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Señora Jefe de la
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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
E. S. D.

Referencia : Expediente No. 00.041.548
Solicitante : LILLY, S.A.
Asunto : Solicitud de patente para: "MODULADORES
EXCITATIVOS RECEPTORES DE AMINOACIDO"
Fecha de solicitud : 2 de junio de 2000

TRAMITE 002 EVENTO 001 ACTUACION 329

1. Yo, Emilio FERRERO, obrando como apoderado de la solicitud en referencia, atentamente, presento con este escrito la copia certificada de la solicitud de patente Europea No. 99500090.8 del 03 de junio de 1999, junto con la respectiva traducción de sus reivindicaciones y certificaciones, de la cual se reclama prioridad en esta solicitud de patente.

2. Ruego a la Señora Jefe se sirva aceptar este escrito con sus anexos, y se continúe con el trámite de la solicitud.

Bogotá, 18 AGO. 2000
Señora Jefe,



EMILIO FERRERO
T.P.A. No. 31.929

COLO 09369-801-003-56
WJR JJC-ID-19



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Bescheinigung

Certificate

Attestation

Die angehefteten Unterlagen stimmen mit der ursprünglich eingereichten Fassung der auf dem nächsten Blatt bezeichneten europäischen Patentanmeldung überein.

The attached documents are exact copies of the European patent application described on the following page, as originally filed.

Les documents fixés à cette attestation sont conformes à la version initialement déposée de la demande de brevet européen spécifiée à la page suivante.

Patentanmeldung Nr. Patent application No. Demande de brevet n°

99500090.8

Der Präsident des Europäischen Patentamts;
Im Auftrag

For the President of the European Patent Office

Le Président de l'Office européen des brevets
p.o.

I.L.C. HATTEN-HECKMAN

DEN HAAG, DEN
THE HAGUE, 25/05/00
LA HAYE, LE



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Blatt 2 der Bescheinigung
Sheet 2 of the certificate
Page 2 de l'attestation

Anmeldung Nr.:
Application no.:
Demande n°: 99500090.8

Anmeldetag:
Date of filing: 03/06/99
Date de dépôt:

Anmelder:
Applicant(s):
Demandeur(s):
LILLY S.A.
E-28100 Alcobendas Madrid
SPAIN

Bezeichnung der Erfindung:
Title of the invention:
Titre de l'invention:
Excitatory amino acid receptor modulators

In Anspruch genommene Priorität(en) / Priority(ies) claimed / Priorité(s) revendiquée(s)

Staat:	Tag:	Aktenzeichen:
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Bemerkungen:
Remarks:
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EXCITATORY AMINO ACID RECEPTOR MODULATORS

In the mammalian central nervous system (CNS), the transmission of nerve impulses is controlled by the interaction between a neurotransmitter, that is released by a sending neuron, and a surface receptor on a receiving neuron, which causes excitation of this receiving neuron. L-Glutamate, which is the most abundant neurotransmitter in the CNS, mediates the major excitatory pathway in mammals, and is referred to as an excitatory amino acid (EAA). The receptors that respond to glutamate are called excitatory amino acid receptors (EAA receptors). See Watkins & Evans, *Ann. Rev. Pharmacol. Toxicol.*, 21, 165 (1981); Monaghan, Bridges, and Cotman, *Ann. Rev. Pharmacol. Toxicol.*, 29, 365 (1989); Watkins, Krogsgaard-Larsen, and Honore, *Trans. Pharm. Sci.*, 11, 25 (1990). The excitatory amino acids are of great physiological importance, playing a role in a variety of physiological processes, such as long-term potentiation (learning and memory), the development of synaptic plasticity, motor control, respiration, cardiovascular regulation, and sensory perception.

Excitatory amino acid receptors are classified into two general types. Receptors that are directly coupled to the opening of cation channels in the cell membrane of the neurons are termed "ionotropic". This type of receptor has been subdivided into at least three subtypes, which are defined by the depolarizing actions of the selective agonists *N*-methyl-D-aspartate (NMDA), α -amino-3-hydroxy-5-methylisoxazole-4-propionic acid (AMPA), and kainic acid

(KA). The second general type of receptor is the G-protein or second messenger-linked "metabotropic" excitatory amino acid receptor. This second type is coupled to multiple second messenger systems that lead to enhanced

5 phosphoinositide hydrolysis, activation of phospholipase D or C, increases or decreases in c-AMP formation, and changes in ion channel function. Schoepp and Conn, *Trends in Pharmacol. Sci.*, 14, 13 (1993). Both types of receptors appear not only to mediate normal synaptic transmission
10 along excitatory pathways, but also participate in the modification of synaptic connections during development and throughout life. Schoepp, Bockaert, and Sladeczek, *Trends in Pharmacol. Sci.*, 11, 508 (1990); McDonald and Johnson, *Brain Research Reviews*, 15, 41 (1990).

15 The excessive or inappropriate stimulation of excitatory amino acid receptors leads to neuronal cell damage or loss by way of a mechanism known as excitotoxicity. This process has been suggested to mediate neuronal degeneration in a variety of conditions. The
20 medical consequences of such neuronal degeneration makes the abatement of these degenerative neurological processes an important therapeutic goal.

The metabotropic glutamate receptors are a highly heterogeneous family of glutamate receptors that are linked
25 to multiple second-messenger pathways. These receptors function to modulate the presynaptic release of glutamate, and the postsynaptic sensitivity of the neuronal cell to glutamate excitation. Compounds which modulate the function of these receptors, in particular agonists and antagonists
30 of glutamate, are useful for the treatment of acute and

chronic neurodegenerative conditions, and as antipsychotic, anticonvulsant, analgesic, anxiolytic, antidepressant, and anti-emetic agents.

Pellicciari et al., J. Med. Chem., 1996, 39, 2259-2269 refers to compounds known as metabotropic glutamate receptor agonists, in particular (2S, 1'S, 2'S)-2-(2-carboxycyclopropyl)glycine, also known as L-CCG-I; (2S, 1'S, 2'R, 3'R)-2-(2'-carboxy-3'-(methoxymethyl)cyclopropylglycine, also known as cis-MCG-I; (2S, 1'S, 2'R, 3'S)-2-(2'-carboxy-3'-(methoxymethyl)cyclopropylglycine, also known as trans-MCG-I; and (2S, 1'R, 2'R, 3'R)-2-(2',3'-dicarboxycyclopropyl)glycine, also known as DCG-IV. The paper also describes the synthesis of the sixteen possible stereoisomers of 2-(2'-carboxy-3'-phenylcyclopropyl)glycine and their evaluation as excitatory amino acid receptor ligands. The compound (2S, 1'S, 2'S, 3'R)-2-(2'-carboxy-3'-phenylcyclopropyl)glycine, also known as PCCG 4 is reported to be a metabotropic glutamate receptor antagonist.

Japanese patent application publication number JP 06179643 discloses MCG and generically discloses (2S, 1'S, 2'R)-2-(2-carboxy-3-alkoxymethyl- and 3-alkoxymethylcyclopropyl)glycines as glutamate receptor agonists.

International patent application publication number WO 97/19049 discloses PCCG 4 and also generically discloses various 2-carboxy-3-aryl cyclopropylglycines having affinity for metabotropic glutamate receptors.

International patent application publication number WO 98/00391 discloses 2-carboxy-3,3-dihalocyclopropylglycines, including (2S, 1'S, 2'S)-2-(2-carboxy-3,3-difluoro)-

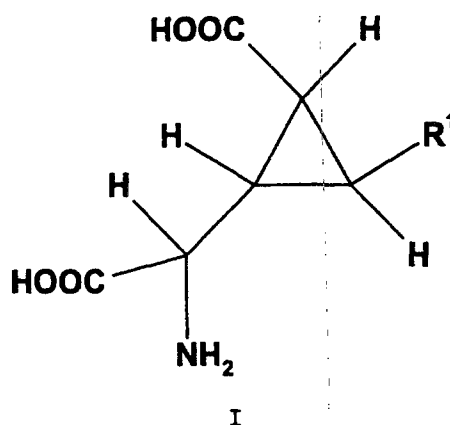
cyclopropylglycine as metabotropic glutamate receptor agonists.

European patent application, publication number EP-A1-0870760 discloses that certain 3-substituted 2-

5 carboxycyclopropyl glycine derivatives are modulators of metabotropic glutamate receptor function. The preferred compounds are said to be those in which the substituents at the 1 and 2 positions are in a trans relationship. The examples illustrate such compounds in which the substituents
10 at the 1 and 3 positions are also in a trans relationship. One such compound is (2S, 1'S, 2'S, 3'S)-2'-carboxy-3'-methylcyclopropylglycine.

Surprisingly, novel 3-substituted 2-carboxycyclopropyl glycine derivatives have now been found which are potent
15 agonists of glutamate at metabotropic glutamate receptors.

Accordingly, the present invention provides a compound of the formula:



20 in which:

R¹ is halo-C₁₋₁₀ alkyl; halo-C₂₋₁₀ alkenyl; or (CH₂)_nY in which n is 1 or 2 and Y is OH, CN, N₃, OR³, S(O)_pR⁴, NH₂, NHR⁵, NR⁶R⁷, NHCOR⁸, NO₂, CO₂H, CONHR⁹, 1H-tetrazol-5-yl or PO₃H₂; R³, R⁵, R⁶, R⁷, R⁸ and R⁹ are each selected

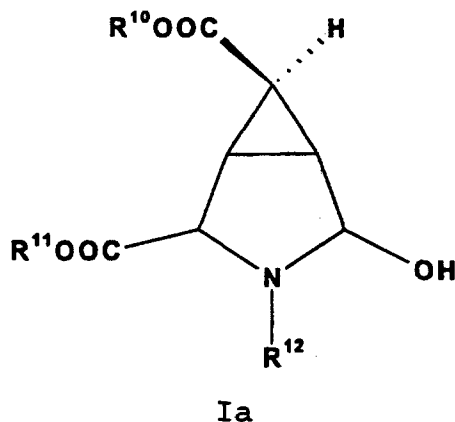
25 independently from C₁₋₄ alkyl, aryl and aryl-C₁₋₄ alkyl; R⁴

is selected from hydrogen, C₁₋₄ alkyl, aryl, aryl-C₁₋₄ alkyl and 1H-tetrazol-5-yl-C₁₋₄ alkyl; and p is 0, 1, 2 or 3; or a salt or ester thereof, provided that R¹ is not methoxymethyl.

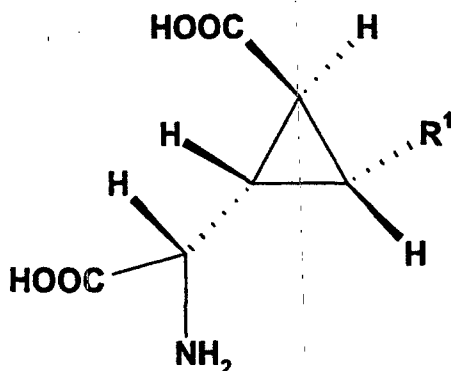
Compounds of the invention have been found to be agonists of glutamate at metabotropic glutamate receptors and are therefore useful in the treatment of diseases of the central nervous system such as neurological diseases, for example neurodegenerative diseases, and as antipsychotic, anxiolytic, drug-withdrawal, antidepressant, anticonvulsant, analgesic and anti-emetic agents.

It will be appreciated that the compounds of formula (I) contain at least four asymmetric carbon atoms, three being in the cyclopropane ring and one being at the α -carbon of the amino acid group. Accordingly, the compounds of the invention may exist in and be isolated in enantiomerically pure form, in racemic form, or in a diastereoisomeric mixture.

Preferred compounds of the invention are those of the formula



The amino acid moiety preferably has the natural amino configuration. Accordingly, preferred compounds according to the invention are those of the formula:-



Ib

As used herein, the term halogen atom, as such or as halo, for example as in haloalkyl, includes a fluorine or chlorine atom; a C₁-10 alkyl group includes a C₁-4 alkyl group and can be straight or branched chain, such as, for example, methyl, ethyl, propyl, isopropyl, butyl and isobutyl, and is preferably methyl or ethyl. A C₂-10 alkenyl group includes, for example, vinyl, prop-2-enyl, but-3-enyl, pent-4-enyl and isopropenyl, and an alkenyl group can contain more than one double bond and, in addition, one or more triple bonds. A preferred alkenyl group is of the formula R'-CH=CH-(CH₂)_r- where R' is hydrogen or C₁-4 alkyl and r is 0, 1 or 2. An aryl group, as such or in an aryl-C₁-4 alkyl may be, for example, a phenyl group which is unsubstituted or substituted, for example with one or two substituents selected independently from halogen, C₁-4 alkyl and C₁-4 alkoxy. An example of an aryl group is phenyl. An example of an aryl-C₁-4 alkyl group is benzyl.

Examples of particular values for R^1 are:-

for a halo- C_{1-10} alkyl group: fluoromethyl; trifluoromethyl; trifluoroethyl; chloromethyl; trichloroethyl; 2-trichloroethyl and 2-fluoroethyl;

for a halo- C_{2-10} alkenyl group: 2-fluorovinyl and 2,2-difluorovinyl;

for a $(CH_2)_nY$ group: hydroxymethyl, cyanomethyl, 2-cyanoethyl, azidomethyl, 2-azidoethyl, 2-methoxyethyl, mercaptomethyl; methanethiomethyl, 2-methanethioethyl, 1H-tetrazol-5-ylthiomethyl, methanesulfinylmethyl, 2-methanesulfinylethyl, methanesulfonylmethyl, 2-methanesulfonylethyl, aminomethyl, acetylaminomethyl, nitromethyl, 1H-tetrazol-5-ylmethyl, carboxymethyl, 2-carboxyethyl, methylcarboxamide, phosphonomethyl, acetamidomethyl and benzamidomethyl.

Examples of particular values for R^3 , R^5 , R^6 , R^7 , R^8 and R^9 are:

for a C_{1-4} alkyl group: methyl or ethyl;

for an aryl group: phenyl; and

for an aryl- C_{1-4} alkyl group: benzyl.

Examples of particular values for R^4 are:

for a C_{1-4} alkyl group: methyl;

for an aryl group: phenyl;

for an aryl- C_{1-4} alkyl group: benzyl; and

for a 1H-tetrazol-5-yl- C_{1-4} alkyl group: 1H-tetrazol-5-ylmethyl.

Preferably R^1 is selected from fluoromethyl, 2-fluoroethyl, trifluoromethyl, trifluoroethyl, chloromethyl, trichloroethyl, 2-trichloroethyl, 2-fluorovinyl, 2,2-difluorovinyl, hydroxymethyl, cyanomethyl, 2-cyanoethyl,

azidomethyl, 2-azidoethyl, 2-methoxyethyl, mercaptomethyl, methanethiomethyl, 2-methanethioethyl, 1H-tetrazol-5-ylthiomethyl, methanesulfinylmethyl, 2-methanesulfinylethyl, methanesulfonylmethyl, 2-methanesulfonylethyl, aminomethyl, acetylaminomethyl, nitromethyl, 1H-tetrazol-5-ylmethyl, carboxymethyl, 2-carboxyethyl, methylcarboxamide, phosphonomethyl, acetamidomethyl or benzamidomethyl.

Especially preferred are compounds in which R^1 is hydroxymethyl.

Particularly preferred compounds are:
(2SR, 1'SR, 2'RS, 3'RS)-2-(3'-hydroxymethyl-2'-carboxy-cyclopropyl)glycine;
and pharmaceutically acceptable salts and esters thereof.

The present invention includes salts of the formula (I) compounds. These salts can exist in conjunction with the acidic or basic portion of the molecule and can exist as acid addition, primary, secondary, tertiary, or quaternary ammonium, alkali metal, or alkaline earth metal salts. Generally, the acid addition salts are prepared by the reaction of an acid with a compound of formula (I). The alkali metal and alkaline earth metal salts are generally prepared by the reaction of the hydroxide form of the desired metal salt with a compound of formula (I).

The salts of the compounds of formula I may be pharmaceutically-acceptable salts. However, other salts are included in the invention. They may serve as intermediates in the purification of compounds or in the preparation of other, for example pharmaceutically-acceptable, acid addition salts, or are useful for identification, characterisation or purification.

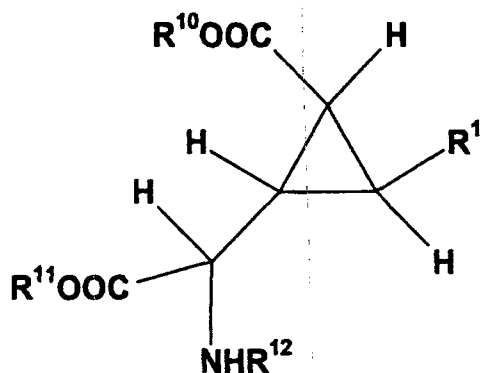
Acid addition salts are preferably the pharmaceutically acceptable, non-toxic addition salts with suitable acids, such as those with inorganic acids, for example hydrochloric, hydrobromic, nitric, sulphuric or phosphoric acids, or with organic acids, such as organic carboxylic acids, for example, glycollic, maleic, hydroxymaleic, fumaric, malic, tartaric, citric, salicyclic, o-acetoxybenzoic, or organic sulphonic, 2-hydroxyethane sulphonic, toluene-p-sulphonic, or naphthalene-2-sulphonic acid.

The present invention includes esters of the formula (I) compounds, such esters being for example aliphatic esters such as alkyl esters.

The esters of the compounds of formula I may be pharmaceutically acceptable metabolically labile esters of compounds of formula I. These are ester derivatives of compounds of formula I that are hydrolyzed in vivo to afford said compound of formula I and a pharmaceutically acceptable alcohol. Examples of metabolically labile esters include esters formed with (1-6C) alkanols in which the alkanol moiety may be optionally substituted by a (1-8C) alkoxy group, for example methanol, ethanol, propanol and methoxyethanol. The most preferred esters are alkyl esters derived from C₁₋₄ alkanols, especially methyl and ethyl esters.

The invention also comprises a process for preparing a compound according to formula (I), or a salt or ester thereof, which comprises:

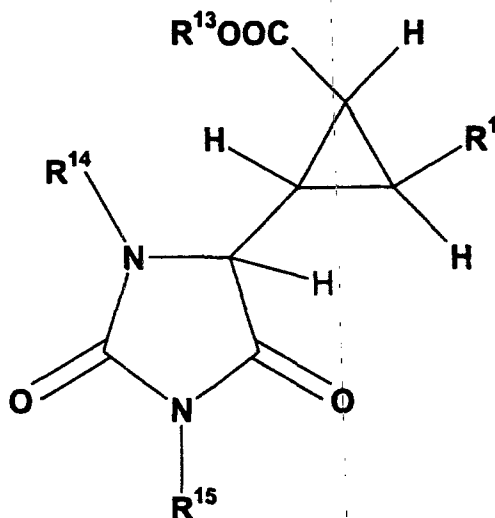
(a) deprotecting a compound of formula



II

in which R^{10} and R^{11} each independently represents hydrogen
 5 or a carboxyl protecting group, and R^{12} represents hydrogen
 or an amine protecting group;

(b) hydrolysing a compound of formula



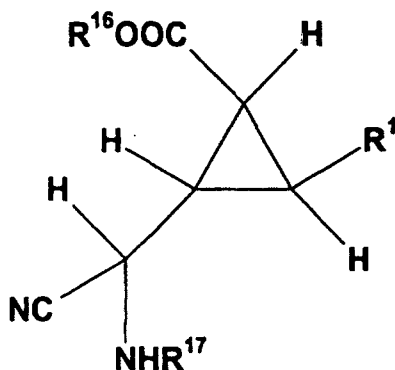
III

10

in which R^{13} represents a hydrogen atom or a carboxyl
 protecting group, and R^{14} and R^{15} each independently
 represents a hydrogen atom, a C_{1-4} alkyl group, or a phenyl
 15 C_{1-4} alkyl group in which the phenyl group is unsubstituted

or substituted by halo, C₁₋₄ alkyl, C₁₋₄ alkoxy or C₃₋₄ alkenyl; or

(c) hydrolysing a compound of formula



IV

in which R¹⁶ represents a hydrogen atom or a carboxy protecting group, and R¹⁷ represents a hydrogen atom or an amine protecting group;

followed when necessary by recovering a diastereomer or isomer of the compound, or

forming a salt or ester thereof.

The protection of carboxylic acid groups is described in McOmie, Protecting Groups in Organic Chemistry, Plenum Press, NY, 1973, and Greene and Wuts, Protecting Groups in Organic Synthesis, 2nd. Ed., John Wiley & Sons, NY, 1991.

Examples of carboxy protecting groups include C₁-C₆ alkyl groups such as methyl, ethyl, t-butyl and t-amyl; aryl(C₁-C₄)alkyl groups such as benzyl, 4-nitrobenzyl, 4-

methoxybenzyl, 3,4-dimethoxybenzyl, 2,4-dimethoxybenzyl, 2,4,6-trimethoxybenzyl, 2,4,6-trimethylbenzyl, benzhydryl and trityl; silyl groups such as trimethylsilyl and t-butyldimethylsilyl; and allyl groups such as allyl and 1-(trimethylsilylmethyl)prop-1-en-3-yl.

Examples of amine protecting groups include acyl groups, such as groups of formula $R^{18}CO$ in which R^{18} represents C_{1-6} alkyl, C_{3-10} cycloalkyl, phenyl C_{1-6} alkyl, phenyl, C_{1-6} alkoxy, phenyl C_{1-6} alkoxy, or a C_{3-10} cycloalkoxy, wherein a phenyl group may be optionally substituted, for example by one or two of halogen, C_1-C_4 alkyl and C_1-C_4 alkoxy. Preferred amino protecting groups include t-butoxycarbonyl (Boc) and benzyl.

Examples of particular values for R^{10} , R^{11} , R^{13} and R^{16} are hydrogen, methyl, ethyl, n-propyl, n-butyl, t-butyl, benzyl, 4-methoxybenzyl, phenylethyl and phenylpropyl.

Examples of particular values for R^{12} and R^{17} include acetyl and tert-butoxycarbonyl.

Examples of particular values for R^{14} and R^{15} are hydrogen and benzyl.

The compounds of formula (II) may be deprotected by conventional methods. Thus, an alkyl carboxyl protecting group may be removed by hydrolysis. The hydrolysis may conveniently be performed by heating the compound of formula (II) in the presence of either a base, for example an alkali metal hydroxide such as lithium, sodium or potassium hydroxide, or an alkaline metal hydroxide, such as barium hydroxide or an acid such as hydrochloric acid. The hydrolysis is conveniently performed at a temperature in the range of from $20^{\circ}C$ to $300^{\circ}C$. An aralkyl carboxyl protecting group may conveniently be removed by hydrogenation. The hydrogenation may be effected by reacting the compound of formula (II) with hydrogen in the presence of a Group VIII metal catalyst, for example a palladium catalyst such as palladium on charcoal. Suitable solvents for the reaction

include alcohols such as ethanol. The reaction is conveniently performed at a temperature in the range of from 0° C to 100° C.

An acyl, amine protecting group is also conveniently removed by hydrolysis, for example as described for the removal of an alkyl carboxyl protecting group. Thus, a tert-butoxycarbonyl, amine protecting group may conveniently be removed in the presence of an acid, for example hydrochloric acid or trifluoroacetic acid. The hydrolysis is performed in the presence of a solvent such as water, ethyl acetate or dichloromethane and at a temperature in the range of from 20°C to 100°C.

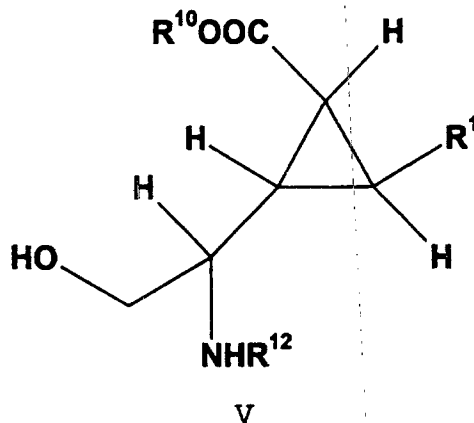
The compounds of formula III are conveniently hydrolyzed in the presence of a base, for example an alkali metal hydroxide such as lithium, sodium or potassium hydroxide, or an alkaline earth metal hydroxide such as barium hydroxide. Suitable reaction media include water. The temperature is conveniently in the range of from 50°C to 150°C.

The compounds of formula IV are conveniently hydrolyzed in the presence of an acid, such as hydrochloric acid or sulfuric acid, or a base, such as an alkali metal hydroxide, for example sodium hydroxide. The hydrolysis is conveniently performed in an aqueous solvent such as water, or in an alkanol such as methanol or ethanol, and at a temperature in the range of from 20°C to 200°C.

Compounds of formula I in the form of diastereomeric mixtures or isomers may be obtained in a conventional manner, for example by chiral synthesis using chiral

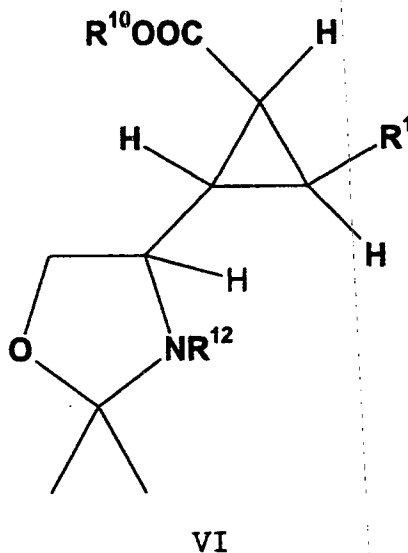
starting materials, or by using conventional separation techniques, for example by forming a crystalline salt with a chiral acid or base.

Compounds of formula (II) in which R^2 and R^{11} each represents hydrogen may be prepared by a procedure analogous to that described in Ohfuné Y., et al., J. Med. Chem., 1996, 39, 407-423. Thus they may be prepared by reacting a compound of formula



with an oxidising agent. Convenient oxidising agents include Jones Reagent.

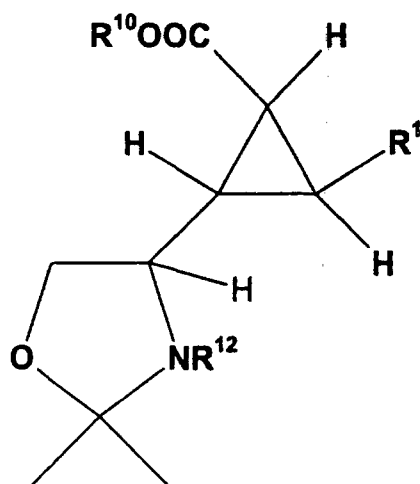
Compounds of formula (V) may be prepared by reacting a compound of formula



218

with a sulfonic acid, such as camphorsulfonic acid (CSA) and an alkanol, such as methanol.

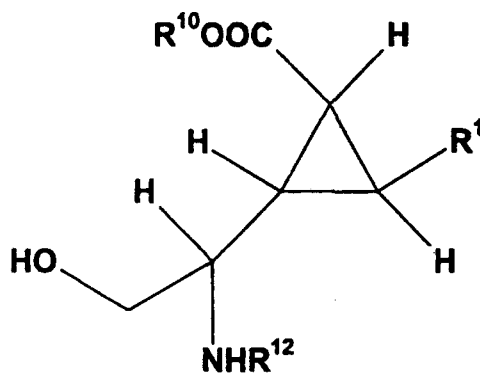
Compounds of formula (VI) may be prepared by reacting a compound of formula



VII

with a strong base, such as potassium hexamethyldisilane.

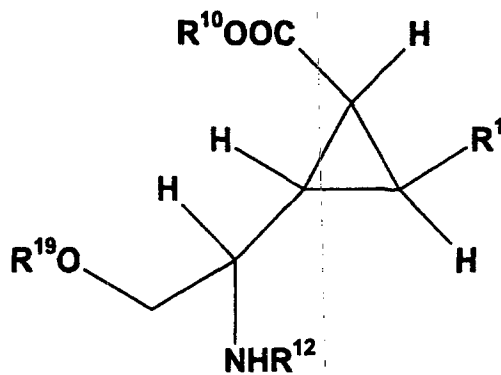
Compounds of formula (VII) may be prepared by reacting a compound of formula



VIII

with acetone dimethyl ketal in the presence of a sulfonic acid, such as camphorsulfonic acid.

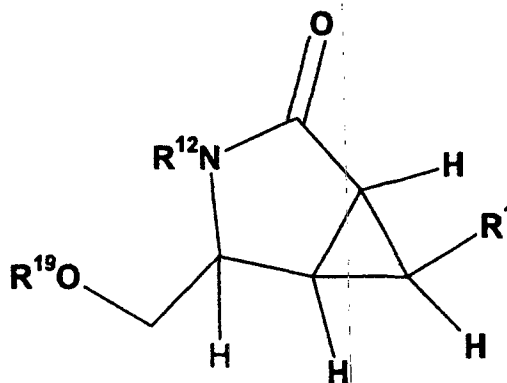
Compounds of formula VIII may be prepared by selectively deprotecting a compound of formula



IX

in which R^{19} represents a hydroxyl protecting group, such as a tert-butyldimethylsilyl (TBS) group. A convenient reagent
 5 for removing a TBS group is camphorsulfonic acid in methanol.

The compounds of formula (IX) may be prepared by reacting a compound of formula

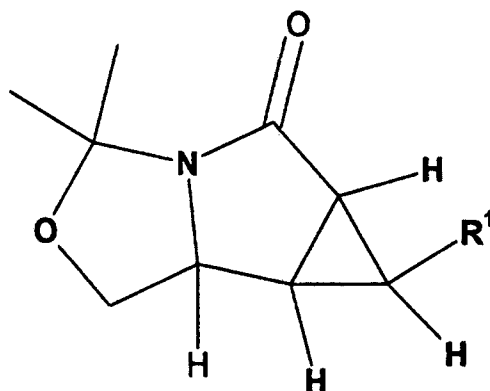


X

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with a base, such as lithium hydroxide, for example in tetrahydrofuran, followed by introduction of the protecting group R^{10} , for example by treatment with diazomethane (to afford a compound in which R^{10} is methyl).

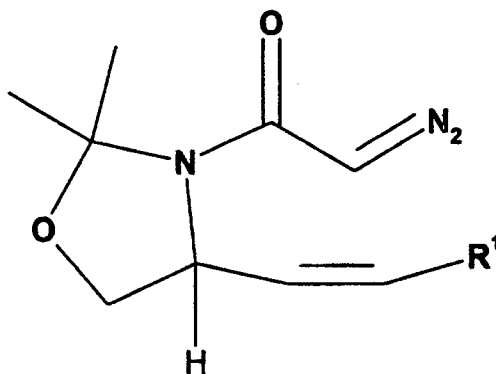
15 Compounds of formula (X) may be prepared by treating a compound of formula



XI

with an ion exchange resin, such as DOWEX 50Wx8, followed by introduction of the protecting groups R^{12} and R^{19} , for example by stepwise reaction with tributylsilyl chloride in the presence of imidazole, followed by Boc_2O in the presence of triethylamine and 4-dimethylaminopyridine.

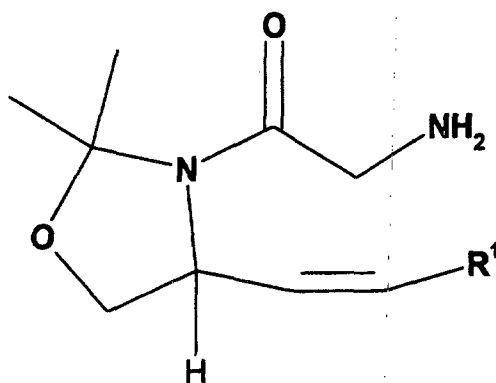
Compounds of formula (XI) may be prepared by reacting a compound of formula



XII

with palladium (II) acetate.

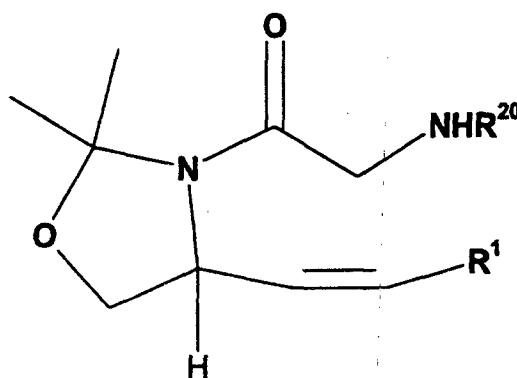
Compounds of formula (XII) may be prepared by diazotizing a compound of formula



XIII

for example by reaction with sodium nitrite.

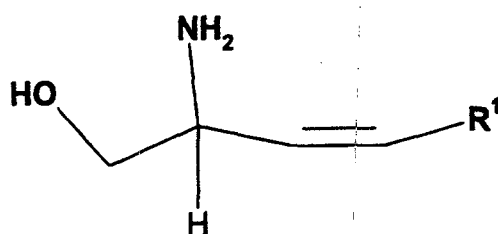
Compounds of formula (XIII) may be prepared by
5 selectively deprotecting a compound of formula



XIV

in which R^{20} represents an amine protecting group, such as
t-butoxycarbonyl. For example a t-butoxycarbonyl (Boc) group
10 may conveniently be removed by treatment with trimethylsilyl
trifluoromethanesulfonate (TMSOTf) and 2,6-lutidine.

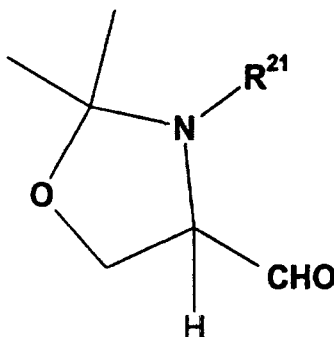
The compounds of formula (XIV) may be prepared by
reacting a compound of formula



XV

with an N-protected glycinate, such as *N*-hydroxysuccinimide *N*-(*tert*-butoxycarbonyl)glycinate, followed by reaction with acetone dimethylketal in the presence of a sulfonic acid such as *p*-toluenesulfonic acid.

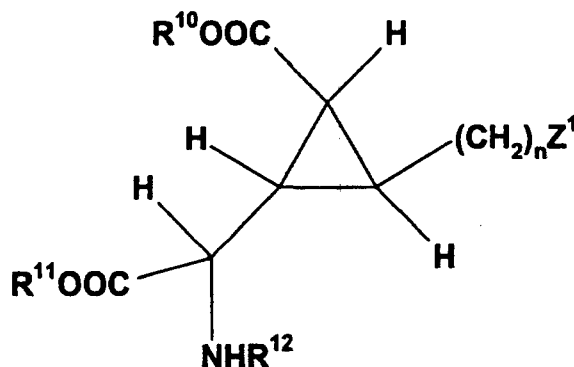
- 5 The compounds of formula (XV) may be prepared by reacting a compound of formula



XVI

- in which R^{21} represents an amine protecting group, such as
 10 *t*-butoxycarbonyl, with a triphenylphosphine halide of formula $Ph_3P^+CH_2R^1 A^-$, in which A^- represents a halide ion such as bromide, in the presence of a strong base, such as potassium hexamethyldisilane, followed by removal of the amine protecting group, and hydrolysis of the acetonide, for
 15 example by reaction with methanolic HCl.

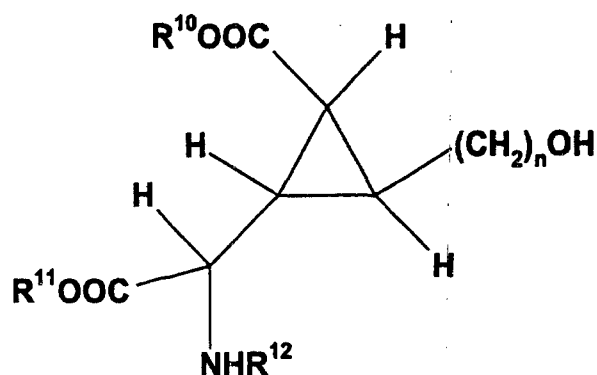
Compounds of formula (II) in which R^2 represents hydrogen and R^1 represents $(CH_2)_nY$ in which n is 1 or 2 may alternatively be prepared by reacting a compound of formula



XVII

13 in which n is 1 or 2 and Z^1 represents a leaving atom or group, such as a chlorine atom or a p-toluenesulfonyl group, with a salt of formula MY in which M represents an alkali metal such as sodium or potassium.

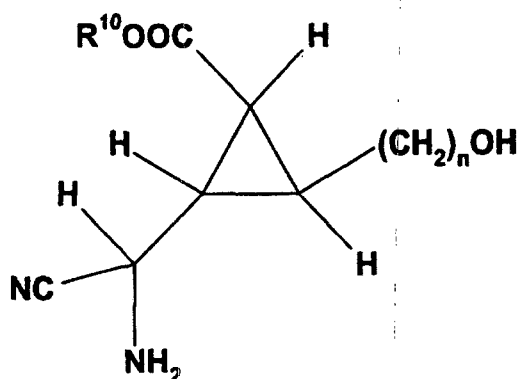
- 5 The compounds of formula (XVII) may be prepared by reacting a compound of formula



XVIII

- 10 with a halogenating or sulphonating reagent such as p-toluenesulfonyl chloride.

The compounds of formula XVIII may be prepared either by hydrolysing a compound of formula XIX

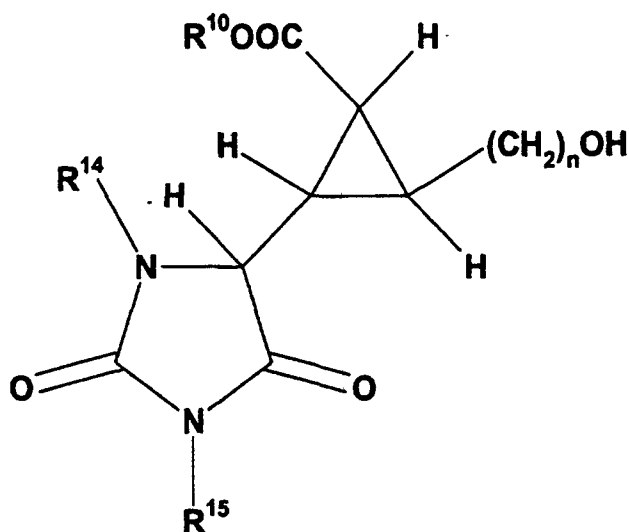


XIX

15

for example using HCl in aqueous ethanol, followed by protecting the amino group, for example by reaction with Boc_2O in tetrahydrofuran or dioxane in the presence of $NaHCO_3$,

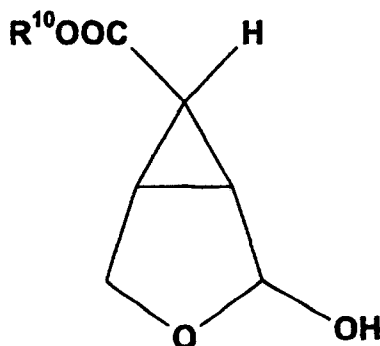
or by hydrolysing a compound of formula XX



XX

- 5 in the presence of a base, for example sodium hydroxide, in an aqueous solution at an elevated temperature, for example about 100°C, followed by protecting the carboxylic acid groups, for example using HCl in anhydrous ethanol, and protecting the amino group, for example by reaction with
- 10 Boc_2O in tetrahydrofuran or dioxane in the presence of NaHCO_3 .

The compounds of formula XIX may be prepared by reacting a compound of formula XXI

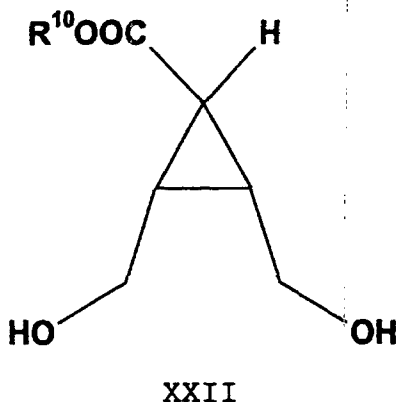


XXI

14
with ammonium chloride and potassium cyanide in the presence of aluminium oxide. A convenient solvent is acetonitrile.

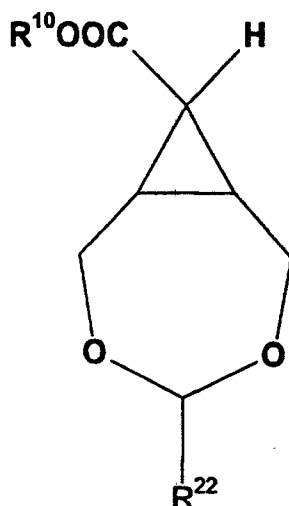
The compounds of formula XX may be prepared by hydrolysing a compound of formula XXI with an alkali metal hydroxide, for example using sodium hydroxide in aqueous ethanol, followed by treatment with an alkali metal cyanide, such as lithium, sodium or potassium cyanide, and ammonium carbonate in an aqueous alcohol, such as aqueous ethanol. Conveniently the reaction is performed at a temperature of
10 from 35°C to 150°C.

Compounds of formula XXI may be prepared by oxidising a compound of formula XXII



15 for example by employing a Swern oxidation.

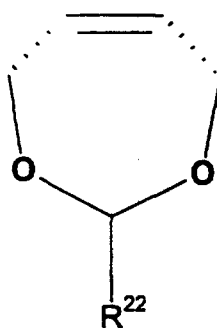
Compounds of formula XXII may be prepared by reacting a compound of formula

223
22.2

XXIII

in which R^{22} represents a hydrogen atom, a C_{1-4} alkyl group or a phenyl group, with HCl or camphorsulphonic acid in an
 5 alkanol such as ethanol.

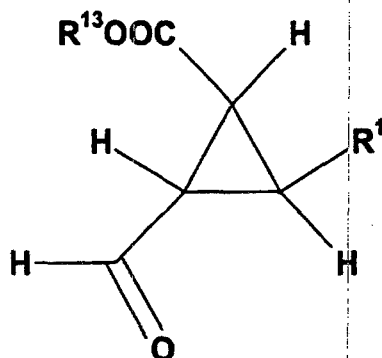
Compounds of formula XXIII may be prepared by reacting a compound of formula



XXIV

10 with $N_2CHCO_2R^{10}$ in the presence of $Rh_2(OAc)_4$. A convenient solvent is pentane.

The compounds of formula (III) may be prepared by reacting a compound of formula



XXV

with an alkali metal cyanide, such as lithium, sodium or potassium cyanide, and ammonium carbonate in an aqueous alcohol, such as aqueous ethanol. Conveniently the reaction is performed at a temperature of from $35^{\circ}C$. to $150^{\circ}C$. If desired, the compounds of formula (III) may then be alkylated, for example using a compound of formula $R^{14}Cl$ or $R^{15}Cl$. The alkylated compounds are readily separated into their diastereomers.

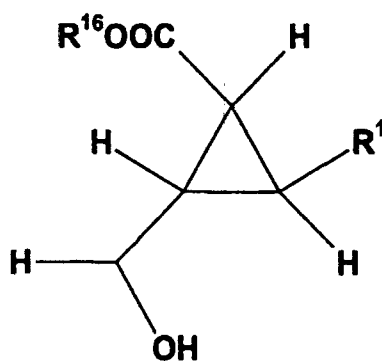
Compounds of formula (IV) may be prepared by reacting a compound of formula (XXV), in which R^{16} is as defined for R^{13} , with an alkali metal cyanide, such as lithium, sodium or potassium cyanide, and an ammonium halide, such as ammonium chloride. It has been found advantageous to perform the reaction in the presence of ultrasound. Thus, the ammonium halide and alkali metal cyanide are advantageously mixed with chromatography grade alumina in the presence of a suitable diluent, such as acetonitrile. The mixture is then irradiated with ultrasound, whereafter the compound of formula XXV is added, and the mixture is again irradiated.

The resultant mixture of diastereoisomeric aminonitriles may then be reacted with an acylating agent, such as acetyl chloride in the presence of a suitable base,

22A
223

for example an amine such as diisopropylamine, and in the presence of a suitable solvent such as dichloromethane, to afford a mixture of diastereomeric acylaminonitriles. The desired stereoisomer may conveniently be separated from this mixture, for example by chromatography.

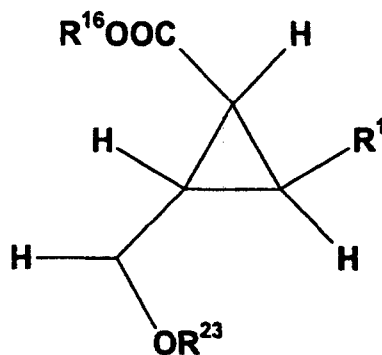
The compounds of formula (XXV) may be prepared by oxidising a compound of formula



XXVI

for example by a Swern oxidation.

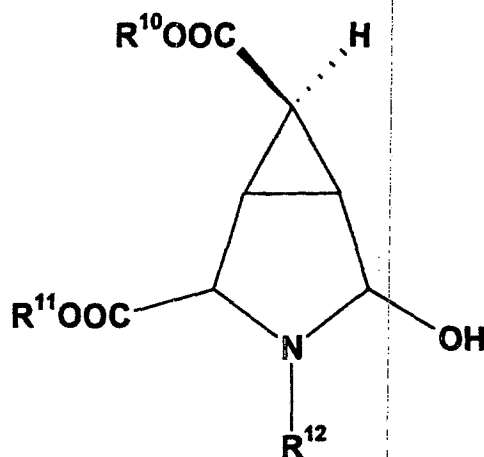
The compounds of formula (XXVI) may be prepared by selectively deprotecting a compound of formula



XXVII

in which R^{23} represent a hydroxyl protecting group, for example a benzyl group. The deprotection may be performed in a conventional manner. For example, a benzyl group may be removed by catalytic hydrogenation using palladium on charcoal as catalyst.

Compounds of formula (II) may also be prepared by reacting a compound of formula

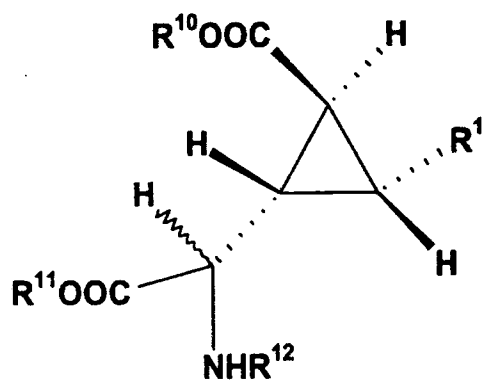


XXXII

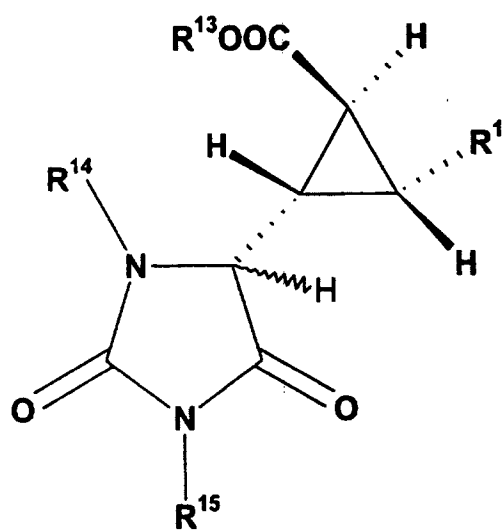
with a Wittig reagent. For example, the compound of formula (XXXII) may be reacted with an alkyl triphenylphosphonium bromide, such as methyl triphenylphosphonium bromide to afford a compound of formula (II) in which R^1 represents a haloalkenyl group, such as vinyl. The resultant product may then, if desired, be converted into another compound of formula (II), for example by catalytic hydrogenation to convert a haloalkenyl group to a haloalkyl group.

Compounds of formula (XXXII) may be prepared by Swern oxidation of a compound of formula (II) in which R^1 represents hydroxymethyl.

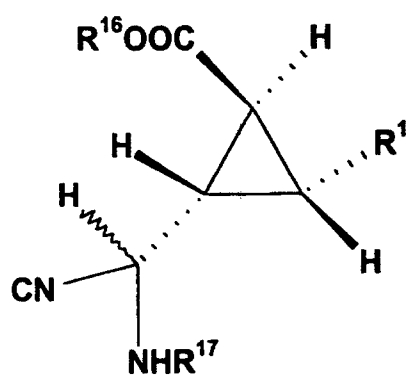
It will be appreciated that in order to obtain a compound of formula I which is in the configuration of formula Ia, the intermediates must be prepared in the appropriate configurations. The following formulae illustrate the respective configurations for each of the intermediates.



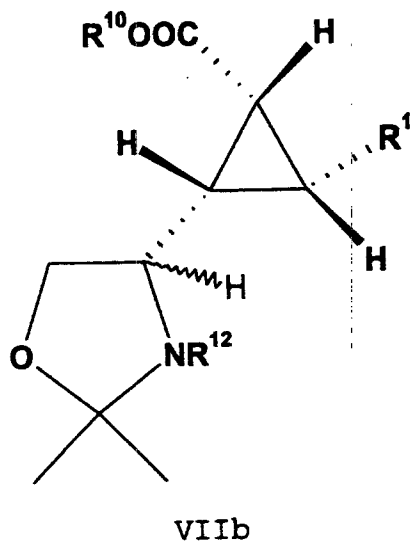
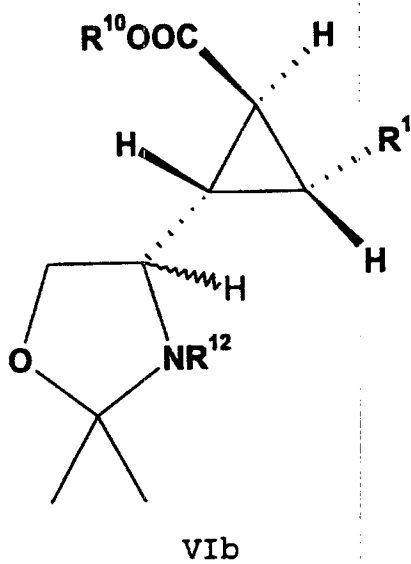
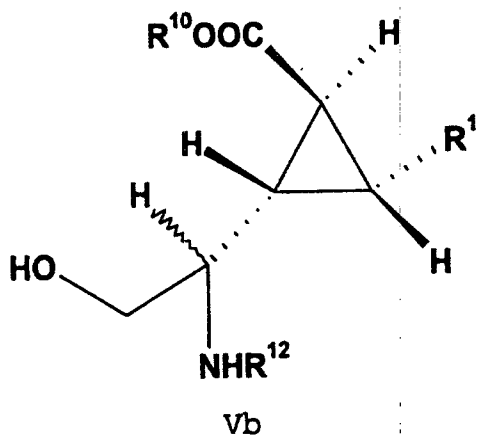
IIb

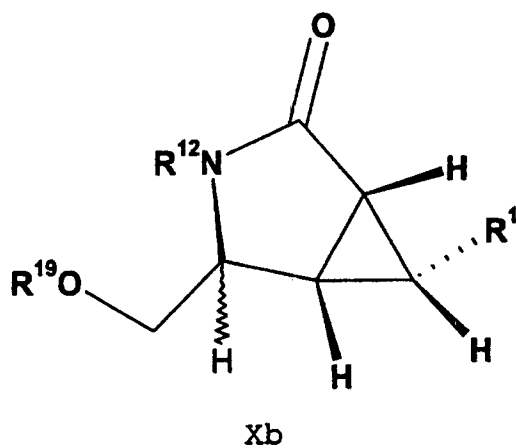
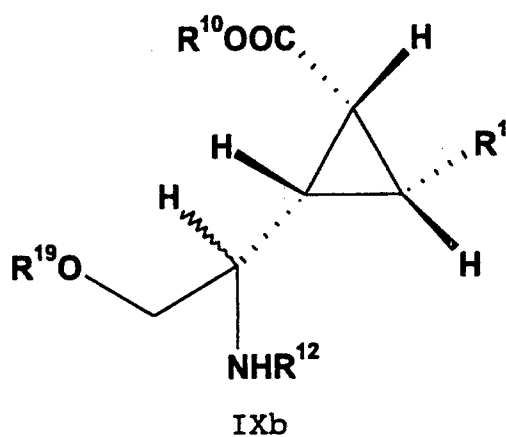
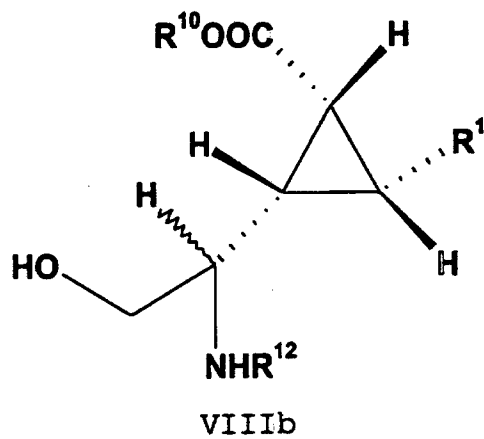


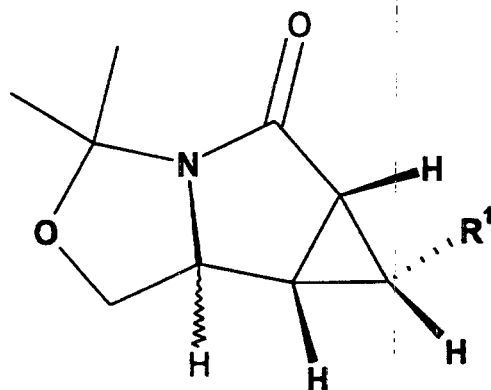
IIIb



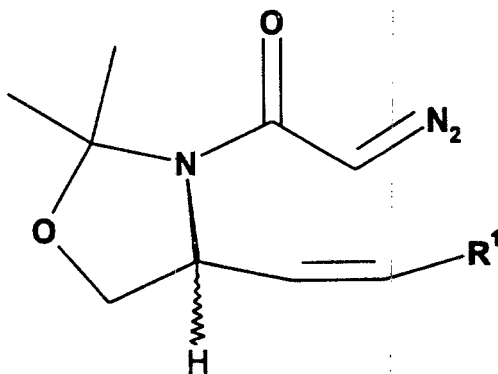
IVb



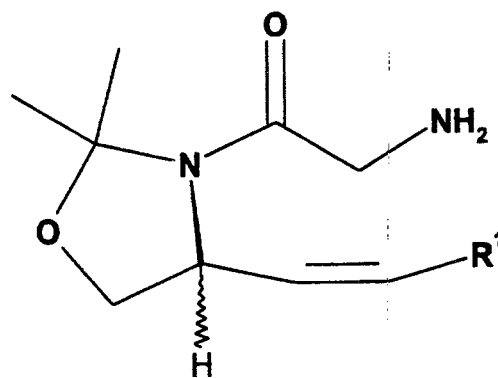




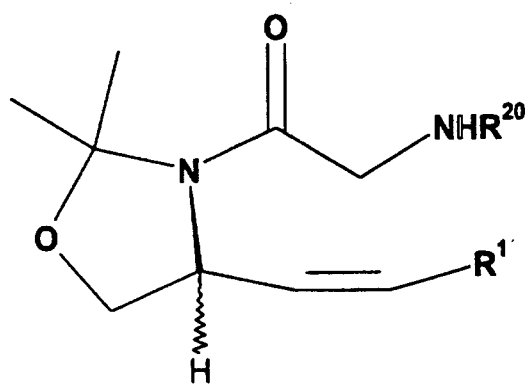
XIb



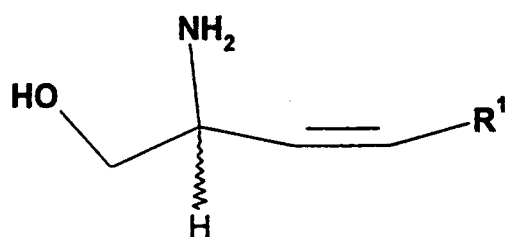
XIIb



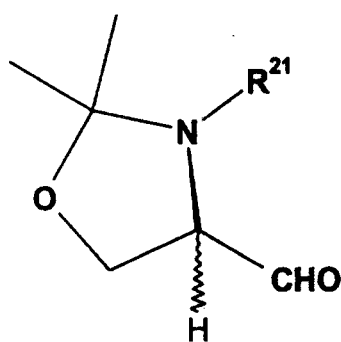
XIIIb



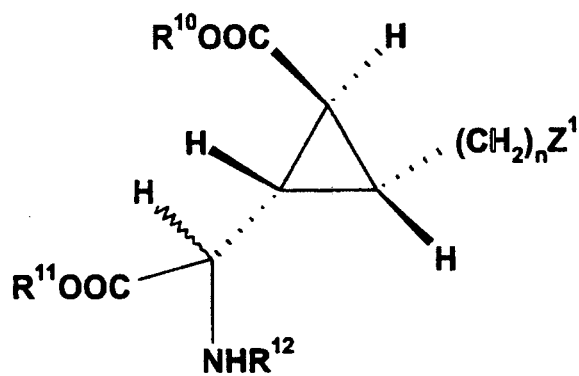
XIVb



XVb

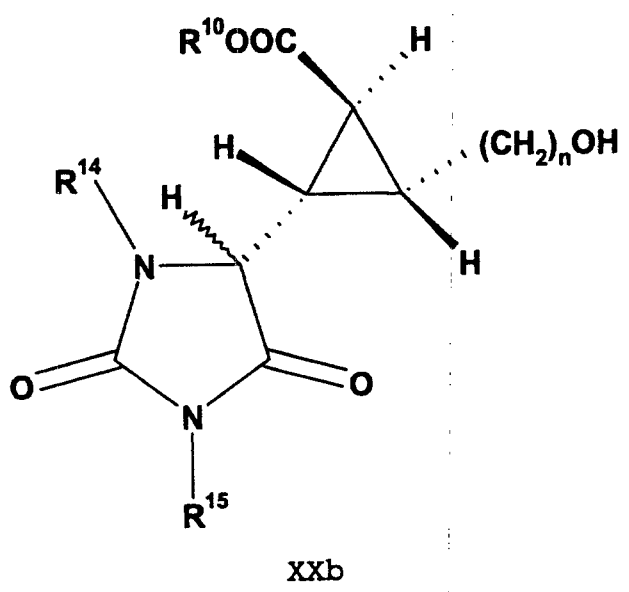
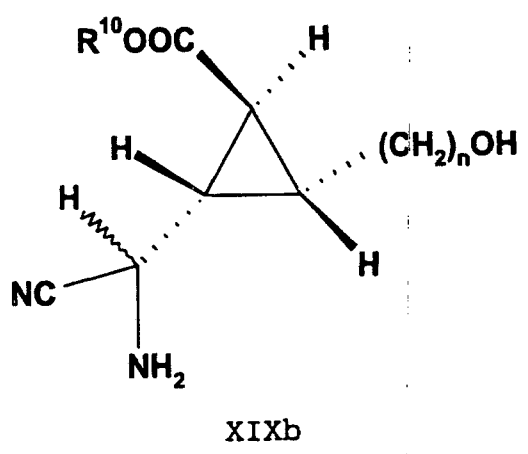
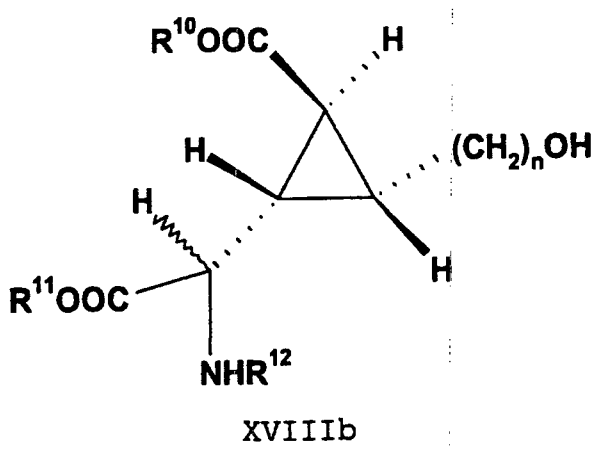


XVIb



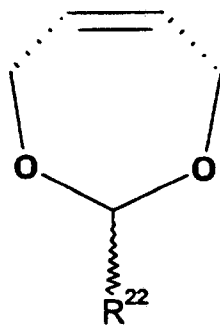
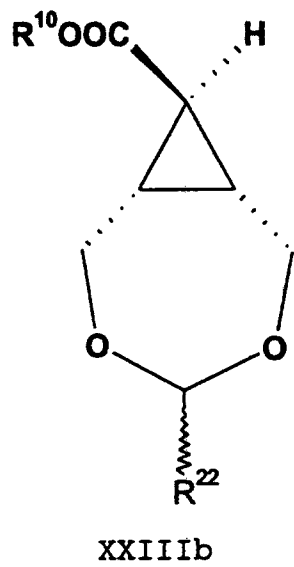
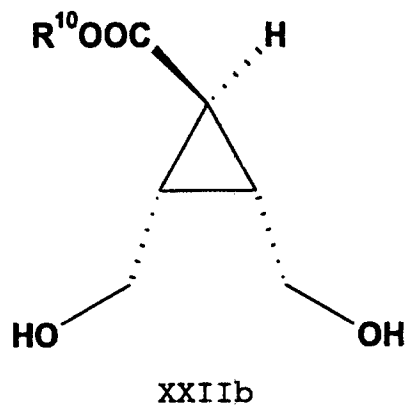
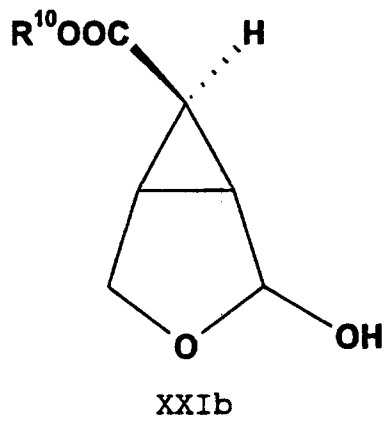
XVIIb

19.

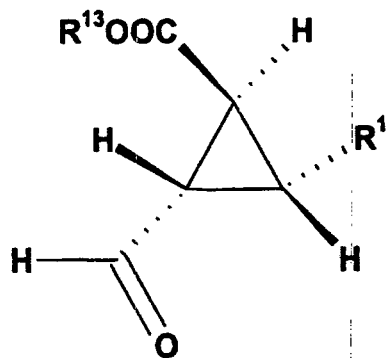


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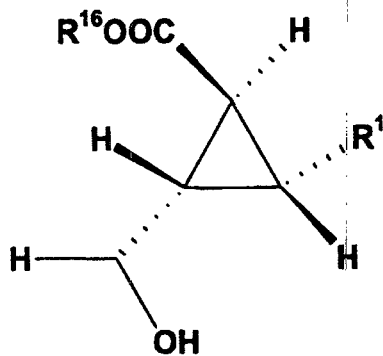
227



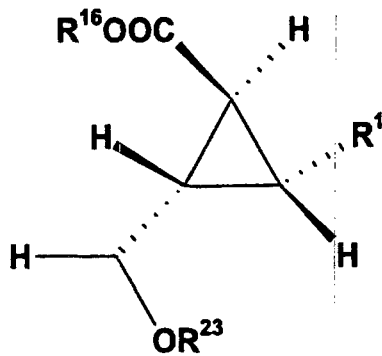
XXIVb



XXVb

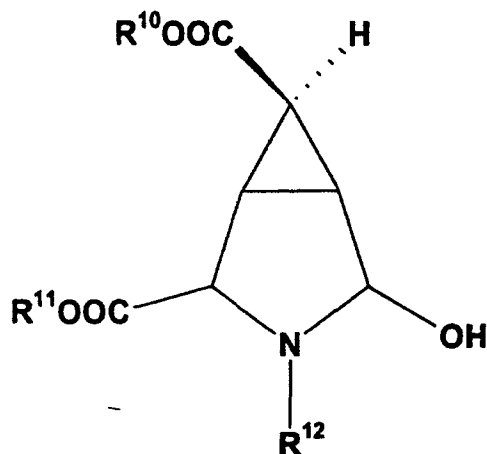


XXVIb



XXVIIb

5

229
228

XXXIIb

As described hereinabove, the compounds of the invention are useful for the treatment of disorders of the central nervous system.

According to another aspect therefore, the present invention provides a method of treating a patient suffering from or susceptible to a disorder of the central nervous system, which comprises administering an effective amount of a compound of formula I as defined hereinabove, or a pharmaceutically acceptable metabolically labile ester thereof, or a pharmaceutically acceptable salt thereof.

The particular effective amount or dose of compound administered according to this invention will of course be determined by the particular circumstances surrounding the case, including the compound administered, the route of administration, the particular condition being treated, and similar considerations. The compounds can be administered by a variety of routes including oral, rectal, transdermal, subcutaneous, intravenous, intramuscular, or intranasal routes. Alternatively, the compound may be administered by continuous infusion. A typical daily dose will contain from about 0.01 mg/kg to about 100 mg/kg of the active compound

21
of this invention. Preferably, daily doses will be about 0.05 mg/kg to about 50 mg/kg, more preferably from about 0.1 mg/kg to about 25 mg/kg.

A variety of physiological functions have been shown to be subject to influence by excessive or inappropriate stimulation of excitatory amino acid transmission. The formula I compounds of the present invention are believed to have the ability to treat a variety of neurological disorders in patients associated with this condition, including acute neurological disorders such as cerebral deficits subsequent to cardiac bypass surgery and grafting, stroke, cerebral ischemia, spinal cord trauma, head trauma, perinatal hypoxia, cardiac arrest, and hypoglycemic neuronal damage. The formula I compounds are believed to have the ability to treat a variety of chronic neurological disorders, such as Alzheimer's disease, Huntington's Chorea, amyotrophic lateral sclerosis, AIDS-induced dementia, ocular damage and retinopathy, cognitive disorders, and idiopathic and drug-induced Parkinson's. The present invention also provides methods for treating these disorders which comprises administering to a patient in need thereof an effective amount of a compound of formula I or a pharmaceutically acceptable metabolically labile ester thereof, or a pharmaceutically acceptable salt thereof.

The formula I compounds of the present invention are also believed to have the ability to treat a variety of other neurological disorders in patients that are associated with glutamate dysfunction, including muscular spasms, convulsions, migraine headaches, urinary incontinence, psychosis, (such as schizophrenia), drug tolerance and

withdrawal (such as nicotine, opiates and benzodiazepines), anxiety and related disorders, emesis, brain edema, chronic pain, and tardive dyskinesia. The formula I compounds are also useful as antidepressant and analgesic agents.

- 5 Therefore, the present invention also provides methods for treating these disorders which comprise administering to a patient in need thereof an effective amount of the compound of formula I, or a pharmaceutically acceptable metabolically labile ester thereof, or a pharmaceutically acceptable salt thereof.
- 10

The term "treating" for purposes of the present invention, includes prophylaxis, amelioration or elimination of a named condition once the condition has been established.

- 15 The term "patient" for purposes of the present invention is defined as any warm blooded animal such as, but not limited to, a mouse, guinea pig, dog, horse, or human. Preferably, the patient is human.

- According to another aspect, the present invention provides a compound of formula I as defined hereinabove, or a pharmaceutically acceptable metabolically labile ester thereof, or a pharmaceutically acceptable salt thereof, for use as a pharmaceutical.
- 20

- According to yet another aspect, the present invention provides the use of a compound of formula I as defined hereinabove, or a pharmaceutically acceptable metabolically labile ester thereof, or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for treating a disorder of the central nervous system.
- 25

22

The ability of compounds to modulate metabotropic glutamate receptor function may be demonstrated by examining their ability to influence either cAMP production (mGluR 2, 3, 4, 6, 7 or 8) or phosphoinositide hydrolysis (mGluR 1 or 5 5) in cells expressing these individual human metabotropic glutamate receptor (mGluR) subtypes. (D. D. Schoepp, et al., *Neuropharmacol.*, 1996, 35, 1661-1672 and 1997, 36, 1-11).

In these tests the compound of Example 1 of the present application was found to reverse [3H] LY341495 binding with a K_i of 55.2 nM at mGluR2.

The compounds of the present invention are preferably formulated prior to administration. Therefore, another aspect of the present invention is a pharmaceutical 15 formulation comprising a compound of formula I, a pharmaceutically acceptable metabolically labile ester thereof, or a pharmaceutically acceptable salt thereof, and a pharmaceutically-acceptable carrier, diluent, or excipient. The present pharmaceutical formulations are 20 prepared by known procedures using well-known and readily available ingredients. In making the compositions of the present invention, the active ingredient will usually be mixed with a carrier, or diluted by a carrier, or enclosed within a carrier, and may be in the form of a capsule, 25 sachet, paper, or other container. When the carrier serves as a diluent, it may be a solid, semi-solid, or liquid material which acts as a vehicle, excipient, or medium for the active ingredient. The compositions can be in the form of tablets, pills, powders, lozenges, sachets, cachets, 30 elixirs, suspensions, emulsions, solutions, syrups,

aerosols, ointments containing, for example, up to 10% by weight of active compound, soft and hard gelatin capsules, suppositories, sterile injectable solutions, and sterile packaged powders.

- 5 Some examples of suitable carriers, excipients, and diluents include lactose, dextrose, sucrose, sorbitol, mannitol, starches, gum, acacia, calcium phosphate, alginates, tragacanth, gelatin, calcium silicate, microcrystalline cellulose, polyvinylpyrrolidone, cellulose, 10 water syrup, methyl cellulose, methyl and propyl hydroxybenzoates, talc, magnesium stearate, and mineral oil. The formulations can additionally include lubricating agents, wetting agents, emulsifying and suspending agents, preserving agents, sweetening agents, or flavoring agents.
- 15 Compositions of the invention may be formulated so as to provide quick, sustained, or delayed release of the active ingredient after administration to the patient by employing procedures well known in the art.

- The compositions are preferably formulated in a unit 20 dosage form, each dosage containing from about 5 mg to about 500 mg, more preferably about 25 mg to about 300 mg of the active ingredient. The term "unit dosage form" refers to a physically discrete unit suitable as unitary dosages for human subjects and other mammals, each unit containing a 25 predetermined quantity of active material calculated to produce the desired therapeutic effect, in association with a suitable pharmaceutical carrier, diluent, or excipient. The following formulation examples are illustrative only and are not intended to limit the scope of the invention in any 30 way.

Formulation 1

Hard gelatin capsules are prepared using the following ingredients:

5		
		Quantity (mg/capsule)
10	Active Ingredient	250
	Starch, dried	200
	Magnesium stearate	<u>10</u>
15	Total	460 mg

The above ingredients are mixed and filled into hard gelatin capsules in 460 mg quantities.

Formulation 2

Tablets each containing 60 mg of active ingredient are made
as follows:

5

10

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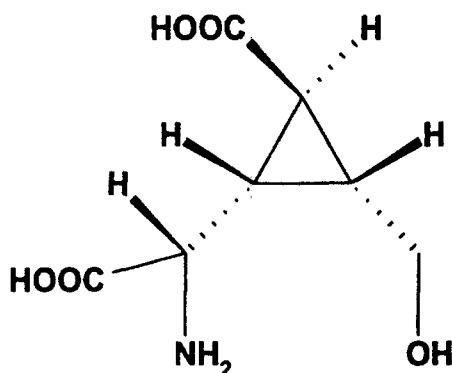
Active Ingredient	60 mg
Starch	45 mg
Microcrystalline cellulose	35 mg
Polyvinylpyrrolidone	4 mg
Sodium carboxymethyl starch	4.5 mg
Magnesium stearate	0.5 mg
Talc	<u>1 mg</u>
Total	150 mg

The active ingredient, starch, and cellulose are passed
through a No. 45 mesh U.S. sieve and mixed thoroughly. The
solution of polyvinylpyrrolidone is mixed with the resultant
powders which are then passed through a No. 14 mesh U.S.
sieve. The granules so produced are dried at 50°C and
passed through a No. 18 mesh U.S. sieve. The sodium
carboxymethyl starch, magnesium stearate, and talc,
previously passed through a No. 60 mesh U.S. sieve, are then
added to the granules which, after mixing, are compressed on
a tablet machine to yield tablets each weighing 150 mg.

The following Examples illustrate the invention. In
the Examples, the term "Garner's aldehyde" signifies 1,1-

- 24
- dimethylethyl (S) or (R)-4-formyl-2,2-dimethyl-3-oxazolidine
carboxylate, Ph_3PEtBr signifies (ethyl)triphenylphosphonium
bromide, KHDMS and LiHDMS signify potassium and lithium
hexamethyldisilazane respectively, Et_2O signifies
5 diethylether, AcOEt signifies ethyl acetate, MeOH signifies
methanol, Boc signifies t-butoxycarbonyl, Et_3N signifies
triethylamine, THF signifies tetrahydrofuran, TMSOTf
signifies trimethylsilyl trifluoromethanesulfonate, $\text{Pd}(\text{OAc})_2$
signifies palladium acetate, DMF signifies
10 dimethylformamide, DMAP signifies 4-dimethylaminopyridine,
Jones Reagent signifies a solution of 1.0g of $\text{Na}_2\text{Cr}_2\text{O}_7 \cdot 2\text{H}_2\text{O}$
and 1.34 g of sulfuric acid in H_2O (total volume 5 ml), DBU
signifies 1,8-diazabicyclo[5.4.0]undec-7-ene and DME
signifies ethylene glycol dimethyl ether.

Example 1



(2SR, 1'SR, 2'RS, 3'RS)-2-(3'-hydroxymethyl-2'-
carboxycyclopropyl)glycine

a) Ethyl 2,3-dihydroxymethylcyclopropane carboxylate.

To a solution of cis-4,7-dihydro-1,3-dioxepin (4.57 g, 45.6 mmol) in pentane (25 mL) under nitrogen at room temperature, Rh₂(OAc)₄ (220 mg, 0.5 mmol) was added. To the resulting suspension vigorously stirred, a solution of ethyl diazoacetate (10.5 mL, 100 mmol) in pentane (75 mL) was added dropwise at room temperature over a period of 3-4 hours. After the addition was completed, solvent was removed under vacuo and residue was chromatographed using a gradient of AcOEt/Hexane 1:10 to 1:5 as eluent. 6.75 g of an inseparable mixture of cyclopropanated product and EtO₂CCH=CHCO₂Et was obtained. A solution of this mixture in ethanol saturated with hydrogen chloride (250 mL) was stirred overnight at room temperature. The following day, solvent was removed under vacuo and residue taken into ethanol (100 mL). This solution was neutralized with NaHCO₃ (solid), filtered and concentrated. The resulting residue was chromatographed using a gradient of AcOEt/Hexane 1:1 to 3:1 as eluent to give 4.3 g (56% yield) of diol. ¹H-NMR

25
(200MHz, CDCl₃): 1.23 (t, J=7.1 Hz, 3H), 1.49 (t, J=3.5, 1H), 1.89-2.00 (m, 2H), 2.72 (br s, 2H), 3.31-3.42 (m, 2H), 4.05-4.16 (m, 2H) and 4.10 ppm (c, J=7.1 Hz, 2H).

¹³C-NMR (50MHz, CDCl₃): 14.0, 23.8, 27.1 (2C), 60.3 (2C),
5 60.8 and 172.8 ppm.

b) Ethyl (1*RS*, 5*SR*, 6*RS*)-2-hydroxy-3-oxabicyclo[3.1.0]-hexane-6-carboxylate

To a solution of oxalyl chloride (0.38 mL, 4.48 mmol)
10 in CH₂Cl₂ (20 mL) at -78°C under nitrogen atmosphere, dimethylsulfoxide (0.66 mL, 9.33 mmol) was added and stirred for 20 minutes. To this mixture, a solution of the product of step a) (650 mg, 3.73 mL) in CH₂Cl₂ was added and reaction was stirred at the same temperature for 30 minutes.
15 Then, triethylamine (2.6 mL, 18.65 mmol) was added and mixture allowed to react at room temperature. After 30 minutes, the reaction mixture was quenched with water, the layers were separated and the aqueous layer was extracted with CH₂Cl₂ (2X). The combined organic layers were dried
20 (Na₂SO₄), filtered and evaporated to give a residue which was chromatographed using a gradient of AcOEt/Hexane 1:2 to 1:1 as eluent to give 470 mg (73% yield) of lactol. ¹H-NMR (200MHz, CDCl₃): 1.23 (t, J=7.1 Hz, 3H), 1.43 (t, J=3.3 Hz, 1H), 2.21-2.23 (m, 2H), 2.76 (d, J=3.0 Hz, 1H), 3.85 (d, J=8.7 Hz, 1H), 4.06 (d, J=8.7 Hz, 1H), 4.10 (c, J=7.1 Hz, 2H) and 5.32 (d, J=3.0 Hz, 1H). ¹³C-NMR (50MHz, CDCl₃):
25 14.1, 22.1, 25.0, 31.2, 60.8, 67.3, 97.8 and 171.9 ppm.

c) (2SR) and (2RS)-2-(1'SR, 2'RS, 3'RS)-2'-(ethoxycarbonyl)-3'-hydroxymethylcyclopropylglycinonitrile.

A suspension of ammonium chloride (2.42 g, 45.3 mmol) and neutral aluminium oxide (1.4 g) in acetonitrile (50 mL) was ultrasonicated for one hour. A solution of the product of step b) (780 mg, 4.53 mmol) in acetonitrile (20 mL) was then added and ultrasonicated for one hour. After potassium cyanide (3.54 g, 54.36 mmol) finely powdered was added, the mixture was allowed to react for 15 hours. Then, additional aluminium oxide (3.2 g) was added and the reaction mixture was ultrasonicated for 4 days. The mixture was then filtered through celite and the inorganics washed with acetonitrile to give 710 mg (78% yield) of the four possible aminonitriles as a yellow oil.

d) (Alternative 1) Ethyl (2SR, 1'SR, 2'RS, 3'RS)-N-(tert-butoxycarbonyl)-2-[2'-(ethoxycarbonyl)-3'-hydroxymethylcyclopropyl]glycinate

A solution of the product of step c) (380 mg, 1.92 mmol) in ethanol saturated with hydrogen chloride (20 mL) and H₂O (0.10 mL, 5.75 mmol) was stirred for one hour at 0°C and for 48 hours at room temperature. The following day, the solvent was removed in vacuo and the residue was dissolved in ethanol (25 mL). Then, the solution was neutralized with NaHCO₃ (solid), filtered through celite and concentrated to dryness. The resulting residue was taken into dioxane (20 mL), and a saturated aqueous solution of NaHCO₃ (5 mL) was added. Then, a solution of di-tert-butylidicarbonate (500 mg, 2.3 mmol) in dioxane (5 mL) was added and mixture stirred overnight. The layers were then separated and the aqueous

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layer was extracted with ethyl acetate (AcOEt). The combined organic layers were dried (Na_2SO_4), filtered and concentrated to dryness. The residue was purified by column chromatography using AcOEt/Hexane 1:2 as eluent to give 400
5 mg of a 1:2 mixture of diastereoisomers (61% overall yield). The minor and desired isomer (lower R_f) was separated by column chromatography using AcOEt/Hexane 1:3 as eluent giving rise to ethyl (2SR, 1'SR, 2'RS, 3'RS)-N-(tert-butoxycarbonyl)-2-[2'-(ethoxycarbonyl)-3'-hydroxymethyl-
10 cyclopropyl]glycinate as a mixture of enantiomers.

d) (Alternative 2) Ethyl (2SR, 1'SR, 2'RS, 3'RS)-N-(tert-butoxycarbonyl)-2-[2'-(ethoxycarbonyl)-3'-hydroxymethyl-cyclopropyl]glycinate

15 A solution of the product of step b) (1.8 g, 10.45 mmol) in EtOH (65 mL) and NaOH(1N) (63 mL, 63.0 mmol) was stirred at 60°C for 1 hour. The mixture was then cooled to 0°C and the pH was adjusted to ~6 by addition of 1N KHSO_4 . To the resulting solution, $(\text{NH}_4)_2\text{CO}_3$ (10.1 g, 104.5 mmol) and
20 NaCN (1.02 g, 20.9 mmol) were added. The mixture was stirred under reflux overnight (16-17 hours) and then cooled to room temperature. The solution was then evaporated to dryness under vacuo to give a residue that was taken into MeOH and filtered off. The inorganics were washed with MeOH and the
25 combined methanolic filtrates were concentrated in vacuo. The resulting residue was dissolved in 1N NaOH (200 mL) and the mixture was stirred under reflux for 48 hours and then cooled to 0°C. The pH was then adjusted to 1-2 by addition of 1N HCl, and the solvent was removed under vacuo.

The resulting residue was dissolved in a 1N HCl/ethanol solution (250 mL) and the mixture was stirred overnight at room temperature. The solvent was then removed under vacuo and the residue was taken into EtOH (200 mL). After the solvent was removed under vacuo, the residue was again taken into EtOH (200 mL) and the solution neutralized with NaHCO₃ (solid), the inorganics filtered off and the filtrate concentrated to dryness. The residue was taken into dioxane (200 mL) at room temperature and a saturated aqueous solution of NaHCO₃ (50 mL) was added. Then, a solution of di-tert-butylidicarbonate (2.75 g, 12.54 mmol) in dioxane (50 mL) was added dropwise and the mixture was vigorously stirred at room temperature overnight. The mixture was then diluted with AcOEt and the layers were separated. The aqueous layer was extracted with AcOEt (2X) and the combined organic layers were dried (Na₂SO₄), filtered and concentrated to dryness. The residue was purified by column chromatography using AcOEt/hexane (1:2) as eluent to give 2.15 g of a 2.3:1 mixture of diastereoisomers (60% overall yield). The major and desired isomer (lower R_f) was separated by column chromatography using Et₂O/Hexane 1:1 as eluent giving rise to ethyl (2SR, 1'SR, 2'RS, 3'RS)-N-(tert-butoxycarbonyl)-2-[2'-(ethoxycarbonyl)-3'-hydroxymethylclopropyl]glycinate as a mixture of enantiomers.

¹H-NMR (200MHz, CDCl₃): 1.25 (t, J=7.1 Hz, 3H), 1.32 (t, J=7.1 Hz, 3H), 1.45 (s, 9H), 1.70-1.81 (m, 2H), 1.91-2.11 (m, 1H), 3.17 (dd, J=3.1, 10.1 Hz, 1H), 3.54-3.67 (m, 1H), 3.95-4.33 (m, 6H), and 5.20 (br d, J=7.3 Hz, 1H).

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 ^{13}C -NMR (50MHz, CDCl_3): 14.0, 14.1, 22.5, 28.2 (3C), 28.9, 29.2, 52.3, 60.8, 61.0, 62.5, 80.4, 155.3, 171.8 and 172.4 ppm.

- 5 e) (2SR, 1'SR, 2'RS, 3'RS)-2-(3'-hydroxymethyl-2'-carboxycyclopropyl)glycine.

To a solution of ethyl (2SR, 1'SR, 2'RS, 3'RS)-N-(tert-butoxycarbonyl)-2-[2'-(ethoxycarbonyl)-3'-hydroxymethylcyclopropyl]glycinate (145 mg, 0.42 mmol) in
10 THF (35 mL) was added 2.5N LiOH (6.7 mL, 16.8 mmol). The mixture was vigorously stirred overnight. The organic layer was separated and discarded and the aqueous layer was washed with Et_2O . After the aqueous solution was adjusted to pH~1 by addition of 1N HCl at 0°C, it was extracted four times
15 with AcOEt, and the combined organic layers were dried over Na_2SO_4 and evaporated in vacuo. A solution of the residue in 2N HCl (35 mL) was stirred overnight. The solvent was then removed in vacuo and the resulting solid was washed with Et_2O . The hydrochloride was dissolved in MeOH (3 mL) and
20 propylene oxide (10 mL) was added. The mixture was stirred overnight and the resulting insoluble solid was filtered and washed with Et_2O to give the title compound (55 mg, 69%).

^1H -NMR (200MHz, D_2O): 1.77-2.11 (m, 3H), 3.62 (d, $J=11.0$ Hz, 1H), 3.66 (dd, $J=8.6, 12.5$ Hz, 1H) and 3.90 ppm
25 (dd, $J=6.0, 12.5$ Hz, 1H).

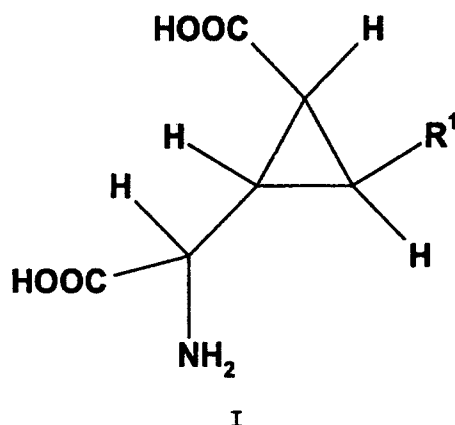
^{13}C -NMR (50MHz, D_2O): 25.0, 27.7, 29.1, 54.8, 61.0, 173.9 and 177.9 ppm.

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CLAIMS

1. A compound of the formula:

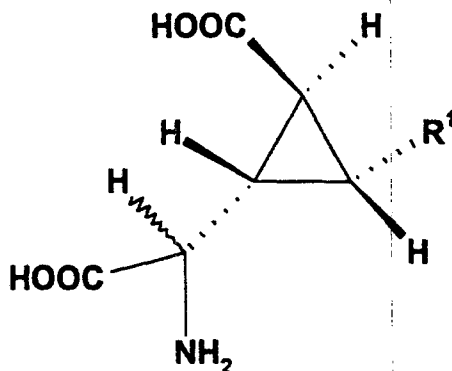
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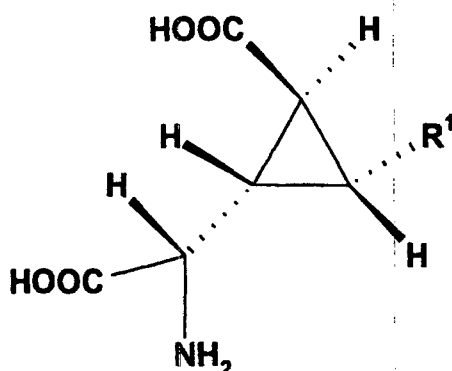
in which:

R^1 is halo- C_{1-10} alkyl; halo- C_{2-10} alkenyl; or $(CH_2)_nY$ in
 10 which n is 1 or 2 and Y is OH, CN, N_3 , OR^3 , $S(O)_pR^4$, NH_2 ,
 NHR^5 , NR^6R^7 , $NHCOR^8$, NO_2 , CO_2H , $CONHR^9$, 1H-tetrazol-5-yl or
 PO_3H_2 ; R^3 , R^5 , R^6 , R^7 , R^8 and R^9 are each selected
 independently from C_{1-4} alkyl, aryl and aryl- C_{1-4} alkyl; R^4
 is selected from hydrogen, C_{1-4} alkyl, aryl, aryl- C_{1-4} alkyl
 15 and 1H-tetrazol-5-yl- C_{1-4} alkyl; and p is 0, 1, 2 or 3;
 or a salt or ester thereof, provided that R^1 is not
 methoxymethyl.

2. A compound as claimed in Claim 1, which has the
 configuration



3. A compound as claimed in Claim 1, which has the configuration



4. A compound according to any one of Claims 1 to 3, in which R¹ is selected from fluoromethyl, 2-fluoroethyl, trifluoromethyl, trifluoroethyl, chloromethyl, trichloroethyl, 2-trichloroethyl, 2-fluorovinyl, 2,2-difluorovinyl, hydroxymethyl, cyanomethyl, 2-cyanoethyl, azidomethyl, 2-azidoethyl, 2-methoxyethyl, mercaptomethyl, methanethiomethyl, 2-methanethioethyl, 1H-tetrazol-5-ylthiomethyl, methanesulfinylmethyl, 2-methanesulfinylethyl, methanesulfonylmethyl, 2-methanesulfonylethyl, aminomethyl, acetylaminomethyl, nitromethyl, 1H-tetrazol-5-ylmethyl, carboxymethyl, 2-carboxyethyl, methylcarboxamide, phosphonomethyl, acetamidomethyl or benzamidomethyl.
5. A compound as claimed in Claim 4, in which R¹ is hydroxymethyl.

6. A compound as claimed in Claim 1 which is selected from:

(2SR, 1'SR, 2'RS, 3'RS)-2-(3'-hydroxymethyl-2'-carboxy-cyclopropyl)glycine;

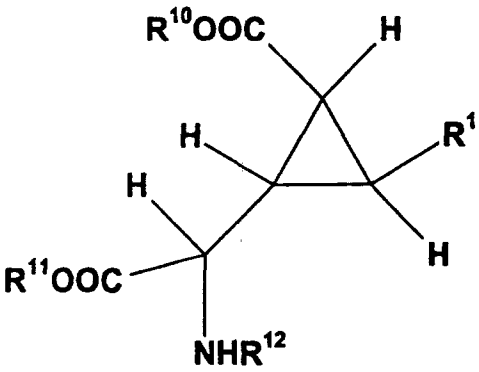
5 and pharmaceutically acceptable salts and esters thereof.

7. A pharmaceutical formulation comprising a compound of formula I as claimed in any one of Claims 1 to 6, or a pharmaceutically acceptable metabolically labile ester thereof, or a pharmaceutically acceptable salt thereof,

10 together with a pharmaceutically acceptable carrier, diluent or excipient.

8. A process for preparing a compound of formula I as claimed in any one of Claims 1 to 6, or a salt or ester thereof, which comprises:

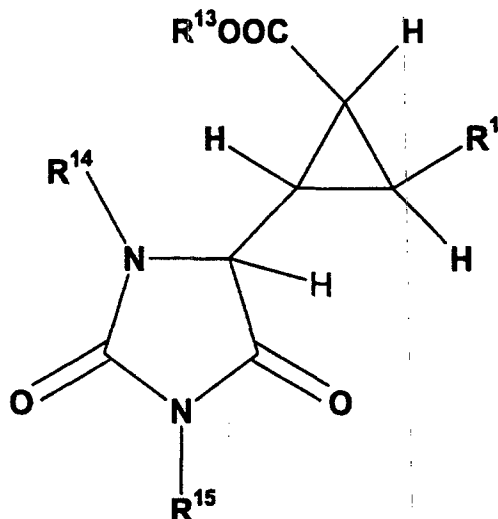
15 (a) deprotecting a compound of formula



II

20 in which R¹⁰ and R¹¹ each independently represents hydrogen or a carboxyl protecting group, and R¹² represents hydrogen or an amine protecting group;

(b) hydrolysing a compound of formula

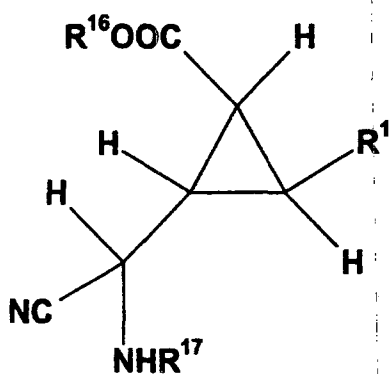


III

in which R^{13} represents a hydrogen atom or a carboxyl protecting group, and R^{14} and R^{15} each independently represents a hydrogen atom, a C_{1-4} alkyl group or a phenyl C_{1-4} alkyl group in which the phenyl group is unsubstituted or substituted by halo, C_{1-4} alkyl, C_{1-4} alkoxy or C_{3-4} alkenyl; or

(c) hydrolysing a compound of formula

10



IV

in which R^{16} represents a hydrogen atom or a carboxy protecting group, and R^{17} represents a hydrogen atom or an amine protecting group;

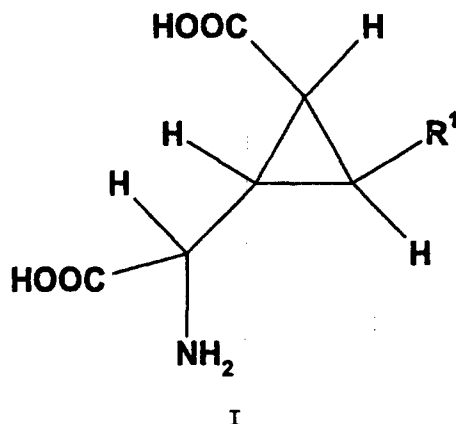
followed when necessary by recovering a diastereomer or isomer of the compound, or

forming a salt or ester thereof.

9. A compound of formula I as claimed in any one of Claims 1 to 6, or a pharmaceutically acceptable metabolically labile ester thereof, or a pharmaceutically acceptable salt thereof, for use as a pharmaceutical.
10. Use of a compound of formula I as claimed in any one of Claims 1 to 6, or a pharmaceutically acceptable metabolically labile ester thereof, or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for treating a disorder of the central nervous system.
11. A method of treating a patient suffering from or susceptible to a disorder of the central nervous system, which comprises administering an effective amount of a compound of formula I according to Claim 1, or a pharmaceutically acceptable metabolically labile ester thereof, or a pharmaceutically acceptable salt thereof.

ABSTRACT

Compounds of the formula



5 in which:

R^1 is halo-C₂-10 alkyl; halo-C₂-10 alkenyl; or $(CH_2)_nY$ in which n is 1 or 2 and Y is OH, CN, N_3 , OR^3 , $S(O)_pR^4$, NH_2 , NHR^5 , NR^6R^7 , $NHCOR^8$, NO_2 , CO_2H , $CONHR^9$, 1H-tetrazol-5-yl or PO_3H_2 ; R^3 , R^5 , R^6 , R^7 , R^8 and R^9 are each selected

10 independently from C₁-4 alkyl, aryl and aryl-C₁-4 alkyl; R^4 is selected from hydrogen, C₁-4 alkyl, aryl-C₁-4 alkyl and 1H-tetrazol-5-yl-C₁-4 alkyl; and p is 0, 1, 2 or 3;

or a salt or ester thereof, provided that R^1 is not methoxymethyl, modulate metabotropic glutamate receptor

15 function and are useful in treating disorders of the central nervous system.

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TRADUCCION: Se traduce la carátula y las reivindicaciones anexas a una copia de la solicitud de patente europea N° 99500090.8, escrita en inglés para el invento denominado: **MODULADORES EXCITATIVOS RECEPTORES DE AMINOACIDO.**

A N E X O S

OFICINA DE PATENTES EUROPEA

Certificado

Los documentos adjuntos son copias exactas de la solicitud de patente europea descrita en la siguiente página, como fue presentada originalmente.

Solicitud de patente N°. 99500090.8

Por el Presidente de la Oficina de Patentes Europea

(Firmado Ilegible)

I.L.C. HATTEN-HECKMAN

La Haya, 25/05/00

240-272

OFICINA DE PATENTES EUROPEA

Página 2 del certificado

Solicitud N° 99500090.8 Fecha de presentación 03/06/99

Solicitante(s)

LILLY S.A.

E-28100 Alcobendas Madrid

España

Título del invento: **MODULADORES EXCITATIVOS RECEPTORES DE
AMINOACIDO**

Prioridades reivindicadas

País	Fecha	Archivo N°
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Clasificación Internacional de Patente: C07C229/28, A61K31/198

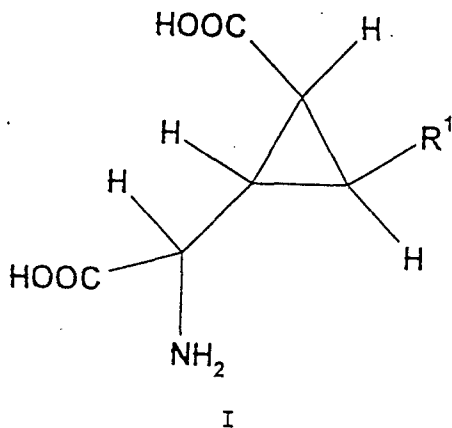
Países contratantes designados en la fecha de presentación:

AT/BE/CH/CY/DE/DK/ES/FI/FR/GB/GR/IE/IT/LI/LU/MC/NL/PT/SE

Observaciones:

REIVINDICACIONES

1. Un compuesto de fórmula

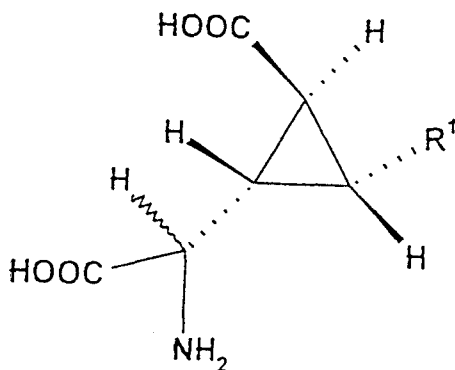


en el cual:

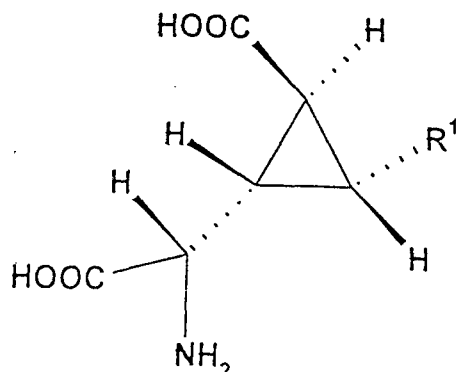
R^1 es halo C_{1-10} alquilo; halo C_{2-10} alquenilo; o $(CH_2)_nY$ en el cual n es 1 o 2 y Y es OH, CN, N_3 , OR^3 , $S(O)_pR^4$, NH_2 , NHR^5 , NR^6R^7 , $NHCOR^8$, NO_2 , CO_2H , $CONHR^9$, 1H-tetrazol-5-ilo o PO_3H_2 ; R^3 , R^5 , R^6 , R^7 , R^8 , y R^9 son cada uno seleccionados independientemente de C_{1-4} alquilo, arilo y arilo C_{1-4} alquilo; R^4 se selecciona de hidrógeno, C_{1-4} alquilo, arilo, arilo C_{1-4} alquilo y 1H-tetrazol-5-ilo, C_{1-4} alquilo; y p es 0, 1, 2 o 3;

O una sal o éster de este, siempre y cuando R^1 no sea metoximetilo.

2. Un compuesto como se reivindicó en la reivindicación 1, el cual tiene la configuración

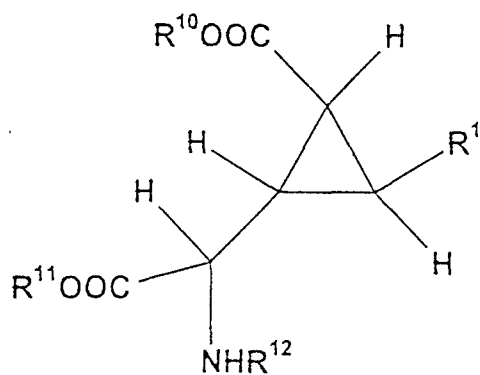


3. Un compuesto como se reivindicó en la reivindicación 1, el cual tiene la configuración



4. Un compuesto de acuerdo con una cualquiera de las reivindicaciones 1 a 3, en la cual R¹ se selecciona a partir de fluorometilo, 2 fluoroetilo, trifluorometilo, trifluoroetilo, clorometilo, tricloroetilo, 2 tricloroetilo, 2-fluorovinilo, 2,2-difluorovinilo, hidroximetilo, cianometilo, 2-cianoetilo, azidometilo, 2-azidoetilo, 2-metoxietilo, mercaptometilo, metanotiométilo, 2-metanotioetilo, 1H-tetrazol-5-iltiométilo, metanosulfinilmétilo, 2-metanosulfoniletilo, aminometilo, acetilaminometilo, nitrometilo, 1H-tetrazol-5-ilmetilo, metanosulfonilmétilo, 2-metanosulfoniletilo, aminometilo, acetilaminometilo, nitrometil, 1H-tetrazol-5-ilmetilo, carboximetilo, 2 carboxietilo, metilcarboxamida, fosfonometilo, acetamidometilo o benzamidometilo.
5. Un compuesto de acuerdo a la reivindicación 4, el cual R¹ es hidroximetilo.
6. Un compuesto de acuerdo con la reivindicación 1 la cual es seleccionada de, en la cual R¹ se selecciona a partir de (2SR, 1'SR, 2'RS, 3'RS)-2-(3'-hidroximetil-2'-carboxi-ciclo propil)glicina; y sales y ésteres farmacéuticamente aceptables de estos.

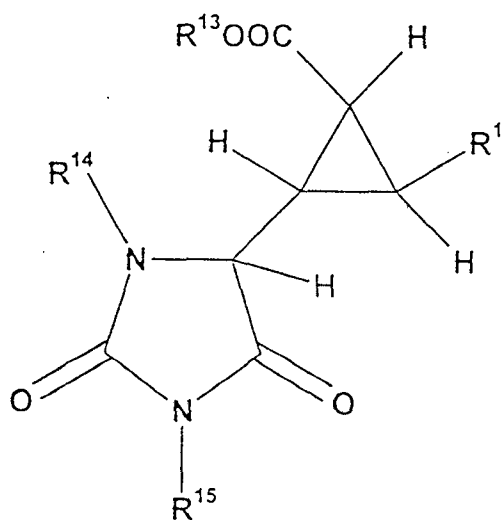
7. Una formulación farmacéutica que comprende un compuesto de fórmula I como se reivindicó en una cualquiera de las reivindicaciones 1 a 6, o un éter lábil farmacéuticamente aceptable metabólicamente de estos, o una sal farmacéuticamente aceptable de estos, junto con un portador farmacéuticamente aceptable, diluyente o excipiente.
8. Un proceso para preparar un compuesto de fórmula I como se reivindicó en una cualquiera de las reivindicaciones 1 a 6, o una sal o éster del mismo, que comprende:
 - a) desproteger un compuesto de fórmula



II

En el cual R^{10} y R^{11} cada uno independientemente representan hidrógeno o un grupo protector carboxilo, y R^{12} representa hidrógeno o un grupo protector amina;

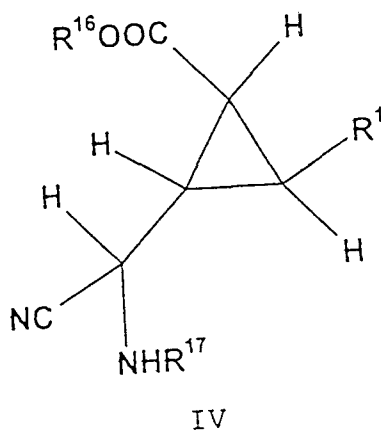
- b) hidrolizar un compuesto de fórmula



III

En el cual R^{13} representa un átomo de hidrógeno o un grupo protector carboxilo, y R^{14} y R^{15} cada uno independientemente representan un átomo de hidrógeno, un grupo alquilo con 1 a 4 átomos de carbono o un grupo fenilalquilo con 1 a 4 átomos de carbono en el cual el grupo fenilo no está sustituido o puede estar sustituido por halo, alquilo con 1 a 4 átomos de carbono, alcoxi con 1 a 4 átomos de carbono o alquenilo con 3 a 4 átomos de carbono; o

c) hidrolizar un compuesto de fórmula



En el cual R^{16} representa un átomo de hidrógeno o un grupo protector carboxi, y R^{17} representa un átomo de hidrógeno o un grupo protector amina;

Seguido cuando sea necesario por la recuperación de diastereómeros o isómeros del compuesto, o una sal o ester del mismo.

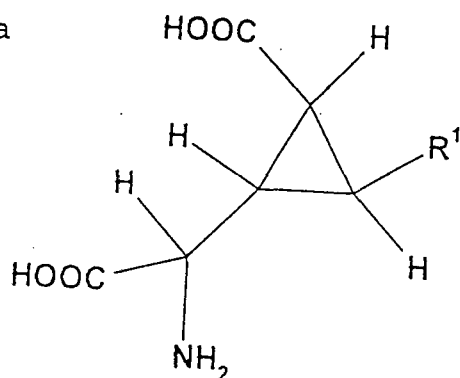
9. Una formulación farmacéutica que comprende un compuesto de fórmula I como se reivindicó en una cualquiera de las reivindicaciones 1 a 6, o un éter lábil farmacéuticamente aceptable metabólicamente de estos, o una sal farmacéuticamente aceptable de estos, para uso como farmacéutico.
10. El uso de un compuesto de fórmula I según se reivindicó en una cualquiera de las reivindicaciones 1 a 9, o un éster

11. Un método de tratamiento de un paciente que sufre de o es susceptible a un desorden del sistema nervioso central, que comprende administrar una cantidad efectiva de un compuesto de fórmula I de acuerdo con la reivindicación 1 o un éster metabólicamente lábil farmacéuticamente aceptable del mismo, o una sal farmacéuticamente aceptable del mismo.

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RESUMEN

Compuesto de la fórmula



I
En los cuales R¹ es halo-C₂₋₁₀ alquilo; halo C₂₋₁₀ alquenilo; o (CH₂)_nY en el cual n es 1 o 2 y Y es OH, CN, N₃, OR³, S(O)_pR⁴, NH₂, NHR⁵, NR⁶R⁷, NHCOR⁸, NO₂, CO₂H, CONHR⁹, 1H-tetrazol-5-ilo, o PO₃H₂; R³, R⁵, R⁶, R⁷, R⁸ y R⁹ son cada uno seleccionados independientemente de alquilo C₁₋₄, arilo y arilo C₁₋₄ alquilo; R⁴ se selecciona de hidrógeno, C₁₋₄ alquilo, aril C₁₋₄ alquilo y 1H-tetrazol-5-il-C₁₋₄ alquilo; y p es 0, 1, 2 o 3; o una sal o éster de los anteriores, siempre y cuando R¹ no sea metoximetilo, una función receptor de glutamato metabotrópico modulado y son útiles en el tratamiento de desórdenes del sistema nervioso central.