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

Referencia : Expediente No. 00.024.876
Solicitante : **ELI LILLY AND COMPANY LIMITED**
Asunto : Solicitud de patente para: **"COMPUESTOS FARMACEUTICOS"**
Fecha de solicitud : 05 de abril de 2000

TRAMITE: 002 - EVENTO: 001 - ACTUACION: 009

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 británica No. 9908021.0 del 08 de abril de 1999, junto con la 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, -5 JUL. 2000
Señora Jefe,



EMILIO FERRERO
T.P.A. No. 31.929

COLO 11187-801-004-5

MRE-28



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34
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I, the undersigned, being an officer duly authorised in accordance with Section 74(1) and (4) of the Deregulation & Contracting Out Act 1994, to sign and issue certificates on behalf of the Comptroller-General, hereby certify that annexed hereto is a true copy of the documents as originally filed in connection with the patent application identified therein.

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R. McCreary

Dated 17 March 2000

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Patents
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V. 899 8438577-1 D01348
P01/7700 0.00 9908021.0

Request for grant of a patent

(See the notes on the back of this form. You can also get an explanatory leaflet from the Patent Office to help you fill in this form)

- 8 APR 1999

The Patent Office

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1. Your reference

G.1336

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LLY AND COMPANY LIMITED,
LERE ROAD,
STOKE,
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73056 00001

BRITAIN

CEUTICAL COMPOUNDS

HUDSON

RESEARCH CENTRE,
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SHAM,
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6785075001

Priority application number
(if you know it)

Date of filing
(day / month / year)

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Date of filing
(day / month / year)

UNITED KINGDOM OF GREAT BRITAIN AND NORTHERN IRELAND

D613967

3 April, 2000

This document bears
the signature / seal of

K Greenwood

in the capacity of Notary Public

Signed by: J. M. A. Mason

For Her Majesty's Principal Secretary of State
For Foreign and Commonwealth Affairs



8. Is a statement of inventorship and of right to grant of a patent required in support of this request? (Answer 'Yes' if:

- a) any applicant named in part 3 is not an inventor, or
- b) there is an inventor who is not named as an applicant, or
- c) any named applicant is a corporate body.

See note (d))

3
Patents Form 1/77

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Continuation sheets of this form

Description	33
Claim(s)	3
Abstract	1
Drawing(s)	-

10. If you are also filing any of the following, state how many against each item.

Priority documents

Translations of priority documents

Statement of inventorship and right to grant of a patent (*Patents Form 7/77*)

Request for preliminary examination and search (*Patents Form 9/77*) 1

Request for substantive examination (*Patents Form 10/77*)

Any other documents
(please specify)

11. I/We request the grant of a patent on the basis of this application.

Signature

Date

th April 1999

12. Name and daytime telephone number of person to contact in the United Kingdom

MR. C. M. HUDSON (01276) 853441

Warning

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Notes

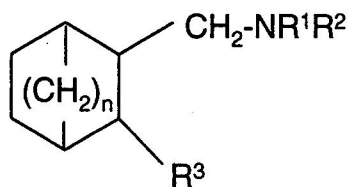
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PHARMACEUTICAL COMPOUNDS

This invention relates to novel compounds having pharmaceutical properties.

5

The compounds of the invention are of the following formula:



(I)

10

in which R^1 and R^2 are each hydrogen or C_{1-4} alkyl, R^3 is a naphthyl, indolyl, benzothienyl, benzofuranyl, benzothiazolyl, quinolinyll or isoquinolinyll group, said group being optionally substituted, and n is 1 or 2; or
15 a salt or ester thereof.

The compounds of the invention and their pharmaceutically acceptable salts and esters are indicated for use in the treatment of disorders of the
20 central nervous system.

In the above formula (I), a C₁₋₄ alkyl group can be methyl, ethyl, or propyl, and can be branched or unbranched and includes isopropyl and tert. butyl.

Preferably R¹ and R² are each hydrogen, methyl or ethyl, and especially hydrogen or methyl. The -NR¹R² group is most preferably -N(CH₃)₂ or -NH(CH₃).

Compounds of formula (I) are preferably bicycloheptyl derivatives (n is 1).

10

It is preferred that the R³ substituent be attached to the bicyclo ring at certain positions on the substituent, and preferred R³ groups are β-naphthyl, 2-,3-,5- or 6-indolyl, 2-,3-,5- or 6-benzothienyl, 2-,3-,5- or 6-benzofuranyl, 2- or 5-benzothiazolyl, 2-,3-,6- or 7-quinolinyl or 3-,6- or 7-isoquinolinyl.

15

The R³ group can also be substituted, substitution being in one or both rings, with one or more, preferably 1 to 3, substituents. Preferred substituents include C₁₋₄ alkyl, C₁₋₄ alkoxy, carboxy, hydroxy, cyano, halo, trifluoromethyl, -NR'R'' and -CONR'R'' where R' and R'' are each hydrogen or C₁₋₄ alkyl.

20

A preferred value of R^3 is optionally substituted β -naphthyl, and especially unsubstituted β -naphthyl.

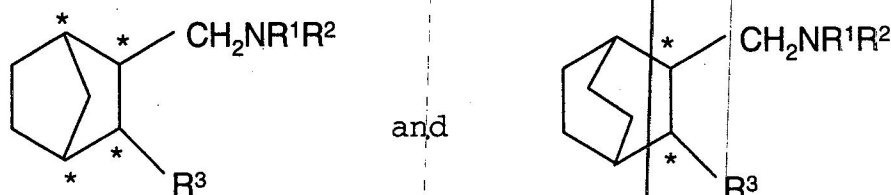
As indicated above, it is, of course, possible to
5 prepare salts of the compound of the invention and such salts are included in the invention. Acid addition salts are preferably the pharmaceutically acceptable, non-toxic addition salts with suitable acids, such as those with inorganic acids, for example hydrochloric,
10 hydrobromic, nitric, sulphuric or phosphoric acids, or with organic acids, such as organic carboxylic acids, for example, maleic, fumaric, tartaric or citric acid.

In addition to the pharmaceutically acceptable salts,
15 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
20 purification.

It will be appreciated that when a substituent on an R^3 group is acidic such as, for example, a carboxy group, the opportunity exists for esters. These can be
25 aliphatic or aromatic, being preferably alkyl esters

derived from C₁₋₄ alkanols, especially methyl and ethyl esters. An example of an ester substituent is -COOR' where R' is C₁₋₄ alkyl.

- 5 The compounds of the invention contain asymmetric carbon atoms as indicated by asterisks in the following structures:



10

This asymmetry gives rise to cis- and trans-isomers as well as, in the case of the bicycloheptyl derivatives, exo- and endo-forms. Thus the bicycloheptyl derivatives exist as trans exo, trans endo, cis exo and cis endo forms, and in each instance R and S enantiomers. In the case of the bicyclooctyl derivatives, there are cis and trans derivatives only, each of which exist in R and S enantiomeric form. The compounds can be prepared as racemic mixtures and can conveniently be used as such, but individual isomers can be isolated by conventional techniques, or are preferably prepared by chiro-selective methods. Both racemic mixtures and individual isomers are included in the present invention.

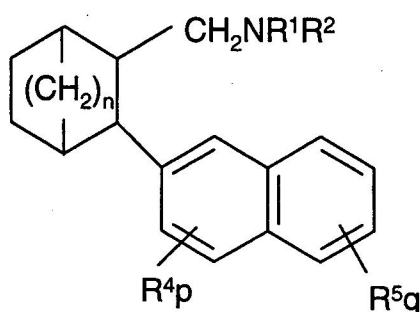
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A preferred group of compounds of formula (I) above is one in which R^1 and R^2 are each hydrogen or C_{1-4} alkyl, R^3 is optionally substituted β -naphthyl.

5

A particularly preferred group of compounds of the invention can be represented as follows:



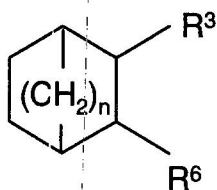
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in which R^1 and R^2 are each hydrogen or C_{1-4} alkyl, R^4 and R^5 are each C_{1-4} alkyl, C_{1-4} alkoxy, carboxy, hydroxy, cyano, halo, trifluoromethyl, $-NR'R''$ or $-CONR'R''$, where R' and R'' are each hydrogen or C_{1-4}

15 alkyl, and p and q are each 0 or 1 to 3, such that the sum of p and q is preferably 0 or 1 to 3. When the naphthyl group is substituted there is preferably a single substituent at the 6-position. Of the above compounds, the most preferred are the unsubstituted
20 compounds in which p and q are both 0, and furthermore

the compounds in which n is 1, the bicycloheptyl derivatives, are most preferred.

The invention also includes processes for the production
5 of compounds of the formula (I) above by any of the normal methods for preparing substituted alkyl amines. For example, they can be made from intermediates of the formula:



(II)

10 where R³ and n have the values given above, and R⁶ is -CN, -CONR¹R², -CH₂NCO, -CHO or -COOR⁷ where R⁷ is C₁₋₄ alkyl. Such intermediates are novel and are included as
15 part of the present invention.

The compounds of formula (II) are readily converted to compounds of formula (I) by reduction, optionally followed by alkylation. In the case of the nitriles and
20 amides of formula (II), the reduction is preferably carried out using a complex hydride reducing agent such as lithium aluminium hydride or sodium borohydride,

whilst in the case of the isocyanates of formula (II), treatment with a concentrated mineral acid such as hydrochloric acid produces the desired conversion. The aldehydes and esters of formula (II) may be reductively aminated to the desired compounds of formula (I) by reduction to the corresponding alcohols using, for example, a complex hydride reducing agent conversion of the alcohols to the corresponding alkyl or aryl sulphonates by reaction with an alkyl or aryl sulphonyl chloride such as methyl sulphonyl chloride or p.toluene sulphonyl chloride and reaction of the sulphonates with an amine of formula HNR_1R_2 . Reductive amination of the aldehydes of formula (II) may also be carried out by catalytic reduction, for example by catalytic hydrogenation in the presence of an amine of formula HNR_1R_2 .

The compounds are most conveniently prepared from the nitriles and amides of formula (II) and these are the preferred intermediates of the invention.

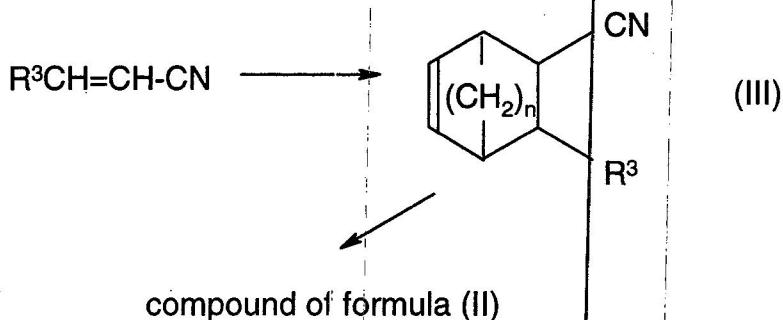
A primary amine produced by the above routes may be converted to a secondary or tertiary amine by alkylation. The alkylation may be carried out in conventional manner, for example by reductive alkylation, reaction with an alkyl halide or sulphate,

reaction with an alkyl chloroformate followed by reduction of the resultant urethane, or when methylation is to be carried out, preferably by reaction with formic acid/formaldehyde (Eschweiler-Clarke).

5

Intermediate compounds of formula (II) where R^6 is -CN or -CHO can readily be prepared by a Diels-Alder reaction, by the addition of cyclopentadiene or cyclohexadiene to a compound of the formula $R^3CH=CH-CN$

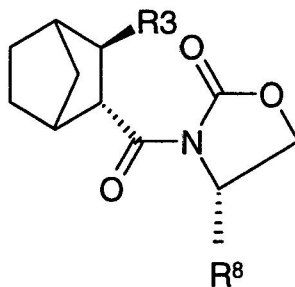
10 or $R^3CH=CH-CHO$, optionally employing, for example, diethylaluminium chloride as catalyst. The reaction is prolonged and has to be carried out at an elevated temperature, for example, from $100^\circ C.$ to $200^\circ C.$, especially about $160^\circ C.$, yielding bicycloheptenyl or
15 bicyclooctenyl derivatives, which can be catalytically reduced to give the compounds of formula (II), as illustrated below.



20 29

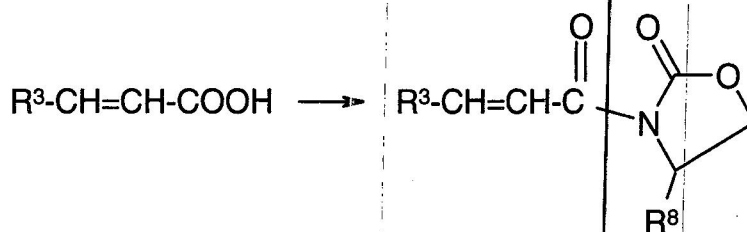
Compounds of formula (III) are novel and are included as part of the present invention. The reaction results in cis- and trans-enantiomers in racemic mixtures, and can
5 be used to produce both the bicycloheptane and bicyclooctane derivatives of formula (I) above.

A reaction which can conveniently be employed to produce chiral enantiomers of the cycloheptyl derivatives
10 utilises Evans chiral auxiliaries as, for example, oxazolidine amide intermediates of the formula:



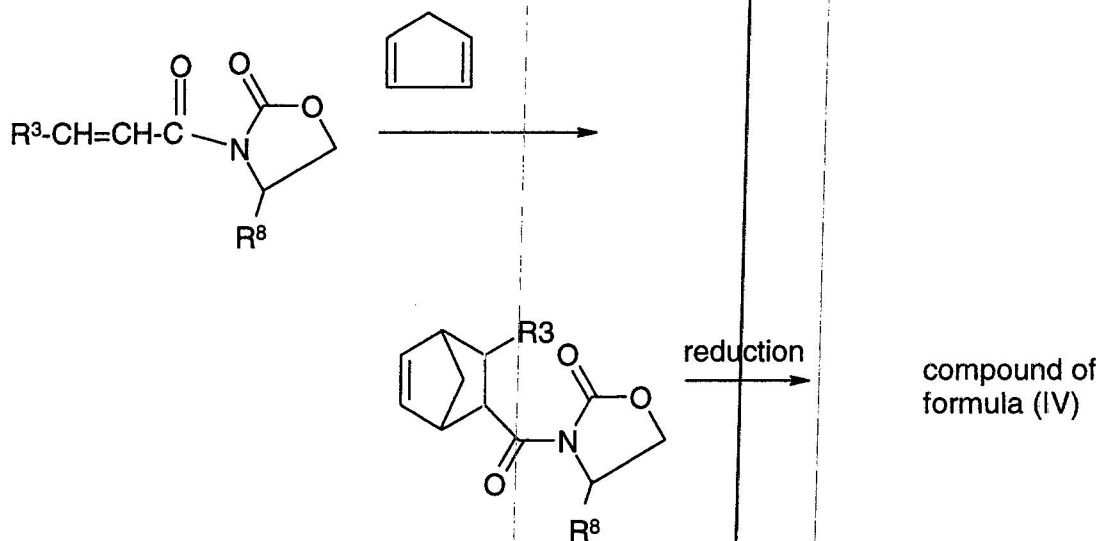
(IV)

15 where R⁸ is alkyl, aryl or aralkyl, from the corresponding α -unsaturated acid, as follows:



followed by a Diels-Alder reaction with cyclopentadiene
in the presence of a Lewis acid and solvent such as
5 dichloromethane, at a low temperature for example
between -10°C. and -30°C. The reaction proceeds
readily to give a bicycloheptenyl derivative, which on
reduction yields the compound of formula (IV) above, as
follows:

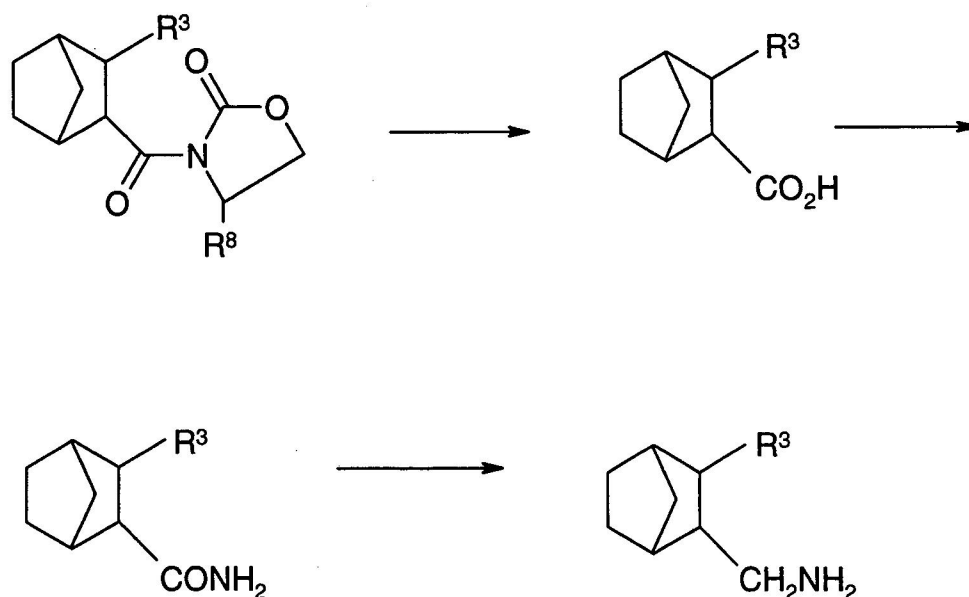
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Alternatively, instead of employing a chiral compound of
formula (IV), an oxazolidine compound in which R^8 is
15 hydrogen can be used, together with a chiral catalyst.

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The compound of formula (IV) is readily converted by
 action of lithium hydroxide and hydrogen peroxide to the
 free acid, which on reaction with amine and further
 5 reduction yields a compound of formula (I), as follows.



Choice of the appropriate α -unsaturated acid starting
 10 material allows the production of enantiomerically pure
 cis- and trans-isomers.

As mentioned above, the compounds of the invention and
 their pharmaceutically acceptable salts have useful
 15 central nervous system activity. The compounds inhibit
 the uptake of neurotransmitters such as serotonin,
 dopamine and noradrenalin. They are surprisingly
 effective serotonin reuptake inhibitors, as evidenced by

their displacement of [³H] citalopram at the binding sites on membranes derived from rat cortex, as in the test described below. In a similar test, also employing rat cortex membrane, the compounds displace nisoxetine, demonstrating their ability to inhibit noradrenalin reuptake, see Journal of Pharmacology and Experimental Therapeutics Vol. 272, No. 3, 1176-1186, 1995. The dopamine reuptake properties of the compounds of the invention are demonstrated in the test described in Molecular Pharmacology 45: 125-135, using membranes derived from rat striatum. In this test displacement of WIN 35,428 from its reuptake site, is measured.

Because of their profile of neurotransmitter reuptake properties, the compounds of the present invention are indicated for use in treating a variety of conditions such as depression, obesity, bulimia, alcoholism, pain, hypertension, ageing, senile dementia, Alzheimer's, memory loss, attention-deficit hyperactivity disorder, sexual dysfunction, Parkinsonism, anxiety, chronic fatigue syndrome, panic disorders, obsessive compulsive disorder, schizophrenia, gastrointestinal disorders, headache, cardiovascular disorders, smoking cessation, drug addiction including cocaine abuse, emesis and sleep disorders.

The compounds of the invention are effective over a wide dosage range, the actual dose administered being dependent on such factors as the particular compound being used, the condition being treated and the type and size of mammal being treated. However, the dosage required will normally fall within the range of 0.01 to 20 mg/kg per day, for example in the treatment of adult humans, dosages of from 0.5 to 100 mg per day may be used.

The compounds of the invention will normally be administered orally or by injection and, for this purpose, the compounds will usually be utilised in the form of a pharmaceutical composition. Such compositions are prepared in a manner well known in the pharmaceutical art and comprise at least one active compound.

Accordingly the invention includes a pharmaceutical composition comprising as active ingredient a compound of formula (I) or a pharmaceutically acceptable salt or ester thereof, associated with a pharmaceutically acceptable excipient. In making the compositions of the invention, the active ingredient will usually be mixed with a carrier, or diluted by a carrier, or enclosed

within a carrier which may be in the form of a capsule, sachet, paper or other container. The excipient may be a solid, semi-solid or liquid material which acts as a vehicle, excipient or medium for the active ingredient.

5 Some examples of suitable excipients are lactose, dextrose, sucrose, sorbitol, mannitol, starches, gum acacia, calcium phosphate, alginates, tragacanth, gelatin syrup, methyl cellulose, methyl- and propyl-hydroxybenzoate, talc, magnesium stearate or oil. The
10 compositions of the invention may, if desired, be formulated so as to provide quick, sustained or delayed release of the active ingredient after administration to the patient.

15 Depending on the route of administration, the foregoing compositions may be formulated as tablets, capsules or suspensions for oral use and injection solutions or suspensions for parenteral use or as suppositories. Preferably the compositions are formulated in a dosage
20 unit form, each dosage containing from 0.5 to 100 mg, more usually 1 to 100 mg, of the active ingredient.

The following Examples illustrate routes to the synthesis of the compounds of the invention.

25

EXAMPLE 1

Ethyl (Z)-3-(2-naphthyl)prop-2-enoate

5

To a slurry of magnesium chips (0.62g, 0.026mol) in THF (200ml) under N₂ was added a solution of 2-bromonaphthalene (5g, 0.024mol) in THF (10ml). The mixture was heated under reflux overnight. On cooling, 10 solid ZnBr₂ (3.62g, 0.016mol) was added in one portion and the resulting white precipitate left to stir at room temperature for 20 hours. DMF (20ml) was added, followed by bis(acetonitrile) palladium(II) chloride (0.02g, 0.8mmol) and ethyl *cis*-iodoacrylate (1.03ml, 8.0mmol). 15 After 1 hour, 2N HCl was added, the mixture diluted with diethyl ether and washed with a saturated solution of ammonium chloride. The ethereal phase was dried and the solvent removed *in vacuo*. Chromatography on flash silica gel using hexane:dichloromethane (1:1) gave Ethyl 20 (Z)-3-(2-naphthyl)prop-2-enoate as a white solid, M/e 227 (M+H⁺).

EXAMPLE 2

25

(Z)-3-(2-Naphthyl)prop-2-enoic acid

A solution of (Z)-naphthalene-2-acrylic acid ethyl ester (1.38g, 6.0mmole) in a mixture of tetrahydrofuran (10ml) and water (10ml) was treated with lithium hydroxide (0.88g, 37mmol) and heated to 60°C for 6 hours. On cooling, the organic phase was separated and the aqueous phase was acidified and extracted with diethyl ether. The ethereal phase was dried and the solvent removed in vacuo to give (Z)-3-(2-naphthyl)prop-2-enoic acid as a white solid which was used without further purification, Mp 207-209°C.

15 EXAMPLE 3

3-[(E)-3-Naphthalen-2-ylprop-2-enoyl]-1,3-oxazolidin-2-one

To a stirred solution of (E)-3-(2-naphthyl)prop-2-enoic acid (10g, 0.05mole) at -78°C, was added triethylamine (8.42ml, 0.06mole) and pivaloyl chloride (7.5ml, 0.06mole). Stirring was continued for 1 hour. To a stirred solution of oxazolidinone (5.14g, 0.06mole) in dry tetrahydrofuran (200ml) at -78°C was added slowly n-butyl lithium (1.6M in hexanes, 38ml, 0.06mole).

Stirred for 1 hour. The suspension of the mixed anhydride was transferred into the oxazolidinone anion by means of a canula maintaining the temperature below - 60°C. The resulting reaction mixture was stirred for 2 5 hours. Water was added cautiously and the reaction extracted with ethyl acetate. The solvent was washed with brine, dried and evaporated to dryness *in-vacuo*. Chromatography on flash silica using ethyl acetate/hexane (1:1) gave 3-[(*E*)-3-naphthalen-2-ylprop- 10 2-enoyl]-1,3-oxazolidin-2-one as a white solid, M/e 268 (M+H).

Similarly prepared were:

15 4(R)-3-[(*E*)-3-naphthalen-2-ylprop-2-enoyl]-4-benzyl-1,3-oxazolidin-2-one, Mp121-123°C.

4(S)-3-[(*E*)-3-naphthalen-2-ylprop-2-enoyl]-4-benzyl-1,3-oxazolidin-2-one, Mp121-123°C.

20

3-[(*Z*)-3-naphthalen-2-ylprop-2-enoyl]-1,3-oxazolidin-2-one, M/e 268 (M+H⁺), 290 (M+Na⁺).

4(R)-3-[(*Z*)-3-naphthalen-2-ylprop-2-enoyl]-4-benzyl-1,3- 25 oxazolidin-2-one, M/e 358 (M+H⁺).

EXAMPLE 4

5 trans-endo-3-[(3-Naphthalen-2-ylbicyclo[2.2.1]hept-5-en-2-yl)carbonyl]-1,3-oxazolidin-2-one and trans-exo-3-[(3-naphthalen-2-ylbicyclo[2.2.1]hept-5-en-2-yl)carbonyl]-1,3-oxazolidin-2-one

10 To a solution of 3-[(E)-3-naphthalen-2-ylprop-2-enoyl]-1,3-oxazolidin-2-one (2g, 7.5mmole) in dry dichloromethane (20ml) at -20°C was added freshly cracked cyclopentadiene (3.2g, 37mmole) and diethylaluminium chloride (5.4ml, 9.7mmole). The
15 reaction mixture was stirred for 2 hours. The reaction was poured into ice water and the solvent separated. The aqueous was extracted with dichloromethane and the combined solvent washed with brine, dried and evaporated to dryness *in-vacuo*. Chromatography on flash silica
20 using ethyl acetate/hexane (3:7) gave trans-endo-3-[(3-naphthalen-2-ylbicyclo[2.2.1]hept-5-en-2-yl)carbonyl]-1,3-oxazolidin-2-one, M/e 334 (M+H⁺), and trans-exo-3-[(3-naphthalen-2-ylbicyclo[2.2.1]hept-5-en-2-yl)carbonyl]-1,3-oxazolidin-2-one, M/e 334 (M+H⁺).

25

Similarly prepared were:

trans-endo-4(R)-3-[(3-naphthalen-2-ylbicyclo[2.2.1]hept-5-en-2-yl)carbonyl]-4-benzyl-1,3-oxazolidin-2-one,

5 Mp135-136°C.

trans-endo-4(S)-3-[(3-naphthalen-2-ylbicyclo[2.2.1]hept-5-en-2-yl)carbonyl]-4-benzyl-1,3-oxazolidin-2-one,

Mp135-136°C.

10

cis-endo-3-[(3-naphthalen-2-ylbicyclo[2.2.1]hept-5-en-2-yl)carbonyl]-1,3-oxazolidin-2-one, Mp194-196°C.

cis-exo-3-[(3-naphthalen-2-ylbicyclo[2.2.1]hept-5-en-2-yl)carbonyl]-1,3-oxazolidin-2-one

15

EXAMPLE 5

trans-endo-3-[(3-Naphthalen-2-ylbicyclo[2.2.1]hept-5-en-2-yl)carbonyl]-1,3-oxazolidin-2-one

20

A solution of the catalyst was prepared under nitrogen by stirring together anhydrous copper(II)chloride

(0.0046g, 0.034×10^{-3} mol), 2,2'-isopropylidenebis(4-S)-

25 4-tert-butyl-2-oxazoline (0.012g, 0.038×10^{-3} mol) and

silver(II)hexafluoroantimonate (0.024g, 0.068×10^{-3} mol) in dry dichloromethane (0.34ml) at room temperature for 8 hours. The solid precipitate was removed by filtration through a celite pad and the bright blue catalyst solution was added under nitrogen to a stirred slurry of 3-[(E)-3-naphthalen-2-ylprop-2-enoyl]-1,3-oxazolidin-2-one (0.05g, 0.00019mol) in dry dichloromethane (1ml). Freshly cracked cyclopentadiene (0.2ml, 0.0023mol) was added and the mixture stirred at room temperature for 24 hours. After this time, the solvent was removed *in vacuo* and the residue purified by column chromatography, eluent 7:3 hexane:ethyl acetate, to give trans-endo-3-[(3-naphthalen-2-ylbicyclo[2.2.1]hept-5-en-2-yl)carbonyl]-1,3-oxazolidin-2-one as a white solid. Mp 135-136°C.

EXAMPLE 6

trans-endo-3-[(3-Naphthalen-2-ylbicyclo[2.2.1]hept-2-yl)carbonyl]-1,3-oxazolidin-2-one

To a solution of trans-endo-3-[(3-naphthalen-2-ylbicyclo[2.2.1]hept-5-en-2-yl)carbonyl]-1,3-oxazolidin-2-one (1g, 3mmole) in ethyl acetate (20ml) was added 10%Pd-C (0.1g). The reaction was hydrogenated at 60psi using a Parr hydrogenator for 1 hour. The catalyst was

removed by filtration through celite and the solvent removed by evaporation *in-vacuo*. The product was purified by chromatography on flash silica using ethyl acetate/hexane (3:7) to give trans-endo-3-[(3-naphthalen-2-ylbicyclo[2.2.1]hept-2-yl)carbonyl]-1,3-oxazolidin-2-one as a colourless oil, M/e 336(M+H⁺).

Similarly prepared were:

10 trans-exo-3-[(3-naphthalen-2-ylbicyclo[2.2.1]hept-2-yl)carbonyl]-1,3-oxazolidin-2-one, M/e 336 (M+H⁺).

trans-endo-4(R)-3-[(3-naphthalen-2-ylbicyclo[2.2.1]hept-2-yl)carbonyl]-4-benzyl-1,3-oxazolidin-2-one, Mp141-15 143°C.

trans-endo-4(S)-3-[(3-naphthalen-2-ylbicyclo[2.2.1]hept-2-yl)carbonyl]-4-benzyl-1,3-oxazolidin-2-one, Mp141-143°C.

20 cis-endo-3-[(3-naphthalen-2-ylbicyclo[2.2.1]hept-2-yl)carbonyl]-1,3-oxazolidin-2-one.

cis-exo-3-[(3-naphthalen-2-ylbicyclo[2.2.1]hept-2-yl)carbonyl]-1,3-oxazolidin-2-one.

EXAMPLE 7

5 trans-endo-3-Naphthalen-2-ylbicyclo[2.2.1]heptane-2-carboxylic acid

To a solution of trans-endo-3-[(3-naphthalen-2-ylbicyclo[2.2.1]hept-2-yl)carbonyl]-1,3-oxazolidin-2-one
10 (0.29g, 0.86mmole) in a mixture of tetrahydrofuran (20ml) and water (5ml) at -5°C was added hydrogen peroxide (2ml) dropwise. To the resulting slurry was added a solution of lithium hydroxide (42mg, 0.18mmole) in water (5ml) dropwise keeping the temperature below
15 0°C. The resulting mixture was stirred 1 hour at 0°C and then for 2 hours at room temperature. The reaction was quenched with a solution of sodium sulphide in water () made acid with 6NHCl and extracted with dichloromethane. The solvent was washed with brine, dried and evaporated
20 to dryness *in-vacuo*. Chromatography on flash silica using ethyl acetate:hexane (1:1) gave trans-endo-3-naphthalen-2-ylbicyclo[2.2.1]heptane-2-carboxylic acid, M/e 267 (M+H⁺).

25 Similarly prepared were:

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trans-exo-3-naphthalen-2-ylbicyclo[2.2.1]heptane-2-carboxylic acid, M/e 267 ($M+H^+$).

5 trans-endo-(2*R*,3*R*)-3-naphthalen-2-ylbicyclo[2.2.1]heptane-2-carboxylic acid, Mp135-137°C.

trans-endo-(2*S*,3*S*)-3-naphthalen-2-ylbicyclo[2.2.1]heptane-2-carboxylic acid, Mp135-137°C.

10

cis-endo-3-naphthalen-2-ylbicyclo[2.2.1]heptane-2-carboxylic acid.

cis-exo-3-naphthalen-2-ylbicyclo[2.2.1]heptane-2-carboxylic acid.

15

EXAMPLE 8

20 trans-endo-N,N-Dimethyl-3-naphthalen-2-ylbicyclo[2.2.1]heptane-2-carboxamide

To a stirred solution of trans-endo-3-naphthalen-2-ylbicyclo[2.2.1]heptane-2-carboxylic acid (225mg, mole)
25 in dichloromethane (5ml) at 0-5°C was added oxalyl

chloride (81 μ l, 0.93mmole) followed by dry
dimethylformamide (1 drop). The mixture was allowed to
attain room temperature and stirred for 2 hours. The
solution was evaporated to dryness *in-vacuo*, re-
5 dissolved in dry tetrahydrofuran and added to a stirred
solution of dimethylamine in tetrahydrofuran (2M
solution, 0.9ml, 1.7mmole). The mixture was stirred for
2-hours. The reaction mixture was diluted with ice-
water, extracted with ethyl acetate, washed with water,
10 dried and evaporated to dryness *in-vacuo*. Chromatography
on flash silica using ethyl acetate:hexane (1:1) gave
trans-endo-N,N-dimethyl-3-naphthalen-2-
ylbicyclo[2.2.1]heptane-2-carboxamide as a colourless
oil, M/e 294 (M+H⁺).

15

Similarly prepared were:

trans-exo-N,N-dimethyl-3-naphthalen-2-
ylbicyclo[2.2.1]heptane-2-carboxamide, M/e 294 (M+H⁺).

20

trans-endo-(2R,3R)-N,N-dimethyl-3-naphthalen-2-
ylbicyclo[2.2.1]heptane-2-carboxamide, Mp140-142°C.

trans-endo-(2S,3S)-N,N-dimethyl-3-naphthalen-2-
25 ylbicyclo[2.2.1]heptane-2-carboxamide, Mp140-142°C.

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trans-endo-N-methyl-3-naphthalen-2-
ylbicyclo[2.2.1]heptane-2-carboxamide.

5 trans-endo-(2*R*,3*R*)-N-methyl-3-naphthalen-2-
ylbicyclo[2.2.1]heptane-2-carboxamide.

trans-endo-(2*S*,3*S*)-N-methyl-3-naphthalen-2-
ylbicyclo[2.2.1]heptane-2-carboxamide, M/e 280 (M+H⁺).

10
cis-endo-N,N-dimethyl-3-naphthalen-2-
ylbicyclo[2.2.1]heptane-2-carboxamide.

cis-exo-N,N-dimethyl-3-naphthalen-2-
15 ylbicyclo[2.2.1]heptane-2-carboxamide.

EXAMPLE 9

20 trans-endo-N,N-Dimethyl(3-naphthalen-2-
ylbicyclo[2.2.1]hept-2-yl)methanamine

To a stirred solution of trans-endo-N,N-dimethyl-3-
naphthalen-2-ylbicyclo[2.2.1]heptane-2-
25 carboxamide (0.45g, 1.53mmole) in dry ether (20ml) was
added a solution of lithium aluminium hydride in

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tetrahydrofuran (2M, 0.84ml, 1.7mmole). The reaction
was heated at reflux for 1 hour. After cooling to room
temperature water (1ml) was added dropwise with caution
followed by 2N NaOH (1ml). When gas evolution ceased the
5 reaction mixture was filtered through a pad of celite
which was well washed with ether. The ether solution
was dried and after removal of the solvent *in-vacuo* the
product was converted to the hydrochloride salt and re-
crystallised from ethanol/ether to give *trans-endo-N,N-*
10 *dimethyl(3-naphthalen-2-ylbicyclo[2.2.1]hept-2-*
yl)methanamine, Mp 249-250 °C, $\alpha_D +44.4$ (c 0.5, MeOH, 25
°C).

Similarly prepared were:

15

trans-exo-N,N-dimethyl(3-naphthalen-2-
ylbicyclo[2.2.1]hept-2-yl)methanamine, M/e 280 ($M+H^+$).

trans-endo-N,N-dimethyl[(2R,3R)-3-naphthalen-2-
20 *ylbicyclo[2.2.1]hept-2-yl]methanamine*, $\alpha_D +44.4$ (c 0.5,
MeOH, 25 °C).

trans-endo-N,N-dimethyl[(2S,3S)-3-naphthalen-2-
ylbicyclo[2.2.1]hept-2-yl]methanamine $\alpha_D +44.4$ (c 0.5,
25 MeOH, 25 °C).

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trans-endo-N-methyl (3-naphthalen-2-ylbicyclo[2.2.1]hept-2-yl)methanamine.

5 trans-endo-N-methyl [(2R,3R)-3-naphthalen-2-ylbicyclo[2.2.1]hept-2-yl)methanamine.

trans-endo-N-methyl [(2S,3S)-3-naphthalen-2-ylbicyclo[2.2.1]hept-2-yl)methanamine, Mp210-212 °C.

10

cis-endo-N,N-dimethyl (3-naphthalen-2-ylbicyclo[2.2.1]hept-2-yl)methanamine.

cis-exo-N,N-dimethyl (3-naphthalen-2-

15 ylbicyclo[2.2.1]hept-2-yl)methanamine.

EXAMPLE 10

20 trans-3-Naphthalen-2-ylbicyclo[2.2.2]oct-5-ene-2-carbonitrile

A mixture of (E)-(2-naphthyl)-acrylonitrile (1.8g, 0.01mole) and 1,3-cyclohexadiene (8g, 0.1mole) in 1,2-dichlorobenzene (10ml) was placed in a teflon lined
25 stainless steel bomb and heated at 180°C for 3 days.

The vessel was allowed to cool to room temperature and the contents transferred to a Buchi flask. The solvent was removed under high vacuum and the product purified by chromatography on flash silica by elution with
 5 dichloromethane to give trans-3-naphthalen-2-ylbicyclo[2.2.2]oct-5-ene-2-carbonitrile, M/e 260 (M+H⁺).

10 Similarly prepared were:

cis-3-naphthalen-2-ylbicyclo[2.2.2]oct-5-ene-2-carbonitrile.

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EXAMPLE 11

trans-3-Naphthalen-2-ylbicyclo[2.2.2]octane-2-carbonitrile

20

To a solution of trans-3-naphthalen-2-ylbicyclo[2.2.2]oct-5-ene-2-carbonitrile (1.2g, mole) in ethyl acetate (50ml) was added 10%Pd-C (120mg). The reaction was hydrogenated at 60psi using a Parr
 25 hydrogenator for 1 hour. The catalyst was removed by filtration through celite and the solvent removed by

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evaporation *in-vacuo*. The product was recrystallised from ethyl acetate/hexane to give trans-3-naphthalen-2-ylbicyclo[2.2.2]octane-2-carbonitrile, Mp108-110°C.

5 Similarly prepared were:

cis-3-naphthalen-2-ylbicyclo[2.2.2]octane-2-carbonitrile.

10

EXAMPLE 12

trans-(3-Naphthalen-2-ylbicyclo[2.2.2]oct-2-yl)methanamine

15

To a stirred solution of trans-3-naphthalen-2-ylbicyclo[2.2.2]octane-2-carbonitrile(1g, mole) in dry ether (30ml) was added a solution of lithium aluminium hydride in tetrahydrofuran (ml, mole). The reaction was heated at reflux for 2 hours. After cooling to room temperature water (1ml) was added dropwise with caution followed by 2NNaOH (1ml). When gas evolution ceased the reaction mixture was filtered through a pad of celite which was well washed with ether. After removal of the solvent *in-vacuo* the product was converted to the hydrochloride salt and re-crystallised from

20

25

ethanol/ether to give trans-(3-naphthalen-2-ylbicyclo[2.2.2]oct-2-yl)methanamine, mp 272-274°C.

Similarly prepared were:

5

cis-(3-naphthalen-2-ylbicyclo[2.2.2]oct-2-yl)methanamine.

10 EXAMPLE 13

trans-*N,N*-Dimethyl(3-naphthalen-2-ylbicyclo[2.2.2]oct-2-yl)methanamine

15 A mixture of trans-(3-naphthalen-2-ylbicyclo[2.2.2]oct-2-yl)methanamine (0.8, mole), 90% formic acid (5ml) and 40% aqueous formaldehyde (5ml) in dimethylformamide (10ml) was heated at reflux for 2 hours. The reaction was poured into ice water and extracted with diethyl
20 ether. The solvent was washed with brine, dried and evaporated to dryness *in-vacuo*. Chromatography on flash silica by elution with 10% methanol/dichloromethane followed by crystallisation of the hydrochloride salt from ethanol ether gave trans-*N,N*-dimethyl(3-naphthalen-
25 2-ylbicyclo[2.2.2]oct-2-yl)methanamine, Mp 236-238°C.

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Similarly prepared were:

cis-*N,N*-dimethyl(3-naphthalen-2-ylbicyclo[2.2.2]oct-2-yl)methanamine.

EXAMPLE 14

10 Tablets each containing 10 mg of active ingredient are made up as follows:

	Active ingredient	10 mg
	Starch	160 mg
15	Microcrystalline cellulose	100 mg
	Polyvinylpyrrolidone (as 10% solution in water)	13 mg
	Sodium carboxymethyl starch	14 mg
	Magnesium stearate	3 mg

20	Total	300 mg

The active ingredient, starch and cellulose are mixed thoroughly. The solution of polyvinylpyrrolidone is mixed with the resultant powders and passed through a sieve. The granules so produced are dried and re-passed

through a sieve. The sodium carboxymethyl starch and magnesium stearate are then added to the granules which, after mixing, are compressed on a tablet machine to yield tablets each weighing 300 mg.

5

EXAMPLE 15

Capsules each containing 20 mg of medicament are made as follows:

10

Active ingredient	20 mg
Dried starch	178 mg
Magnesium stearate	2 mg
Total	200 mg

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The active ingredient, starch and magnesium stearate are passed through a sieve and filled into hard gelatine capsules in 200 mg quantities.

20

EXAMPLE 16

[³H]-Citalopram Binding Assay

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The ability of compounds of the invention to displace [³H]-citalopram from binding sites on rat cerebral cortical membranes was measured in the following way:

5 In each well of a 96 deep well plate was added:

100ml 2nM[³H]-citalopram

600ml 50mM Tris.HCl pH 7.4 containing 150mM NaCl and 5mM KCl

10 100ml Diluted compound, 50mM Tris.HCl pH 7.4 containing 150mM NaCl and 5mM KCl (total binding) or 100mM fluoxetine (non-specific binding)

200ml Membrane preparation (0.75mg protein per ml)

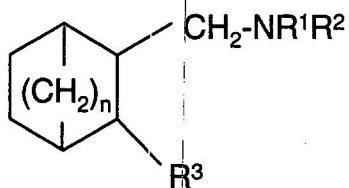
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The microtitre plates were incubated at 37°C for 90 minutes followed by filtration through GF/B filters soaked in 50mM Tris.HCl/0.1% (w/v) polyethylenimine pH 7.4. The filter was washed 5 times with 50mM Tris.HCl.

20 pH 7.4. The filters were removed, dried and the bound tritium determined by liquid scintillation spectrometry. The results were analysed using an automatic spline fitting programme to provide K_i values for each of the compounds.

CLAIMS

1. A compound of the formula:



(I)

in which R^1 and R^2 are each hydrogen or C_{1-4} alkyl, R^3 is a naphthyl, indolyl, benzothienyl, benzofuranyl, benzothiazolyl, quinolinyl or isoquinolinyl group, said group being optionally substituted, and n is 1 or 2; or a salt or ester thereof.

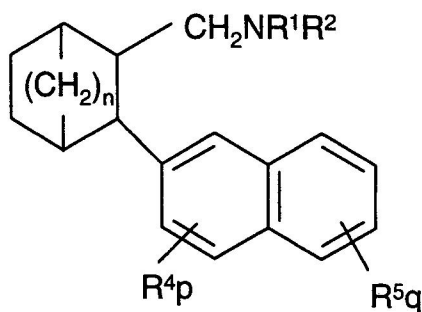
2. A compound according to Claim 1 in which R^3 is β -naphthyl, 2-,3-,5- or 6-indolyl, 2-,3-,5- or 6-benzothienyl, 2-,3-,5- or 6-benzofuranyl, 2- or 5-benzothiazolyl, 2-,3-,6- or 7-quinolinyl or 3-,6- or 7-isoquinolinyl, said group being optionally substituted.

3. A compound according to Claim 2 in which R^3 is optionally substituted β -naphthyl.

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4. A compound according to any of Claims 1 to 3 in which n is 1.

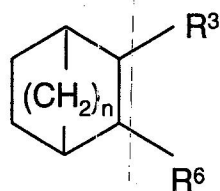
5. A compound according to Claim 1 of the formula



10 in which R¹ and R² are each hydrogen or C₁₋₄ alkyl, R⁴ and R⁵ are each C₁₋₄ alkyl, C₁₋₄ alkoxy, carboxy, hydroxy, cyano, halo, trifluoromethyl, -NR'R'' or -CONR'R'', where R' and R'' are each hydrogen or C₁₋₄ alkyl, and p and q are each 0 or 1
15 to 3, such that the sum of p and q is 0 or 1 to 3.

6. A compound according to Claim 5 in which p and q are both 0, and n is 1.

20 7. A compound of the formula



(II)

where R^3 and n have the values defined in Claim 1,
and R^6 is $-CN$, $-CONR^1R^2$, $-CH_2NCO$, $-CHO$ or $-COOR^7$

5 where R^1 and R^2 are as defined in Claim 1 and R^7 is
 C_{1-4} alkyl.

8. A pharmaceutical formulation comprising a compound
according to any of Claims 1 to 6 together with a
10 pharmaceutically acceptable salt or ester thereof.

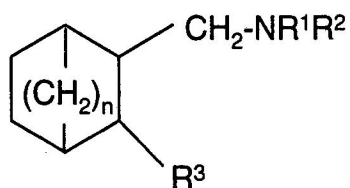
9. A compound according to any of Claims 1 to 6, or a
pharmaceutically acceptable salt thereof, for use
as a pharmaceutical.

15 10. The use of a compound according to any of Claims 1
to 6, or a pharmaceutically acceptable salt or
ester thereof, in the manufacture of a medicament
for treating a central nervous system disorder.

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ABSTRACT

A pharmaceutical compound of the formula



(I)

5 in which R^1 and R^2 are each hydrogen or C_{1-4} alkyl, R^3
 is a naphthyl, indolyl, benzothienyl, benzofuranyl,
 benzothiazolyl, quinolinyl or isoquinolinyl group, said
 10 group being optionally substituted, and n is 1 or 2; or
 a salt or ester thereof.

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TRADUCCION: Se traduce la carátula y las reivindicaciones anexas a una copia de la solicitud de patente inglesa No. 9908021.0 escrita en inglés para el invento denominado: **COMPUESTOS FARMACEUTICOS.**

La Oficina de Patentes de Inglaterra

Oficina de Patentes
Concepto House
Cardiff Road
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NP10 8QQ

Yo, el abajo firmante, estando debidamente autorizado y de conformidad con la sección 74(1) y (4) del Acta de Deregulación y Contratación Externa 1994, para firmar y expedir certificados en nombre del Contralor General, certifico por el presente, que el documento anexo a este es una copia fiel de los documentos que se presentaron originalmente en relación con la solicitud de la Patente identificada aquí.

De acuerdo con la Reglamentación de Patentes de 1982, (Doble registro de Compañías), si una compañía mencionada en este certificado y cualquier documento que lo acompañe, ha registrado bajo el Acta de Sociedades de 1980 con el mismo nombre con el que fue registrada inmediatamente antes del doble registro, salvo para la sustitución o la inclusión, la última parte del nombre, las palabras "compañía pública limitada" o sus equivalentes en Galés, se refieren al nombre de la compañía en este certificado y todo documento que lo acompañe deberá ser tratados como referencias al nombre con el cual fue registrado así dos veces.

De acuerdo con el Reglamento, las palabras, "compañía pública limitada" pueden reemplazarse por c.p.l., cpl, C.P.L., o PLC.

El doble registro bajo el Acta de Compañías no constituye una entidad legal nueva, sino simplemente somete la compañía a algunos reglamentos legales adicionales de la compañía.

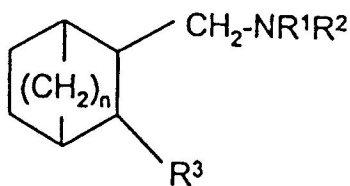
Firmado : (Ilegible)

Fechado: 17 de marzo de 2000

Agencia Administrativa del Departamento de Comercio e Industria

REIVINDICACIONES

1. Un compuesto de la fórmula:



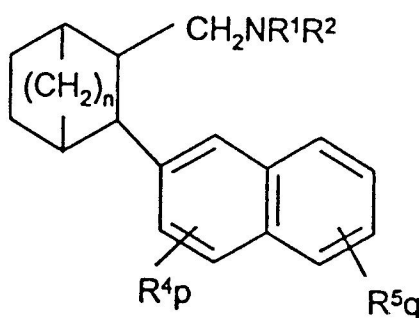
(I)

En la cual R^1 y R^2 son cada uno hidrógeno o alquilo C_{1-4} , R^3 es uno de los grupos naftilo, indolilo, benzotienilo, benzofuranilo, benzotiazolilo, quinolinilo o isoquinolinilo, dicho grupo está opcionalmente sustituido, y n es 1 o 2; o una sal o éster de este.

2. Un compuesto de acuerdo a la reivindicación 1 en la cual R^3 es β -naftilo, 2-, 3-, -5-, o 6-indolilo, 2-, 3-, 5-, o benzotienilo, 2-, 3-, 5- o 6- benzofuranilo, 2- o 5- benzotiazolilo, 2-, 3-, 6- o 7- quinolinilo o 3-, 6-, o 7- isoquinolinilo, dicho grupo siendo opcionalmente sustituido.

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3. Un compuesto de acuerdo a la reivindicación 2 en el cual R^3 es opcionalmente sustituido β -naftilo.
4. Un compuesto de acuerdo con una cualquiera de las reivindicaciones 1 a 3 en el cual n es 1.
5. Un compuesto de acuerdo a la reivindicación 1 de la fórmula



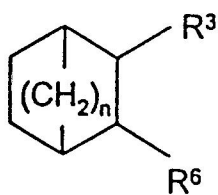
En el cual R^1 y R^2 es cada uno hidrógeno o alquilo C_{1-4} , R^4 y R^5 es cada uno alquilo C_{1-4} , alcoxi C_{1-4} , carboxi, hidroxí, ciano, halo, trifluorometilo, $-NR'R''$ o $-CONR'R''$,

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en donde R' y R'' son cada uno hidrógeno o alquilo C_{1-4} , y p y q son cada uno 0 o 1 a 3.

6. Un compuesto de acuerdo a la reivindicación 5 en el cual p y q son ambos 0, y n es 1.

7. Un compuesto de la fórmula



(II)

En donde R^3 y n tienen los valores definidos en la reivindicación 1, y R^6 es $-CN$, $-CONR^1R^2$, $-CH_2NCO_2$, $-CHO$ o $-COOR^7$ en donde R^1 y R^2 son como se definió en la reivindicación 1 y R^7 es alquilo C_{1-4} .

8. Una formulación farmacéutica comprende un compuesto de acuerdo con una de las

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reivindicaciones 1 a 6 junto con una sal farmacéuticamente aceptable o éster de ellas.

9. Un compuesto de acuerdo a una cualquiera de las reivindicaciones 1 a 6, o una sal farmacéuticamente aceptable de ella, para usar como un farmacéutico.

10. El uso de un compuesto de acuerdo a una cualquiera de las reivindicaciones 1 a 6, o una sal farmacéuticamente aceptable o éster de ellas, en la fabricación de un medicamento para el tratamiento de desórdenes del sistema nervioso central.