meclofenamic acid, mefenamic acid, nabumetone, naproxen, oxaprozin, phenylbutazone, piroxicam, sulindac, tolmetin or zomepirac;
- a barbiturate sedative, e.g. amobarbital, aprobarbital, butabarbital, butabital, mephobarbital, metharbital, methohexital, pentobarbital, phenobartital, secobarbital, talbutal, theamylal or thiopental;
- a benzodiazepine having a sedative action, e.g. chlordiazepoxide, clorazepate, diazepam, flurazepam, lorazepam, oxazepam, temazepam or triazolam;
- an H_1 antagonist having a sedative action, e.g. diphenhydramine, pyrilamine, promethazine, chlorpheniramine or chlorcyclizine;
- a sedative such as glutethimide, meprobamate, methaqualone or dichloralphenazone;
- a skeletal muscle relaxant, e.g. baclofen, carisoprodol, chlorzoxazone, cyclobenzaprine, methocarbamol or orphrenadine;

- an NMDA receptor antagonist, e.g. dextromethorphan ((+)-3-hydroxy-N-methylmorphinan) or its metabolite dextrorphan ((+)-3-hydroxy-N-methylmorphinan), ketamine, memantine, pyrroloquinoline quinone or cis-4-(phosphonomethyl)-2-piperidinecarboxylic acid;
- an alpha-adrenergic, e.g. doxazosin, tamsulosin, clonidine or 4-amino-6,7-dimethoxy-2-(5-methanesulfonamido-1,2,3,4-tetrahydroisoquinol-2-yl)-5-(2-pyridyl) quinazoline;
- a tricyclic antidepressant, e.g. desipramine, imipramine, amytriptiline or nortriptiline;
- an anticonvulsant, e.g. carbamazepine or valproate;
- a tachykinin (NK) antagonist, particularly an NK-3, NK-2 or NK-1 antagonist, e.g. (αR,9R)-7-[3,5-bis(trifluoromethyl)benzyl]-8,9,10,11-tetrahydro-9-methyl-5-(4-methylphenyl)-7H-[1,4]diazocino[2,1-g][1,7]naphthridine-6-13-dione (TAK-637), 5-[[(2R,3S)-2-[(1R)-1-[3,5-bis(trifluoromethyl)phenyl]ethoxy-3-(4-fluorophenyl)-4-morpholinyl]methyl]-1,2-dihydro-3H-1,2,4-triazol-3-one (MK-869), lanepitant, dapitant or 3-[[2-methoxy-5-(trifluoromethoxy)phenyl]methylamino]-2-phenyl-piperidine (2S,3S);
- a muscarinic antagonist, e.g oxybutin, tolterodine, propiverine, tropsium chloride or darifenacin;
- a selective COX-2 inhibitor, e.g. celecoxib, rofecoxib or valdecoxib;
- a non-selective COX inhibitor (preferably with GI protection), e.g. nitroflurbiprofen (HCT-1026);
- a coal-tar analgesic, in particular paracetamol;
- a neuroleptic such as droperidol;
- a vanilloid receptor agonist (e.g. resinferatoxin) or antagonist (e.g. capsazepine);
- a beta-adrenergic such as propranolol;
- a local anaesthetic such as mexiletine;
- a corticosteriod such as dexamethasone;
- a 5-HT receptor agonist or antagonist, particularly a 5-$HT_{1B/1D}$ agonist such as eletriptan, sumatriptan, naratriptan, zolmitriptan or rizatriptan;
- a cholinergic (nicotinic) analgesic;

- Tramadol (trade mark);
- a PDEV inhibitor, such as sildenafil, vardenafil, taladafil, 5-[2-ethoxy-5-(4-ethylpiperazin-1-ylsulphonyl)pyridin-3-yl]-3-ethyl-2-[2-methoxyethyl]-2,6-dihydro-7*H*-pyrazolo[4,3-*d*]pyrimidin-7-one, 5-(5-acetyl-2-butoxy-3-pyridinyl)-3-ethyl-2-(1-ethyl-3-azetidinyl)-2,6-dihydro-7*H*-pyrazolo[4,3-*d*]pyrimidin-7-one, 1-{6-ethoxy-5-[3-ethyl-6,7-dihydro-2-(2-methoxyethyl)-7-oxo-2H-pyrazolo[4,3-d]pyrimidin-5-yl]-3-pyridylsulfonyl}-4-ethylpiperazine, or *N*-[1-(2-ethoxyethyl)-5-(*N*-ethyl-*N*-methylamino)-7-(4-methylpyridin-2-ylamino)-1H-pyrazolo[4,3-d]pyrimidine-3-carbonyl]methanesulfonamide;
- a canabinoid;
- metabotropic glutamate subtype 1 receptor (mGluR1) antagonist;
- a serotonin reuptake inhibitor such as sertraline;
- a noradrenaline reuptake inhibitor, especially a selective noradrenaline reuptake inhibitor such as (S,S)-reboxetine;
- a dual serotonin/noradrenaline reuptake inhibitor such as duloxetine;
- an inducible nitric oxide synthase (iNOS) inhibitor such as S-[2-[(1-iminoethyl)amino]ethyl]-2-methyl-L-cysteine or (2S,5Z)-2-amino-2-methyl-7-[(1-iminoethyl)amino]-5-heptenoic acid;
- an acetylcholine esterase inhibitor such as donepezil;
- a dopamine type 2 (D2) antagonist such as ziprazidone;
- an prostaglandin E_2 subtype 4 (EP4) antagonist such as *N*-[({2-[4-(2-ethyl-4,6-dimethyl-1H-imidazo[4,5-c]pyridin-1-yl)phenyl]ethyl}amino)carbonyl]-4-methylbenzenesulfonamide or 4-[(1*S*)-1-({[5-chloro-2-(3-fluorophenoxy)pyridin-3-yl]carbonyl}amino)ethyl]benzoic acid;

and the pharmaceutically acceptable salts and solvates thereof.

Where a combination of active compounds is to be administered, two or more pharmaceutical compositions may conveniently be combined in the form of a kit suitable for co-administration of the compositions.

Such a kit comprises two or more separate pharmaceutical compositions, at least one of which contains an alpha-2-delta receptor antagonist, particularly a

compound of formula (I), and means for separately retaining said compositions, such as a container, divided bottle, or divided foil packet. An example of such a kit is the familiar blister pack used for the packaging of tablets, capsules and the like.

Such a kit is particularly suitable for administering different dosage forms, for example, oral and parenteral formulations, for administering separate compositions at different dosage intervals, or for titrating separate compositions against one another. To assist compliance, the kit typically comprises directions for administration and may be provided with a so-called memory aid.

It will be appreciated that what the invention provides, and what will be claimed, is as follows:

(i) a compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof;

(ii) a process for the preparation of a compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof;

(iii) a pharmaceutical composition including a compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof, together with a pharmaceutically acceptable excipient;

(iv) a compound of formula (I) or a pharmaceutically acceptable salt, solvate or composition thereof, for use as a medicament;

(v) the use of a compound of formula (I) or of a pharmaceutically acceptable salt, solvate or composition thereof, for the manufacture of a medicament to treat a disease for which an alpha-2-delta receptor ligand is indicated;

(vi) the use of a compound of formula (I) or of a pharmaceutically acceptable salt, solvate or composition thereof, for the manufacture of a medicament for the treatment of pain;

(vii) a method of treatment of a mammal, including a human being, with an alpha-2-delta receptor ligand, including treating said mammal with an effective amount of a compound of formula (I) or with a pharmaceutically acceptable salt, solvate or composition thereof;

(viii) a method of treatment of a mammal, including a human being, to treat pain, including treating said mammal with an effective amount of a compound of formula (I) or with a pharmaceutically acceptable salt, solvate or composition thereof;

(ix) certain novel intermediates disclosed herein; and

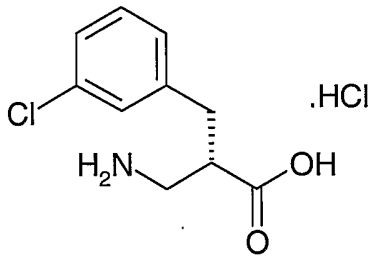
(x) a combination of a compound of formula (I) and one or more further pharmacologically active compounds.

The following Examples illustrate the preparation of compounds of formula (I).

^{1}H Nuclear magnetic resonance (NMR) spectra were in all cases consistent with the proposed structures. Characteristic chemical shifts (δ) are given in parts-per-million downfield from tetramethylsilane using conventional abbreviations for designation of major peaks: e.g. s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad. The mass spectra (MS) were recorded using either electrospray ionisation (ESI) or atmospheric pressure chemical ionisation (APCI). The following abbreviations have been used for common solvents: $CDCl_3$, deuterochloroform; D_6-DMSO, deuterodimethylsulphoxide; CD_3OD, deuteromethanol; THF, tetrahydrofuran. 'Ammonia' refers to a concentrated solution of ammonia in water possessing a specific gravity of 0.88. Where thin layer chromatography (TLC) has been used it refers to silica gel TLC using silica gel 60 F_{254} plates, R_f is the distance travelled by a compound divided by the distance travelled by the solvent front on a TLC plate. Microwave radiation was performed using machines with a power range of 15 to 300W at 2.45GHz, the actual power supplied varying during the course of the reaction to maintain a constant temperature. LCMS indicates liquid chromatography mass spectrometry (R_t = retention time).

EXAMPLE 1

(2*S*)-3-Amino-2-(3-chlorobenzyl)propanoic acid hydrochloride

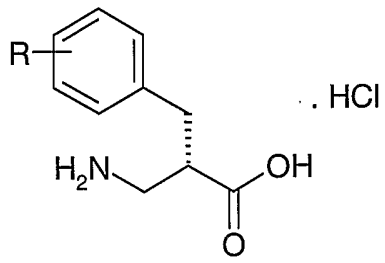


Water (50ml) was added to a solution of the amide of Preparation 1 (4.57g, 12.6mmol) in dioxane (50ml). The reaction mixture was heated under reflux for four days and then concentrated under reduced pressure. The solid residue was triturated in dichloromethane and the crude product (2.22g) was collected by filtration. This was then suspended in methanol (100ml) and the mixture was stirred at room temperature for 1 hour. The mixture was filtered again to provide a white solid, which was suspended in methanol (30ml). A solution of methanolic hydrochloric acid was added. The slightly opaque solution was filtered and the filtrate was concentrated under reduced pressure to give a white solid, which was triturated in ethyl acetate and filtered to provide the title compound (1.429g, 45%).

^{1}H-NMR (400MHz, CD_3OD) : δ = 2.89-3.02 (m, 3H), 3.12 (m, 2H), 7.20 (m, 1H), 7.29 (m, 3H).

EXAMPLES 2 AND 3

The compounds of the following tabulated Examples 2 and 3 of the general formula:

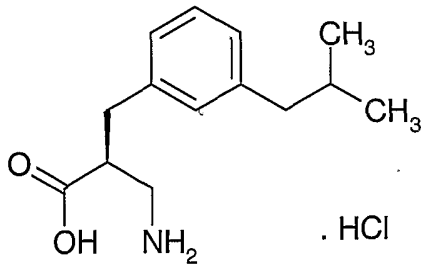


were prepared by a similar method to that of Example 1 using the appropriate benzylpropanamides of Preparations 2 and 3, respectively, as starting material.

Ex No	R	Analytical Data
2	2,5-di-Cl	^{1}H-NMR (400MHz, CD_3OD) : δ = 2.98 (m, 2H), 3.12 (m, 1H), 3.22 (m, 2H), 7.29 (m, 1H), 7.40 (m, 2H). LRMS : APCI$^+$: m/z 248 [M$^+$] 25% yield
3	3-OCF_3	^{1}H-NMR (400MHz, $CDCl_3$) : δ = 2.94-3.04 (m, 3H), 3.15 (m, 2H), 7.19 (m, 2H), 7.27 (d, 1H), 7.42 (t, 1H). LRMS : APCI$^+$: m/z 264 [MH$^+$]. 44% yield

EXAMPLE 4

(2*S*)-3-Amino-2-(3-isobutylbenzyl)propanoic acid hydrochloride



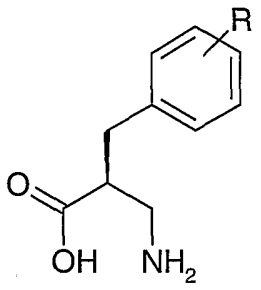
The tetrahydropyrimidinone of Preparation 8 (144mg, 0.34mmol) was suspended in 6M aqueous hydrochloric acid (15ml) and the reaction mixture was heated at reflux for twenty four hours. Upon cooling, the reaction was diluted with water (10ml) and then extracted with ethyl acetate (2x25ml). The organic phases were discarded and the aqueous layer was concentrated under reduced pressure to provide the title compound (58mg, 62%) as a pale brown solid, containing methylamine hydrochloride as an impurity (1:1 ratio).

^{1}H-NMR (400MHz, CD_3OD) : δ = 0.89 (d, 6H), 1.85(m, 1H), 2.45 (d, 2H), 2.54 (s, 3H, $MeNH_2$.HCl), 2.84-2.99 (m, 3H), 3.09 (m, 2H), 7.03 (m, 3H), 7.21 (t, 1H).

LRMS : APCI$^+$: m/z 236 [MH$^+$].

EXAMPLES 5 AND 6

The compounds of the following tabulated Examples 5 and 6 of the general formula:



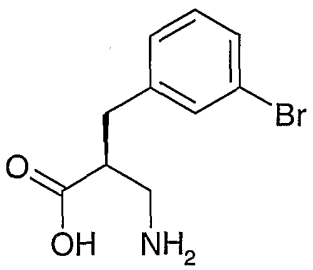
. HCl

were prepared by a similar method to that of Example 4 using the appropriate benzyl-tetrahydropyrimidinone of Preparations 12 and 13, respectively, as starting materials.

Ex No	R	Analytical Data
5	3,5-di-Cl	^{1}H-NMR (400MHz, CD_3OD) : δ = 2.54 (s, 3H, $MeNH_2$.HCl), 2.92 (m, 1H), 2.98-3.15 (m, 4H), 7.27 (s, 2H), 7.34 (s, 1H). LRMS : ESI^+ : m/z 248 [MH^+]. 99% yield, 1:1 mixture with $MeNH_2$.HCl
6	3-SCH_3	^{1}H-NMR (400MHz, CD_3OD) : δ = 2.46(s, 3H), 2.54 (s, 3H, $MeNH_2$.HCl), 2.87(m, 1H), 2.93-3.04 (m, 2H), 3.11 (m, 2H), 7.01 (d, 1H), 7.15 (m, 2H), 7.24 (m, 1H). LRMS : $APCI^+$: m/z 226 [MH^+] ; $APCI^-$ m/z 224 [M-H]. 100% yield, 1:1 mixture with $MeNH_2$.HCl

EXAMPLE 7

(2*S*)-3-Amino-2-(3-bromobenzyl)propanoic acid



The tetrahydropyrimidinone of Preparation 15 (200mg, 0.45mmol) was suspended in 6M aqueous hydrochloric acid (20ml) and dioxane (3ml). The

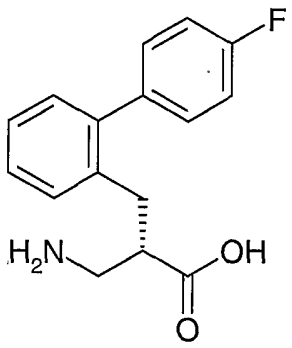
reaction mixture was heated at reflux for 18 hours. The cooled mixture was concentrated under reduced pressure and the residue was dissolved in water and filtered. The filtrate was extracted with ethyl acetate. The organic phases were discarded and the aqueous layer was concentrated under reduced pressure. The crude product was then purified by ion-exchange chromatography eluting with water then water:ammonia:methanol (60:20:20, by volume) to provide the title compound (71mg, 61%) as a pale white solid.

^{1}H-NMR (400MHz, D_2O) : δ = 2.62-2.71 (m, 2H), 2.77-2.91 (m, 3H), 7.07-7.12 (m, 2H), 7.31 (m, 2H).

LRMS : APCI$^+$: m/z 258 [M$^+$].

EXAMPLE 8

(2*S*)-3-Amino-2-((2-(4-fluorophenyl)phenyl)methyl)propanoic acid



The title compound was prepared by a similar method to that of Example 1 using the compound of Preparation 16 as starting material.

^{1}H-NMR (400MHz, CD_3OD) : δ = 2.47(m, 2H), 2.71(m, 2H), 3.22(m, 1H), 7.15(m, 3H), 7.26(m, 1H), 7.31(m, 3H), 7.40(m, 1H). Three exchangeable protons were not seen.

LRMS : APCI$^+$: m/z 274 (MH$^+$).

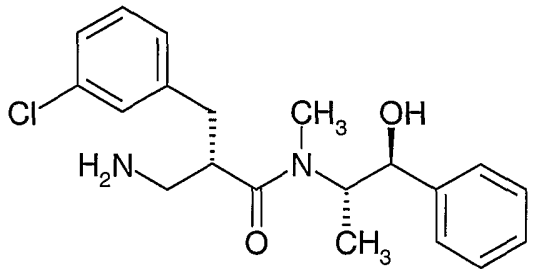
The corresponding HCl salt was also prepared by standard means.

^{1}H-NMR (400MHz, CD_3OD) : δ = 2.71(m, 2H), 2.77(m, 1H), 2.91(m,1H), 3.23(m, 1H), 7.19(m, 3H), 7.34(m, 5H). Exchangeable protons were not seen.

The following preparations show how intermediates used in the preparation of the Examples described above may themselves be synthesised.

PREPARATION 1

(2*S*)-3-Amino-2-(3-chlorobenzyl)-*N*-[(1*S*,2*S*)-2-hydroxy-1-methyl-2-phenylethyl]-*N*-methylpropanamide



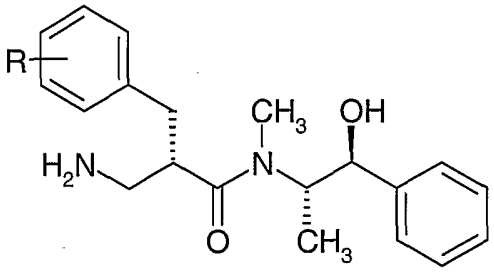
Dry lithium chloride (8.38g, 197.7mmol) was added to a solution of 3-amino-*N*-[(1*S*,2*S*)-2-hydroxy-1-methyl-2-phenylethyl]-*N*-methylpropanamide (see *Organic Letters*, *2000*, **2**(22), 3527-3529, 11.69g, 49.4mmol) in anhydrous tetrahydrofuran (200ml) at 0°C. Lithium hexamethyldisilazide (1M in tetrahydrofuran, 156.8ml, 156.8mmol) was then added dropwise, keeping the internal temperature between -5°C and 0°C. The resulting yellow solution was then stirred at 0°C for 1 hour. 3-Chlorobenzyl bromide (6.43ml, 49.4mmol) was then added dropwise at 0°C and the reaction mixture was stirred at 0°C for 1.5 hours. The mixture was quenched with water (400ml) and extracted with ethyl acetate (2x500ml). The organics were combined, dried over magnesium sulphate and concentrated under reduced pressure to yield an oil that crystallised on standing. Trituration with diethyl ether:pentane 1:1(100ml) and filtration gave the crude product (6.34g) as a white solid. This was recrystallised from toluene to provide the title compound as fine white needles (4.57g, 26%). All mother liquors were then evaporated to an oil which was purified by flash chromatography on silica gel eluting with ethyl acetate:methanol:ammonia (100:0:0 to 90:10:0 to 90:10:1 to 80:20:3, by volume) to provide another crop of the title compound (1.49g, 8.5%) after trituration in diethyl ether:pentane 1:1.

^{1}H-NMR (400MHz, $CDCl_3$, rotamers) : δ = 0.72 (d, 3H), 2.62 (m, 1H), 2.66 (s, 3H), 2.84 (m, 1H), 2.93 (m, 1H), 3.10 (m, 1H), 3.17-3.27 (brm, 4H), 4.37 (d, 1H), 4.94 (m, 1H), 7.03 (m, 1H), 7.17 (m, 4H), 7.33 (m, 4H).

LRMS : APCI$^+$: m/z 361 [MH$^+$].

PREPARATIONS 2 TO 3

The compounds of the following tabulated Preparations of the general formula:

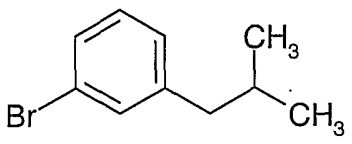


were prepared by a similar method to that of Preparation 1 using 3-amino-*N*-[(1*S*,2*S*)-2-hydroxy-1-methyl-2-phenylethyl]-*N*-methylpropanamide and the appropriate benzyl bromide as starting materials.

Prep No	R	Analytical Data
2	2,5-di-Cl	^{1}H-NMR (400MHz, CD_3OD, rotamers) : δ = 0.83 (d, 3H), 2.77 (s, 3H), 2.84 (m, 1H), 2.90-3.05 (m, 3H), 3.42 (m, 1H), 4.59 (d, 1H), 5.00 (m, 1H), 7.28-7.31 (m, 3H), 7.39-7.44 (m, 5H). LRMS : APCI$^+$: m/z 395 [M$^+$]. 79% yield
3	3-OCF_3	^{1}H-NMR (400MHz, $CDCl_3$) : δ = 0.81 (d, 3H), 2.69 (m, 1H), 2.74 (s, 3H), 2.93-3.05 (m, 3H), 3.14 (m, 1H), 4.44 (d, 1H), 4.94 (m, 1H), 7.06 (m, 2H), 7.13 (m, 1H), 7.30-7.38 (m, 6H). LRMS : APCI$^+$: m/z 411 [MH$^+$]. 17% yield

PREPARATION 4

1-Bromo-3-isobutylbenzene

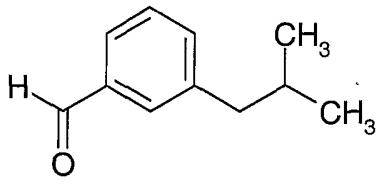


Isobutylmagnesium bromide (2M in diethyl ether, 26.5ml, 53mmol) was added over 30 minutes at room temperature to a solution of 1-bromo-3-iodobenzene (10g, 35.3mmol) and tetrakis(triphenylphosphine)palladium (0) (1.1g, 0.954mmol) in toluene (160ml). The reaction mixture became green and the temperature was not allowed to rise above 40°C. The reaction mixture was then stirred at room temperature for three hours. Aqueous ammonium chloride solution (160ml) was then added (the reaction became red) and the mixture was extracted with diethyl ether (2x100ml). The organics were washed with more ammonium chloride (100ml), dried over magnesium sulphate and concentrated under reduced pressure. The crude product was then purified by distillation to provide the title compound (boiling point 88°C under 25mmHg, 3.20g, 42%).

^{1}H-NMR (400MHz, $CDCl_3$) : δ = 0.90 (d, 6H), 1.85 (m, 1H), 2.44 (d, 2H), 7.07 (d, 1H), 7.14 (t, 1H), 7.30 (m, 2H).

PREPARATION 5

3-Isobutylbenzaldehyde

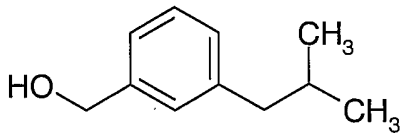


n-Butyl lithium (2.5M in hexanes, 6.4ml, 16.0mmol) was added dropwise over 10 minutes at 0°C to a solution of the bromobenzene of Preparation 4 (3.11g, 14.6mmol) in diethyl ether (30ml). The reaction mixture was stirred at 0°C for 15 minutes and then dry N,N-dimethylformamide (1.13ml, 14.6mmol) was added at 0°C. The reaction was stirred at 0°C for ten minutes, at room temperature for ten minutes and then heated under reflux for four hours. After cooling, the reaction was quenched with water (25ml). The organic phase was separated and the aqueous phase was extracted with more diethyl ether (25ml). The organic phases were combined, washed with water (25ml), dried over magnesium sulphate and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel eluting with ethyl acetate:heptane (0:100 to 10:90, by volume) to provide the title compound (1.35g, 57%) as a yellow oil.

^{1}H-NMR (400MHz, CD_3OD) : δ = 0.92 (d, 6H), 1.91 (m, 1H), 2.58 (d, 2H), 7.48 (m, 2H), 7.69 (s, 1H), 7.73 (m, 1H), 9.96 (s, 1H).

PREPARATION 6

(3-Isobutylphenyl)methanol

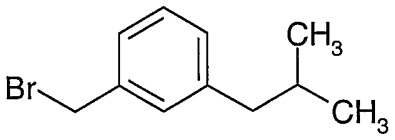


Sodium borohydride (378mg, 9.99mmol) was added portionwise over ten minutes at 0°C to a solution of the benzaldehyde of Preparation 5 (1.35g, 8.32mmol) in ethanol (50ml). The reaction mixture was warmed to room temperature and stirred for eighteen hours. It was then quenched by careful addition of aqueous acetic acid (2ml in 25ml water). The reaction mixture was concentrated under reduced pressure and neutralised with aqueous sodium bicarbonate solution. The mixture was extracted with dichloromethane (50ml) and the organic extracts were dried over magnesium sulphate and concentrated under reduced pressure to provide the title compound (1.33g, 97%) as a pale yellow oil.

^{1}H-NMR (400MHz, $CDCl_3$) : δ = 0.90 (d, 6H), 1.61 (brs, 1H), 1.87 (m, 1H), 2.48 (d, 2H), 4.68 (s, 2H), 7.08 (d, 1H), 7.17 (m, 2H), 7.27 (m, 1H).

PREPARATION 7

3-Isobutylbenzyl bromide

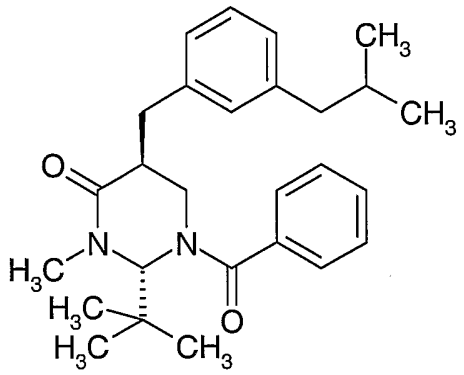


Hydrobromic acid (48% in acetic acid, 4ml, 23.7mmol) was added at room temperature to a stirred solution of the alcohol of Preparation 6 (1.33g, 8.10mmol) in acetic acid (15ml). The reaction was then heated at reflux for two hours. The dark brown reaction mixture was cooled down to 0°C and filtered. The solid was dissolved in dichloromethane and washed with a solution of sodium bicarbonate (2x75ml). The organic phase was separated, dried over magnesium sulphate and concentrated under reduced pressure to provide the title compound (1.13g, 61%) as a brown oil.

^{1}H-NMR (400MHz, $CDCl_3$) : δ = 0.90 (d, 6H), 1.86 (m, 1H), 2.47 (d, 2H), 4.49 (s, 2H), 7.08 (d, 1H), 7.17 (s, 1H), 7.22-7.26 (m, 2H).

PREPARATION 8

(2*R*,5*S*)-1-Benzoyl-5-(3-isobutylbenzyl)-2-*tert*-butyl-3-methyltetrahydropyrimidin-4(1*H*)-one



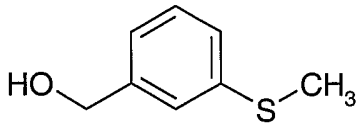
To a stirred solution of lithium diisopropylamide (2M in tetrahydrofuran, 437µl, 0.875mmol) in tetrahydrofuran (3ml) was added, at -78°C, a solution of (2*R*)-1-benzoyl-2-*tert*-butyl-3-methyltetrahydropyrimidin-4(1*H*)-one (see *Tetrahedron Asymmetry* 1996, **7**(8), 2233-2246, 200mg, 0.728mmol) in tetrahydrofuran (1ml). The reaction mixture was stirred at -78°C for eighty minutes and then the benzyl bromide of Preparation 7 (199mg, 0.875mmol) was added at -78°C. The reaction mixture was stirred at -78°C for two hours, then warmed to room temperature over three and a half hours and stirred at room temperature for thirty minutes. The reaction was quenched by addition of an aqueous ammonium chloride solution. The mixture was stirred at room temperature for 18 hours and then concentrated under reduced pressure. The aqueous phase was extracted with dichloromethane. The dichloromethane layer was filtered through a hydrophobic membrane and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel eluting with ethyl acetate:heptane (0:100 to 60:40, by volume) to provide the title compound (149mg, 49%) as a yellow solid.

^{1}H-NMR (400MHz, $CDCl_3$, rotamers) : δ = 0.83 (t, 6H), 1.16 (s, 9H), 1.68 (m, 1H), 2.23-2.32 (m, 3H), 2.64 (m, 1H), 3.00 (brs, 0.5H), 3.19-3.26 (m, 3.5H), 3.69 (m, 2H), 5.93 (s, 1H), 6.41 (m, 2H), 6.86 (m, 1H), 6.94 (m, 1H), 7.2 (m, 5H).

LRMS : APCI$^+$: m/z 421 [MH$^+$].

PREPARATION 9

[3-(Methylthio)phenyl]methanol

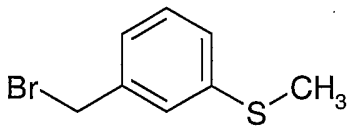


To a solution of lithium aluminium hydride (1M in diethyl ether, 5.35ml, 5.35mmol) in dry diethyl ether (25ml) was added dropwise, under nitrogen, over 15 minutes, a solution of 3-(methylthio)benzoic acid (1.0g, 5.9mmol) in diethyl ether (30ml). The reaction mixture was heated at reflux for one hour, cooled down to -30°C and quenched with water (25ml, added dropwise over five minutes). The organic phase was separated and the aqueous phase was extracted with diethyl ether (3x25ml). The organic phases were combined, washed with water (3x100ml), dried over magnesium sulphate and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel eluting with diethyl ether:pentane (0:1 to 1:2, by volume) to provide the title compound (568mg, 62%) as a colourless oil.

^{1}H-NMR (400MHz, $CDCl_3$): δ = 2.43 (s, 3H), 3.39 (s, 1H), 4.51 (s, 2H), 7.04 (d, 1H), 7.14 (d, 1H), 7.20 (m, 2H).

PREPARATION 10

3-(Methylthio)benzyl bromide



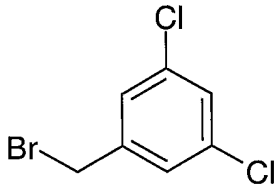
Hydrogen bromide gas was bubbled through a solution of the alcohol of Preparation 9 (568mg, 3.68mmol) in diethyl ether (30ml) at 0°C for one hour. The reaction mixture was then warmed to room temperature and stirred for 30 minutes. TLC showed that the reaction was not complete. The reaction mixture was saturated again with hydrogen bromide gas for fortyminutes at 0°C and then stirred at room temperature for eighteen hours. Nitrogen gas was then bubbled through the reaction to remove any remaining hydrogen bromide gas. The reaction mixture was concentrated under reduced pressure. The crude product

was purified by flash chromatography on silica gel eluting with diethyl ether:pentane (0:1 to 1:2, by volume) to provide the title compound (369mg, 46%).

^{1}H-NMR (400MHz, $CDCl_3$) : δ = 2.49 (s, 3H), 4.45 (s, 2H), 7.16 (m, 2H), 7.26 (m, 2H).

PREPARATION 11

3,5-Dichlorobenzyl bromide

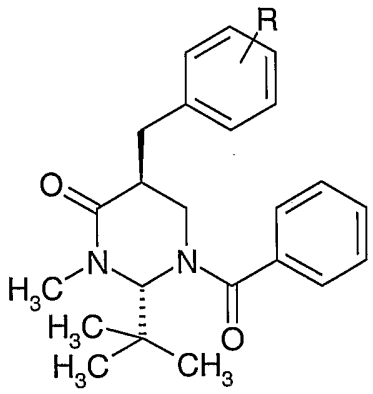


A solution of bromine (3.17ml, 61mmol) in carbon tetrachloride (50ml) was added to a solution of triphenylphosphine (16.13g, 61mmol) in carbon tetrachloride (250ml). 3,5-Dichlorobenzyl alcohol (10.0g, 56mmol) was added as a solution in carbon tetrachloride (50ml) and the reaction mixture was heated at reflux for 45 minutes. Hexane was added. The mixture was filtered through silica and washed with hexane. The filtrate was concentrated under reduced pressure to provide the title compound (12.79g, 95%).

^{1}H-NMR (400MHz, $CDCl_3$) : δ = 4.37 (s, 2H), 7.24-7.28 (m, 3H).

PREPARATIONS 12 AND 13

The compounds of the following tabulated Preparations of the general formula:

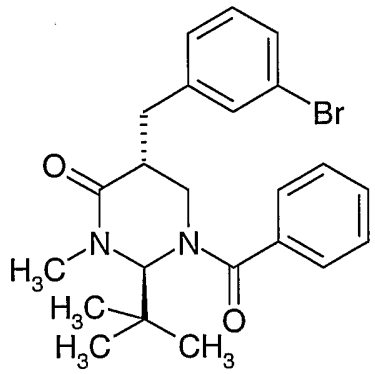


were prepared by a similar method to that of Preparation 8 using (2*S*)-1-benzoyl-2-*tert*-butyl-3-methyltetrahydropyrimidin-4(1*H*)-one and the appropriate benzyl bromide as starting materials.

Prep No	R	Analytical Data
12	3,5-di-Cl	^{1}H-NMR (400MHz, $CDCl_3$, rotamers) : δ = 1.18 (s, 9H), 2.32 (m, 1H), 2.63 (m, 1H), 3.01 (m, 1H), 3.19 (s, 3H), 3.65-3.74 (m, 2H), 5.93 (s, 1H), 6.52 (s, 2H), 7.09 (s, 1H), 7.41-7.53 (m, 5H). LRMS : APCI$^+$: m/z 433 [M$^+$]. 52% yield
13	3-SCH_3	^{1}H-NMR (400MHz, $CDCl_3$, rotamers) : δ = 1.17 (s, 9H), 2.37 (m, 4H), 2.67 (m, 1H), 3.01 (brs, 1H), 3.19 (s, 3H), 3.69 (d, 2H), 5.93 (s, 1H), 6.30(d, 1H), 6.62 (s, 1H), 6.94 (m, 2H), 7.44 (m, 5H). LRMS : APCI$^+$: m/z 411 [MH$^+$]. 56% yield

PREPARATION 14

(*2S,5R*)-1-Benzoyl-5-(3-bromobenzyl)-2-*tert*-butyl-3-methyltetrahydropyrimidin-4(1*H*)-one

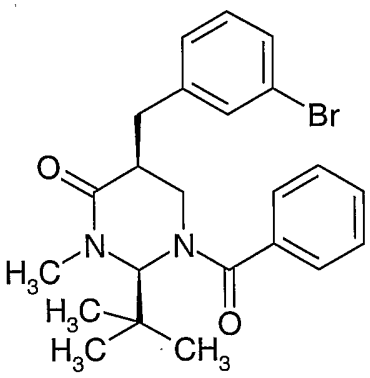


The title compound (2.6g, 44%) was prepared by a similar method to that of Preparation 8 using (2*S*)-1-benzoyl-2-*tert*-butyl-3-methyltetrahydropyrimidin-4(1*H*)-one and 3-bromobenzyl bromide as starting materials.

^{1}H-NMR (400MHz, $CDCl_3$, rotamers) : δ = 1.17 (s, 9H), 2.33 (m, 1H), 2.64 (m, 1H), 3.02 (m, 1H), 3.19 (s, 3H), 3.69 (m, 2H), 5.93 (s, 1H), 6.58 (d, 1H), 6.76 (s, 1H), 6.91 (t, 1H), 7.21 (d, 1H), 7.39-7.52 (m, 5H).

PREPARATION 15

(*2S,5S*)-1-Benzoyl-5-(3-bromobenzyl)-2-*tert*-butyl-3-methyltetrahydropyrimidin-4(1*H*)-one

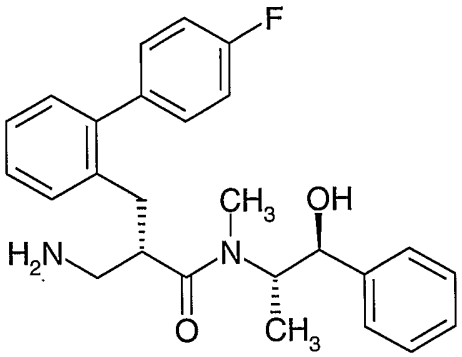


Lithium diisopropylamide (1.5M in tetrahydrofuran, 4.11ml, 6.2mmol) was added dropwise at -78°C, under nitrogen, to a solution of the tetrahydropyrimidinone of Preparation 14 (2.05g, 4.75mmol) in tetrahydrofuran (40ml). The reaction mixture was stirred at -60°C for three hours. It was then quenched by addition of an aqueous ammonium chloride solution. The mixture was stirred at room temperature and then concentrated under reduced pressure. The reaction was extracted with ethyl acetate. The organic layer was separated, washed with 2N hydrochloric acid and aqueous sodium bicarbonate, dried over magnesium sulphate, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel eluting with ethyl acetate:heptane (40:60 to 50:50, by volume) to provide the title compound (1.60g, 78%) as a colourless gum.

^{1}H-NMR (400MHz, $CDCl_3$, rotamers, broad peaks) : δ = 1.03 (s, 9H), 2.74 (m, 2H), 2.98 (m, 1H), 3.15 (s, 3H), 3.28 (m, 1H), 3.56 (m, 1H), 5.79 (s, 1H), 6.99 (m, 2H), 7.20 (s, 1H), 7.33-7.45 (m, 6H).

PREPARATION 16

(2*S*)-3-Amino-2-(2-(4-fluorophenyl)phenyl)methyl)-*N*-[(1*S*,2*S*)-2-hydroxy-1-methyl-2-phenylethyl]-*N*-methylpropanamide



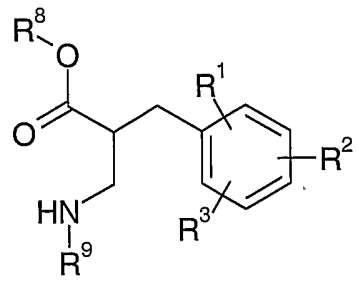
The title compound was prepared by a similar method to that of Preparation 1, using 2-(4-fluorophenyl)phenylmethyl bromide as the starting material (*J. Med. Chem.*, 2004, **47**, 5441).

^{1}H-NMR (400MHz, CD_3OD) : δ = 0.80 (3H, d), 2.35 (1H, dd), 2.55 (3H, s), 2.65-2.85 (4H, m), 4.50 (1H, d), 4.85 (1H, q), 7.15-7.40 (13H, m).

LRMS : APCI$^+$: m/z 421 (MH^+).

Claims

1. A compound of formula (I):



(I)

or a pharmaceutically acceptable salt or solvate thereof, wherein

R^1 and R^2 are each independently H, cyano, halo or -X-Y-R^4, or R^1 and R^2, taken together with two adjacent carbon atoms to which they are attached, form a fused 5- or 6-membered, saturated, partially unsaturated or aromatic ring optionally containing one or two nitrogen, oxygen or sulphur hereroatoms, said ring being optionally substituted by one ore more groups selected from cyano, halo and -X-Y-R^4;

-X- is a direct bond, C_1-C_6 alkylene, C_3-C_8 cycloalkylene, C_2-C_6 alkenylene or C_2-C_6 alkynylene, said C_1-C_6 alkylene, C_3-C_8 cycloalkylene, C_2-C_6 alkenylene and C_2-C_6 alkynylene being optionally substituted by one or more halo (preferably fluoro) groups;

-Y- is a direct bond, -O-, -S-, -SO-, -SO_2-, -NR^5-, -CO-, -OCO-, -C(O)O-, -NR^5CO-, -C(O)NR^5-, -NR^5SO_2- or -SO_2NR^5-;

R^3 is H, cyano, halo, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy or C_3-C_8 cycloalkyl, said C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy and C_3-C_8 cycloalkyl being optionally substituted by one or more halo (preferably fluoro) groups;

R^4 is C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_8 cycloalkyl, aryl, Het^1 or Het^2, said C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_8 cycloalkyl being optionally substituted by one or more halo (preferably fluoro) groups;

R^5 is H, C_1-C_6 alkyl or C_3-C_8 cycloalkyl;

Het^1 is a 3- to 8-membered, saturated or partially unsaturated heterocyclic group comprising one or two ring members selected from -NR^6-, -O-, -S-, -SO- and -SO_2- said heterocyclic group being optionally substituted on a ring carbon atom by one or more substituents selected from oxo, halo, -R^5 or -OR^5 and optionally benzo-fused, said benzo-fused portion being optionally substituted by one or more substituents selected from halo, C_1-C_6 alkyl, C_3-C_8 cycloalkyl, C_1-C_6 alkoxy and cyano;

R^6 is H, C_1-C_6 alkyl, C_3-C_8 cycloalkyl, -COR^7, -SO_2R^7 or a bond to the group which is substituted with Het^1;

R^7 is C_1-C_6 alkyl or C_3-C_8 cycloalkyl;

Het^2 is a 5-membered aromatic heterocyclic group comprising either (a) 1 to 4 nitrogen atoms, (b) one oxygen or one sulphur atom or (c) 1 oxygen atom or 1 sulphur atom and 1 or 2 nitrogen atoms or a 6-membered aromatic heterocyclic group comprising 1 or 2 nitrogen atoms, said 5- or 6-membered heterocyclic group being optionally substituted by one or more substituents selected from halo, -NR^5R^5, C_1-C_6 alkyl, C_3-C_8 cycloalkyl, C_1-C_6 alkoxy and cyano;

aryl is phenyl or naphthyl optionally substituted by one or more substituents selected from halo, -NR^5R^5, C_1-C_6 alkyl, C_3-C_8 cycloalkyl, C_1-C_6 alkoxy and cyano; and

R^8 and R^9 are each independently H or a group which is converted to H following administration of the compound to a mammal;

with the proviso that the compound of formula (I) is not one of the following specific compounds:

3-amino-2-(naphthalen-1-ylmethyl)propionic acid;
3-amino-2-(3,8-dimethoxynaphthalen-1-ylmethyl)propionic acid;
3-amino-2-(3,4-dichlorobenzyl)propionic acid;
3-amino-2-(4-dimethylaminobenzyl)propionic acid;
3-amino-2-(benzo[1,3]dioxol-5-ylmethyl)propionic acid;
3-amino-2-benzylpropanoic acid;
3-amino-2-(2,6-dichlorobenzyl)propanoic acid;
3-amino-2-(4-methylbenzyl)propanoic acid;
3-amino-2-(4-chlorobenzyl)propanoic acid;
3-amino-2-(4-hydroxybenzyl)propanoic acid;
3-amino-2-(4-methoxybenzyl)propanoic acid
3-amino-2-(4-tert-butyloxybenzyl)propanoic acid; or
3-amino-2-(2,4,6-trimethylbenzyl)propanoic acid.

2. A compound of formula (I), as claimed in claim 1, wherein R^8 and R^9 are both H.

3. A compound of formula (I), as claimed in claim 1 or claim 2, wherein R^3 is H.

4. A compound of formula (I), as claimed in any one of the preceding claims, wherein R^1 and R^2 are independently H, halo, C_1-C_6 alkyl, aryl, -O(C_1-C_6 alkyl) or -S(C_1-C_6 alkyl), each of said C_1-C_6 alkyl groups being optionally substituted by one or more halo groups.

5. A compound of formula (I), as claimed in claim one, selected from:

(2*S*)-3-amino-2-(3-chlorobenzyl)propanoic acid;
(2*S*)-3-amino-2-(2,5-dichlorobenzyl)propanoic acid;
(2*S*)-3-amino-2-(3-trifluoromethyloxy)propanoic acid;
(2*S*)-3-Amino-2-(3-isobutylbenzyl)propanoic acid;

(2*S*)-3-amino-2-(3,5-dichlorobenzyl)propanoic acid;
(2*S*)-3-Amino-2-(3-methylthiobenzyl)propanoic acid;
(2*S*)-3-Amino-2-(3-bromobenzyl)propanoic acid; and
(2*S*)-3-Amino-2-((2-(4-fluorophenyl)phenyl)methyl)propanoic acid;

and pharmaceutically acceptable salts and solvates thereof.

6. A pharmaceutical composition comprising a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, as defined in any one of claims 1 to 5, and a pharmaceutically acceptable excipient.

7. A method of treating pain in a mammal, including a human being, comprising administering an effective amount of a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, as defined in any one of claims 1 to 5.

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2006/001209

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07C229/34 A61K31/195 A61P29/02

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)
C07C 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, CHEM ABS Data, BEILSTEIN Data, WPI Data, PAJ

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DATABASE BEILSTEIN Beilstein Institut zur Förderung der Chemischen Wissenschaften, Frankfurt am Main, DE; XP002399446 retrieved from XFIRE Database accession no. BNR 10158765 abstract & ORG LETT, vol. 13, 2005, pages 2571-2573, -----	1
X	DATABASE BEILSTEIN Beilstein Institut zur Förderung der Chemischen Wissenschaften, Frankfurt am Main, DE; XP002399447 retrieved from XFIRE Database accession no. BRN 6399363 abstract -/--	1

[X] Further documents are listed in the continuation of Box C. [X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
19 September 2006	10/10/2006

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

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
	& J MED CHEM, vol. 32, no. 7, 1989, pages 1497-1503, -----	
X	DATABASE BEILSTEIN Beilstein Institut zur Förderung der Chemischen Wissenschaften, Frankfurt am Main, DE; XP002399448 retrieved from XFIRE Database accession no. BRN 6513133 abstract & J MED CHEM, vol. 32, no. 7, 1989, pages 1607-1611, -----	1
X	DATABASE BEILSTEIN Beilstein Institut zur Förderung der Chemischen Wissenschaften, Frankfurt am Main, DE; XP002399449 retrieved from XFIRE Database accession no. BRN 8260461 abstract & J ORG CHEM, vol. 64, no. 9, 1999, pages 3060-3065, -----	1
X	DATABASE BEILSTEIN Beilstein Institut zur Förderung der Chemischen Wissenschaften, Frankfurt am Main, DE; XP002399450 retrieved from XFIRE Database accession no. 5377846 abstract & EUR J ORG CHEM, vol. 1, 1999, pages 335-360, -----	1
X	DATABASE BEILSTEIN Beilstein Institut zur Förderung der Chemischen Wissenschaften, Frankfurt am Main, DE; XP002399451 retrieved from XFIRE Database accession no. BRN 3279771 abstract & J ORG CHEM, vol. 22, 1957, pages 1521-1526, -----	1
X	DATABASE BEILSTEIN Beilstein Institut zur Förderung der Chemischen Wissenschaften, Frankfurt am Main, DE; XP002399452 retrieved from XFIRE Database accession no. BRN 2807401 abstract -/--	1

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2006/001209

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
	& PHYTOCHEMISTRY, vol. 27, no. 3, 1988, pages 711-714,	
X	DATABASE CA [Online] CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; SHEN, TAO ET AL: "Preparation of .alpha.-substituted .beta.-amino acid by one step hydrogenation method" XP002399453 retrieved from STN Database accession no. 142:447408 see RN 851191-83-8 abstract & CN 1 435 408 CN (INSTITUTE OF CHEMISTRY, CHINESE ACADEMY OF SCIENCES, PEOP. REP. CHINA) 13 August 2003 (2003-08-13)	1-4
X	VAUGHT J L ET AL: "A COMPARISON OF THE ANTINOCICEPTIVE RESPONSES TO THE GABA-RECEPTOR AGONISTS THIP AND BACLOFEN" NEUROPHARMACOLOGY, PERGAMON PRESS, OXFORD, GB, vol. 24, no. 3, March 1985 (1985-03), pages 211-216, XP008037569 ISSN: 0028-3908 the whole document	1-7

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB2006/001209

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

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

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

Although claim 7 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

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

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

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

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

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

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

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

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

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/IB2006/001209

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
CN 1435408	CN 13-08-2003	NONE	