

(12) PATENT
(19) AUSTRALIAN PATENT OFFICE

(11) Application No. AU 200065479 B2
(10) Patent No. 774741

(54) Title
New cyano-indole serotonin-reuptake inhibitor compounds, a process for their preparation and pharmaceutical compositions containing them

(51)⁷ International Patent Classification(s)
C07D 401/14 A61P 025/22
A61K 031/404 A61P 025/24
A61K 031/47 C07D 403/14
A61K 031/498 C07D 405/14
A61K 031/53 C07D 417/14

(21) Application No: **200065479**

(22) Application Date: **2000.10.12**

(30) Priority Data

(31) Number	(32) Date	(33) Country
99 12668	1999.10.12	FR

(43) Publication Date : **2001.04.26**

(43) Publication Journal Date : **2001.04.26**

(44) Accepted Journal Date : **2004.07.08**

(71) Applicant(s)
Les Laboratoires Servier

(72) Inventor(s)
Gilbert Lavielle; Olivier Muller; Mark Millan; Didier Cussac; Anne Dekeyne

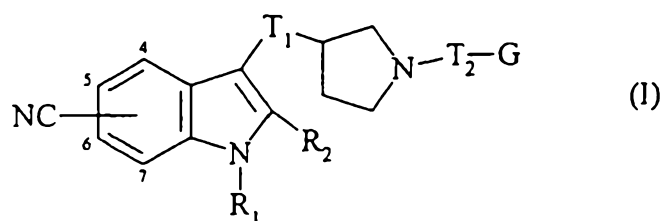
(74) Agent/Attorney
WATERMARK PATENT and TRADEMARK ATTORNEYS, Locked Bag 5, HAWTHORN VIC 3122

(56) Related Art
EP 464558
EP 610134
EP 814084

ABSTRACT

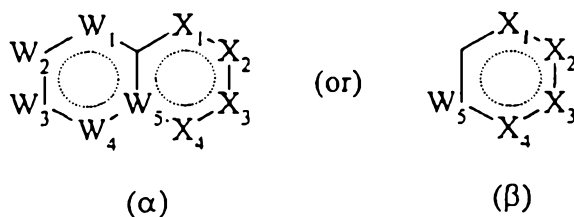
NEW CYANO-INDOLE SEROTONIN-REUPTAKE INHIBITOR COMPOUNDS, A PROCESS FOR THEIR PREPARATION AND PHARMACEUTICAL COMPOSITIONS CONTAINING THEM

Compound of formula (I) :



wherein :

- R_1 and R_2 each independently of the other represents a hydrogen atom or an alkyl group,
- T_1 and T_2 each independently of the other represents an alkylene group,
- G represents a heterocyclic group of formula (α) or (β) :



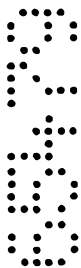
wherein :

W_1 to W_5 and X_1 to X_4 are so selected as to form a chemically stable group and are defined as follows :

- W_1 , W_2 and W_3 each independently of the others represents a nitrogen atom or a group CR_3 , NR_4 or CO ,
- W_4 represents a nitrogen atom or a group CR_3 , NR_4 or CO ,
- W_5 represents a carbon atom or a nitrogen atom,
- X_1 represents a bond, a nitrogen atom or a group CR_3 or NR_4 ,

- X_2 to X_4 each independently of the others represents a group CR_3 , NR_4 , CO , SR_4 or SO_2 or an oxygen, sulphur or nitrogen atom,
- R_3 represents a hydrogen or halogen atom or an alkyl, hydroxy, perhaloalkyl, nitro or optionally substituted amino group,
- 5 - R_4 represents a hydrogen atom or an alkyl group, optionally substituted aryl group or optionally substituted arylalkyl group,
- R_5 represents a group R_3 , or two adjacent groups R_5 form, together with the carbon atoms carrying them, a saturated, partially unsaturated or unsaturated mono- or bi-cyclic group optionally containing from 1 to 5 hetero atoms selected from nitrogen, oxygen and sulphur, the said group being optionally substituted by one or more groups selected from R_3 or oxo.

Medicaments.



AUSTRALIA

Patents Act 1990

ORIGINAL
COMPLETE SPECIFICATION
STANDARD PATENT

Application Number:

Lodged:

Invention Title:

NEW CYANO-INDOLE SEROTONIN-REUPTAKE INHIBITOR COMPOUNDS, A
PROCESS FOR HEIR PREPARATION AND PHARMACEUTICAL
COMPOSITIONS CONTAINING THEM

The following statement is a full description of this invention, including the best method of
performing it known to :- us

The present invention relates to new cyano-indole serotonin-reuptake inhibitor compounds, to a process for their preparation and to pharmaceutical compositions containing them.

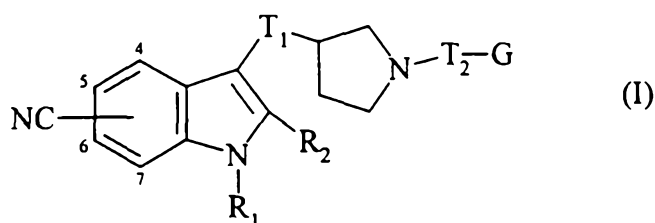
Compounds characterised by the combination of an indole ring system and a 2,3-dihydro-1,4-benzodioxin ring system have been described for their serotonin-reuptake inhibiting properties (WO 9717343). Indoles substituted on the aromatic moiety have also been
5 claimed in Patent Application EP 814 084 for their action at the level of the serotonin-reuptake sites. Other compounds having related properties have been claimed in Patent Application WO 9633710 and have a benzopyran structure.

Serotonin-reuptake inhibitors constitute a heterogeneous group of therapeutic agents. They
10 are used in the treatment of pathologies associated with a serotonin deficit at the level of the central neurone synapses. The inhibition of serotonin reuptake by binding to transporters or presynaptic receptors is a means of restoring nerve transmission.

The use of compounds having those inhibitory properties may constitute an alternative to the use of tricyclic antidepressants or of monoamine oxidase inhibitors in the treatment of
15 depression and associated disorders (Annals of Pharmacotherapy, 1994, 28, 1359), panic attacks and obsessive-compulsive disorders (Human Psychopharmacology, 1995, 10, 5199). The efficacy of compounds having such pharmacological properties (Journal of Psychopharmacology, 1994, 8, 238) is reinforced by the fact that they are better tolerated (International Clinical Psychopharmacology, 1995, 9 suppl. 4, 33) and are safer to use
20 (Annals of Pharmacology, reference cited).

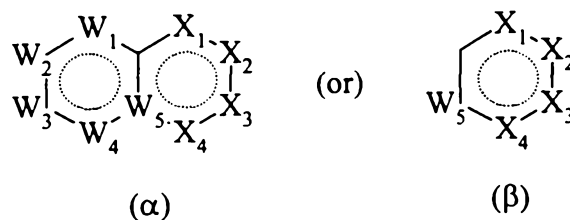
The compounds of the present invention are characterised by an indole ring system substituted on the benzene moiety by a cyano group and in the 3-position by an N-substituted 3-pyrrolylalkyl group. That novel structure confers upon them a powerful
25 serotonin-reuptake inhibiting character. They will therefore be useful therapeutically in the treatment of depression, panic attacks, obsessive-compulsive disorders, phobias, impulsive disorders associated with drug abuse, bulimia nervosa and anxiety.

The present invention relates to compounds of formula (I) :



wherein :

- R_1 and R_2 each independently of the other represents a hydrogen atom or a linear or branched (C_1 - C_6)alkyl group,
- T_1 and T_2 each independently of the other represents a linear or branched (C_1 - C_6)-alkylene group,
- G represents a heterocyclic group of formula (α) or (β) :



wherein :

W_1 to W_5 and X_1 to X_4 are so selected as to form a chemically stable group and are defined as follows :

- W_1 , W_2 and W_3 each independently of the others represents a nitrogen atom or a group CR_5 , NR_4 or CO ,
- W_4 represents a nitrogen atom or a group CR_3 , NR_4 or CO ,
- W_5 represents a carbon atom or a nitrogen atom,
- X_1 represents a bond, a nitrogen atom or a group CR_3 or NR_4 ,

- X_2 to X_4 each independently of the others represents a group CR_3 , NR_4 , CO , SR_4 or SO_2 or an oxygen, sulphur or nitrogen atom,
- R_3 represents a hydrogen or halogen atom or a linear or branched (C_1-C_6) alkyl group, hydroxy group, linear or branched (C_1-C_6) perhaloalkyl group, nitro group, or amino group (optionally substituted by one or two groups selected from linear or branched (C_1-C_6) alkyl and benzyl),
- R_4 represents a hydrogen atom or a linear or branched (C_1-C_6) alkyl group, optionally substituted aryl group or optionally substituted arylalkyl group,
- R_5 represents a group R_3 , or two adjacent groups R_3 form, together with the carbon atoms carrying them, a saturated, partially unsaturated or unsaturated mono- or bi-cyclic group optionally containing from 1 to 5 hetero atoms selected from nitrogen, oxygen and sulphur, the said group being optionally substituted by one or more groups selected from R_3 and oxo,

it being understood that, in formulae (α) and (β) , at least one heteroatom is present, the dotted lines indicate that the groups in question may contain an unsaturated bond or a plurality of conjugated or unconjugated unsaturated bonds and that, if there is no unsaturated bond, the remaining valences are occupied by hydrogen atoms, the groups (α) and (β) being linked to T_2 by any one of their ring junctions,

their enantiomers and diastereoisomers, and addition salts thereof with a pharmaceutically acceptable acid or base.

Among the pharmaceutically acceptable acids there may be mentioned, by way of non-limiting examples, hydrochloric acid, hydrobromic acid, sulphuric acid, phosphonic acid, acetic acid, trifluoroacetic acid, lactic acid, pyruvic acid, malonic acid, succinic acid, glutaric acid, fumaric acid, tartaric acid, maleic acid, citric acid, ascorbic acid, methanesulphonic acid, camphoric acid etc..

Among the pharmaceutically acceptable bases there may be mentioned, by way of non-limiting examples, sodium hydroxide, potassium hydroxide, triethylamine, tert-butylamine etc..

An aryl group is understood to mean a phenyl or naphthyl group.

The expression "optionally substituted" applied to aryl or arylalkyl groups means that the groups in question are optionally substituted by one or more groups selected from halogen atoms, linear or branched (C₁-C₆)alkyl groups, hydroxy groups, linear or branched (C₁-C₆)perhaloalkyl groups, nitro groups, and amino groups (optionally substituted by one or two groups selected from linear or branched (C₁-C₆)alkyl and benzyl).

Advantageously, the invention relates to compounds of formula (I) wherein the cyano group is attached in the 5-position of the indole ring system.

Another advantageous aspect of the invention relates to compounds of formula (I) wherein the cyano group is attached in the 6-position of the indole ring system.

Preferably, in the compounds of formula (I) R₁ and R₂ each represents a hydrogen atom.

Preferred compounds of the invention are those wherein T₁ represents a methylene group.

The preferred aryl group of the invention is the phenyl group.

In preferred groups G of the invention, R₃, R₄ and R₅ are advantageously selected from linear or branched (C₁-C₆)alkyl groups, hydrogen atoms and halogen atoms.

Among preferred groups G of the invention there may be mentioned, without implying any limitation, the groups :

2-furyl; 2,4-dioxo-1,4-dihydro-3(2*H*)-quinazolinyl; 3-oxo-[1,2,4]triazolo[4,3-*a*]pyridin-2(3*H*)-yl; 1-oxo-2(1*H*)-phthalazinyl; 7-methyl-5-oxo-5*H*-[1,3]thiazolo[3,2-*a*]pyrimidin-6-yl; 6-chloro-2-oxo-2,3-dihydro-1*H*-indol-5-yl; 2-oxo-2,3-dihydro-1*H*-indol-5-yl; 2-oxo-1,2,3,4-tetrahydro-6-quinolinyl; 3-benzyl-5-methyl-2,6-dioxo-3,6-dihydro-1(2*H*)-pyrimidinyl; 1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl; 1,1,3-trioxo-1,3-dihydro-2*H*-1,2-benzisothiazol-2-yl; 1,3-dioxo-3,6-dihydropyrrolo[3,4-*c*]carbazol-2(1*H*)-yl; 1,3-dioxo-

1,3-dihydro-2*H*-benzo[c]isoindol-2-yl; 3,5-dimethyl-2,6-dioxo-3,6-dihydro-1(2*H*)-pyrimidinyl.

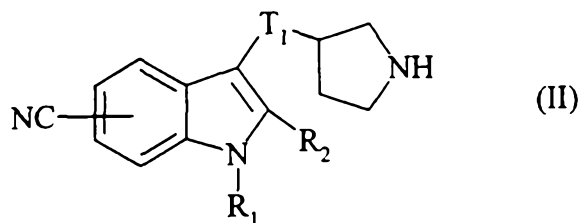
An especially advantageous aspect of the invention relates to compounds of formula (I) wherein R₁ and R₂ each represents a hydrogen atom, T₁ represents a methylene group, T₂ represents an alkylene group (for example methylene or ethylene) and G is selected from the groups 2-furyl; 2,4-dioxo-1,4-dihydro-3(2*H*)-quinazolinyl; 3-oxo-[1,2,4]triazolo-[4,3-*a*]pyridin-2(3*H*)-yl; 1-oxo-2(1*H*)-phthalazinyl; 7-methyl-5-oxo-5*H*-[1,3]thiazolo-[3,2-*a*]pyrimidin-6-yl; 6-chloro-2-oxo-2,3-dihydro-1*H*-indol-5-yl; 2-oxo-2,3-dihydro-1*H*-indol-5-yl; 2-oxo-1,2,3,4-tetrahydro-6-quinolinyl; 3-benzyl-5-methyl-2,6-dioxo-3,6-dihydro-1(2*H*)-pyrimidinyl; 1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl; 1,1,3-trioxo-1,3-dihydro-2*H*-1,2-benzisothiazol-2-yl; 1,3-dioxo-3,6-dihydropyrrolo[3,4-*c*]carbazol-2(1*H*)-yl; 1,3-dioxo-1,3-dihydro-2*H*-benzo[c]isoindol-2-yl; 3,5-dimethyl-2,6-dioxo-3,6-dihydro-1(2*H*)-pyrimidinyl.

Among those compounds preference will be given to those wherein the cyano group is attached in the 5- or 6-position of the indole ring system, more especially those wherein the cyano group is attached in the 5-position.

Among the preferred compounds of the invention, there may be mentioned more especially :

- 3-({1-[2-(7-methyl-5-oxo-5*H*)-[1,3]thiazolo[3,2-*a*]pyrimidin-6-yl)ethyl]-3-pyrrolidinyl)methyl)-1*H*-indole-5-carbonitrile hydrochloride
- 3-({1-[2-(6-chloro-2-oxo-2,3-dihydro-1*H*-indol-5-yl)ethyl]-3-pyrrolidinyl)methyl)-1*H*-indole-5-carbonitrile hydrochloride.

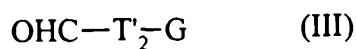
The invention relates also to a process for the preparation of compounds of formula (I), which process is characterised in that there is used as starting material a compound of formula (II) :



wherein R_1 , R_2 and T_1 are as defined for formula (I),

which is subjected :

→ either to the action, in a reducing medium, of an aldehyde of formula (III) :



wherein G is as defined for formula (I) and T'_2 represents a bond or a linear or branched (C_1 - C_5)alkylene group,

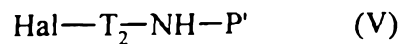
→ or to the action, in a basic medium, of a halogenated compound of formula (IV) :



wherein T_2 is as defined for formula (I) and Hal represents a halogen atom,

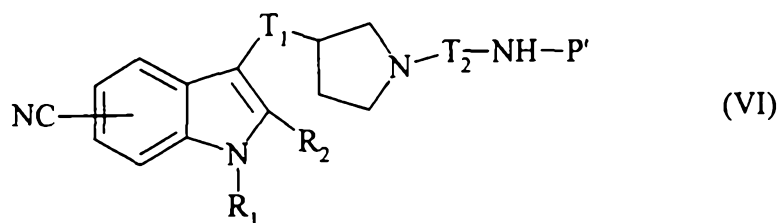
to yield a compound of formula (I),

or which is subjected to the action, in a basic medium, of a compound of formula (V) :



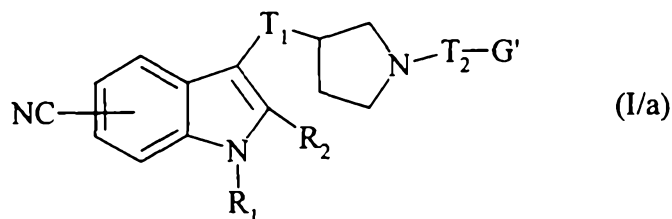
wherein T_2 is as defined for formula (I), Hal represents a halogen atom and P' is a protecting group for the amine,

to yield a compound of formula (VI),



wherein R_1 , R_2 , T_1 , T_2 and P' are as defined hereinbefore,

which compound of formula (VI), after deprotection of the primary amine group, is condensed with a cyclic group that is a precursor of group G defined for formula (I) to yield a compound of formula (I/a) :



a particular case of the compounds of formula (I) wherein R_1 , R_2 , T_1 and T_2 are as defined hereinbefore and G' represents a group as defined for G in formula (I), it being understood that G' is attached to T_2 by a nitrogen atom,

which compounds of formulae (I/a) and (I),

- may be purified, if necessary, according to a conventional purification technique,
- are separated, where appropriate, into their isomers according to a conventional separation technique,
- are converted, if desired, into addition salts thereof with a pharmaceutically acceptable acid or base.

The present invention relates also to pharmaceutical compositions comprising as active ingredient at least one compound of formula (I), alone or in combination with one or more inert, non-toxic pharmaceutically acceptable excipients or carriers.

Among the pharmaceutical compositions according to the invention there may be mentioned more especially those that are suitable for oral, parenteral or nasal administration, tablets or dragées, sublingual tablets, gelatin capsules, lozenges, suppositories, creams, ointments, dermal gels etc..

- 5 The useful dosage varies according to the age and weight of the patient, the nature and severity of the disorder and the route of administration, which may be oral, nasal, rectal or parenteral. The unit dose generally ranges from 0.1 to 500 mg for a treatment in from 1 to 3 administrations per 24 hours.

The following Examples illustrate the invention and do not limit it in any way.

- 10 The starting materials used are known products or are prepared according to known procedures.

PREPARATION A : 3-[(3-Pyrrolidinyl)methyl]-1*H*-indole-5-carbonitrile

- 15 Hydrogenolysis of 0.32 mol (96 g) of 3-(1-benzyl-3-pyrrolidinylmethyl)-1*H*-indole-5-carbonitrile (described in Patent Application EP 610 134) is carried out in 1.7 litres of ethanol in the presence of 9.6 g of carbon containing 20 % palladium hydroxide moist (Pearlman's catalyst) and 0.32 mol of hydrochloric acid in ethanol at 70°C and at atmospheric pressure. After absorption of the theoretical amount of hydrogen, the catalyst is filtered off and the filtrate is then concentrated. The base is precipitated out by 1*N* sodium hydroxide solution and extracted using dichloromethane to yield the expected product.
- 20

PREPARATION B : tert-Butyl 2-bromoethylcarbamate

- Under an inert atmosphere and at ambient temperature, a solution of 62 mmol (10 g) of *N*-(tert-butoxycarbonyl)ethanolamine in 100 ml of acetonitrile is prepared, to which 74.5 mmol (24.7 g) of tetrabromomethane are added. 68.2 mmol (17.9 g) of triphenylphosphine dissolved in 150 ml of acetonitrile are then added dropwise. The reaction
- 25

mixture is stirred at ambient temperature for 30 minutes and is then concentrated. The residue is taken up in isopropyl ether and, after filtration, the filtrate is concentrated to obtain the title product.

EXAMPLE 1 : 3-[[1-(2-Furylmethyl)-3-pyrrolidinyl)methyl]-1*H*-indole-5-carbonitrile oxalate

Under an inert atmosphere and at ambient temperature, 47.3 mmol (10 g) of 3-[3-pyrrolidinylmethyl]-1*H*-indole-5-carbonitrile (described in Preparation A) are dissolved in 650 ml of 1,2-dichloroethane, and then 47.3 mmol (4.26 g) of furaldehyde are added. Stirring is carried out for 10 minutes, and 66.2 mmol (13.79 g) of sodium triacetoxyborohydride are added. After 30 minutes at ambient temperature, 350 ml of saturated sodium hydrogen carbonate solution are added. The organic phase is separated off, washed with water and dried over magnesium sulphate.

Purification is carried out by chromatography on silica using a mixture of dichloromethane/methanol/ammonia 98/2/0.2 as eluant. The compound obtained is converted into the salt by one equivalent of oxalic acid in ethanol.

Melting point : 120-122°C

Elemental microanalysis :

	C	H	N
% calculated	63.79	5.35	10.63
% found	63.54	5.58	10.37

EXAMPLE 2 : 3-[(1-{2-[2,4-Dioxo-1,4-dihydro-3(2*H*)-quinazolinyl]ethyl}-3-pyrrolidinyl)methyl]-1*H*-indole-5-carbonitrile hydrochloride

Under an inert atmosphere and at ambient temperature, 47.3 mmol (10 g) of 3-[3-pyrrolidinylmethyl]-1*H*-indole-5-carbonitrile, 47.3 mmol (9.97 g) of 3-(2-chloroethyl)-2,4-(1*H*,3*H*)-quinazolinedione and 47.3 mmol (3.73 g) of sodium hydrogen carbonate are dissolved in 100 ml of dimethylformamide, and stirring is carried out at 100°C for 6 hours. The reaction mixture is concentrated and the residue is taken up in dichloromethane. The organic phase is washed with water and then with saturated

sodium chloride solution, and is dried over magnesium sulphate. Purification is carried out by chromatography on silica using a mixture of dichloromethane/methanol/ammonia 95/5/0.5 as eluant. The compound obtained is converted into the salt by one equivalent of hydrochloric acid in ethanol.

5 Melting point : 152-154°C

Elemental microanalysis :

	C	H	N	Cl
% calculated	64.07	5.38	15.57	7.88
% found	63.81	5.34	15.20	7.64

10 **EXAMPLE 3 :** 3-[(1-{2-[3-Oxo-[1,2,4]triazolo[4,3-a]pyridin-2(3H)-yl]ethyl}-3-pyrrolidinyl)methyl]-1H-indole-5-carbonitrile hydrochloride

The expected product is obtained according to the procedure described in Example 2, replacing the 3-(2-chloroethyl)-2,4-(1H,3H)-quinazolinedione by 2-(2-chloroethyl)-[1,2,4]triazolo[4,3-a]pyridin-3(2H)-one.

15 Melting point : 140°C

Elemental microanalysis :

	C	H	N	Cl
% calculated	62.48	5.48	19.87	8.38
% found	62.48	5.68	19.54	8.48

20 **EXAMPLE 4 :** 3-[(1-{2-[1-Oxo-2(1H)-phthalazinyl]ethyl}-3-pyrrolidinyl)methyl]-1H-indole-5-carbonitrile hydrochloride

The expected product is obtained according to the procedure described in Example 2, replacing the 3-(2-chloroethyl)-2,4-(1H,3H)-quinazolinedione by 2-(2-chloroethyl)-1(2H)-phthalazinone.

25 Melting point : 125-127°C

Elemental microanalysis :

	C	H	N	Cl
% calculated	66.43	5.57	16.14	8.17
% found	66.74	5.63	15.79	8.27

EXAMPLE 5 : 3-({1-[2-(7-Methyl-5-oxo-(5*H*)-[1,3]thiazolo[3,2-*a*]pyrimidin-6-yl)-ethyl]-3-pyrrolidinyl)methyl)-1*H*-indole-5-carbonitrile hydrochloride

The expected product is obtained according to the procedure described in Example 2, replacing the 3-(2-chloroethyl)-2,4-(1*H*,3*H*)-quinazolinedione by 6-(2-chloroethyl)-7-methyl-5*H*-[1,3]thiazolo[3,2-*a*]pyrimidin-5-one.

Melting point : 234-236°C

Elemental microanalysis :

	C	H	N	S	Cl
% calculated	60.85	5.33	15.43	7.06	7.81
% found	59.83	5.38	14.69	6.90	7.69

EXAMPLE 6 : 3-({1-[2-(6-Chloro-2-oxo-2,3-dihydro-1*H*-indol-5-yl)ethyl]-3-pyrrolidinyl)methyl)-1*H*-indole-5-carbonitrile hydrochloride

The expected product is obtained according to the procedure described in Example 2, replacing the 3-(2-chloroethyl)-2,4-(1*H*,3*H*)-quinazolinedione by 6-chloro-5-(2-chloroethyl)-1,3-dihydro-2*H*-indol-2-one.

Melting point : 115-117°C

Elemental microanalysis :

	C	H	N	Cl
% calculated	63.30	5.31	12.30	15.57
% found	63.57	5.42	12.06	15.27

EXAMPLE 7 : 3-({1-[2-(2-Oxo-2,3-dihydro-1*H*-indol-5-yl)ethyl]-3-pyrrolidinyl)methyl)-1*H*-indole-5-carbonitrile hydrochloride

The expected product is obtained according to the procedure described in Example 2, replacing the 3-(2-chloroethyl)-2,4-(1*H*,3*H*)-quinazolinedione by 5-(2-chloroethyl)-1,3-dihydro-2*H*-indol-2-one.

Melting point : 118-120°C

Elemental microanalysis :

	C	H	N	Cl
% calculated	68.48	5.99	13.31	8.42
% found	68.85	6.30	12.81	8.50

5 **EXAMPLE 8 :** 3-({1-[2-(2-Oxo-1,2,3,4-tetrahydro-6-quinolinyl)ethyl]-3-pyrrolidinyl)methyl}-1*H*-indole-5-carbonitrile hydrochloride

The expected product is obtained according to the procedure described in Example 2, replacing the 3-(2-chloroethyl)-2,4-(1*H*,3*H*)-quinazolinedione by 6-(2-bromoethyl)-3,4-dihydro-2(1*H*)-quinolinone.

10 Melting point : 110°C (dec.)

Elemental microanalysis :

	C	H	N	Cl
% calculated	69.03	6.26	12.88	8.15
% found	69.10	6.40	12.31	8.19

15 **EXAMPLE 9 :** 3-[(1-{2-[3-Benzyl-5-methyl-2,6-dioxo-3,6-dihydro-1(2*H*)-pyrimidinyl]ethyl}-3-pyrrolidinyl)methyl]-1*H*-indole-5-carbonitrile

The expected product is obtained according to the procedure described in Example 2, replacing the 3-(2-chloroethyl)-2,4-(1*H*,3*H*)-quinazolinedione by 1-benzyl-3-(2-chloroethyl)-5-methyl-2,4-(1*H*,3*H*)-pyrimidinedione.

20 Melting point : 130-132°C

Elemental microanalysis :

	C	H	N	Cl
% calculated	66.72	6.00	13.89	7.03
% found	66.49	6.12	13.38	6.99

25 **EXAMPLE 10 :** 3-({1-[2-(1,3-Dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-pyrrolidinyl)methyl}-1*H*-indole-5-carbonitrile hydrochloride

Step 1 : *tert-Butyl 2-{3-[(5-cyano-1H-indol-3-yl)methyl]-1-pyrrolidinyl}ethyl-carbamate*

Under an inert atmosphere, 47.3 mmol (10 g) of 3-[(3-pyrrolidinyl)methyl]-1H-indole-5-carbonitrile, 47.3 mmol (9.95 g) of the product described in Preparation B and 1.55 ml of 2-butanone are mixed together and then 47.3 mmol (4.45 g) of potassium hydrogen carbonate are added. The mixture is stirred at 80°C for 2 hours. After hydrolysis and separating off, the organic phase is washed with saturated sodium chloride solution, dried over magnesium sulphate, filtered and concentrated. Purification is carried out by chromatography on silica, using a mixture of dichloromethane/methanol/ammonia 97/3/0.3 as eluant, to yield the expected product.

Step 2 : *3-{[1-(2-Aminoethyl)-3-pyrrolidinyl]methyl}-1H-indole-5-carbonitrile*

At ambient temperature, 44.4 mmol (5 g) of the product described in the previous Step are dissolved in a mixture of 150 ml of 3N hydrochloric acid and 100 ml of ethyl acetate. The mixture is stirred at that temperature for 30 minutes. After separating the two phases, the acid phase is concentrated. The residue is taken up in 0.1N sodium hydroxide solution and is then extracted with dichloromethane. The organic phase is washed with water and then with saturated sodium chloride solution, and is dried over magnesium sulphate, filtered and concentrated to obtain the title product.

Step 3 : *3-({1-[2-(1,3-Dioxo-1,3-dihydro-2H-isoindol-2-yl)ethyl]-3-pyrrolidinyl}methyl)-1H-indole-5-carbonitrile hydrochloride*

11.2 mmol (3 g) of the product obtained in the previous Step, 12.3 mmol (1.82 g) of phthalic anhydride and then 28 ml of glacial acetic acid are mixed together in succession. The reaction mixture is heated at reflux for 1 hour, and the acetic acid is then evaporated off. The residue is taken up in 1N sodium hydroxide solution and is extracted with dichloromethane. The organic phase is washed with water and then with saturated sodium chloride solution, and is dried over magnesium sulphate, filtered and concentrated. Purification is carried out by chromatography on silica, using a mixture of

dichloromethane/methanol/ammonia 97/3/0.3 as eluant. The product obtained is converted into the salt by one equivalent of hydrochloric acid in ethanol.

Melting point : 140-142°C

Elemental microanalysis :

	C	H	N	Cl
% calculated	66.28	5.33	12.88	8.15
% found	65.68	5.42	12.30	8.32

EXAMPLE 11 : 3-({1-[2-(1,1,3-Trioxo-1,3-dihydro-2*H*-1,2-benzisothiazol-2-yl)-ethyl]-3-pyrrolidinyl)methyl}-1*H*-indole-5-carbonitrile hydrochloride

The expected product is obtained according to the procedure described in Example 10, replacing the phthalic anhydride by methyl 2-chlorosulphonylbenzoate.

EXAMPLE 12 : 3-({1-[2-(1,3-Dioxo-1,3-dihydro-2*H*-benzo[*e*]isoindol-2-yl)ethyl]-3-pyrrolidinyl)methyl}-1*H*-indole-5-carbonitrile hydrochloride

The expected product is obtained according to the procedure described in Example 10, replacing the phthalic anhydride by naphtho[1,2-*c*]furan-1,3-dione.

Melting point : 112-116°C

Elemental microanalysis :

	C	H	N	Cl
% calculated	69.34	5.20	11.55	7.31
% found	68.58	5.49	11.10	6.90

EXAMPLE 13 : 3-[(1-{2-[6-Methyl-1,3-dioxo-3,6-dihydropyrrolo[3,4-*c*]carbazol-2(1*H*)-yl]ethyl}-3-pyrrolidinyl)methyl]-1*H*-indole-5-carbonitrile hydrochloride

The expected product is obtained according to the procedure described in Example 10, replacing the phthalic anhydride by 1*H*-furo[3,4-*c*]carbazole-1,3(6*H*)-dione.

Melting point : 210-215°C

Elemental microanalysis :

	C	H	N	Cl
% calculated	69.20	5.25	13.02	6.59
% found	68.70	5.21	12.65	6.87

EXAMPLE 14 : 3-({1-[2-(3,5-Dimethyl-2,6-dioxo-3,6-dihydro-1(2*H*)-pyrimidinyl)ethyl]-3-pyrrolidinyl}-methyl)-1*H*-indole-5-carbonitrile hydrochloride

The expected product is obtained according to the procedure described in Example 2, replacing the 3-(2-chloroethyl)-2,4-(1*H*,3*H*)-quinazolinedione by 3-(2-chloroethyl)-1,5-dimethyl-2,4-(1*H*,3*H*)-pyrimidinedione.

Elemental microanalysis :

	C	H	N	Cl
% calculated	61.75	6.12	16.37	8.28
% found	61.31	6.54	15.94	8.08

The following compounds are obtained in the same manner :

EXAMPLE 15 : 3-[(1-{2-[2,4-Dioxo-1,4-dihydro-3(2*H*)-quinazolinyl]ethyl}-3-pyrrolidinyl)methyl]-1*H*-indole-6-carbonitrile hydrochloride

EXAMPLE 16 : 3-({1-[2-(7-Methyl-5-oxo-(5*H*)-[1,3]thiazolo[3,2-*a*]pyrimidin-6-yl)ethyl]-3-pyrrolidinyl}-methyl)-1*H*-indole-6-carbonitrile hydrochloride

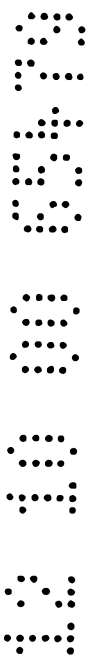
EXAMPLE 17 : 3-({1-[2-(6-Chloro-2-oxo-2,3-dihydro-1*H*-indol-5-yl)ethyl]-3-pyrrolidinyl}-methyl)-1*H*-indole-6-carbonitrile hydrochloride

EXAMPLE 18 : 3-({1-[2-(1,3-Dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-pyrrolidinyl}-methyl)-1*H*-indole-6-carbonitrile hydrochloride

EXAMPLE 19 : 3-[(1-{2-[6-Methyl-1,3-dioxo-3,6-dihydropyrrolo[3,4-*c*]carbazol-2(1*H*)-yl]ethyl}-3-pyrrolidinyl)methyl]-1*H*-indole-6-carbonitrile hydrochloride

EXAMPLE 20 : 3-({1-[2-(3,5-Dimethyl-2,6-dioxo-3,6-dihydro-1(2*H*)-pyrimidinyl)ethyl]-3-pyrrolidinyl}methyl)-1*H*-indole-6-carbonitrile hydrochloride

5



PHARMACOLOGICAL STUDY

EXAMPLE A: Determination of affinity for serotonin-reuptake sites in the rat

Materials and Method:

- 5 The affinity of the compounds of the invention was determined by competition experiments with [³H]-paroxetine. The membranes are prepared from rat frontal cortex and are incubated in triplicate with 0.25nM [³H]-paroxetine and the cold ligand in a final volume of 0.4 ml, for 2 hours at 25°C. The incubation
- 10 specific binding is determined using 10μM citalopram. At the end of the incubation, the mixture is filtered through filters and washed three times with 5 ml of cooled buffer. The radioactivity retained on the filters is determined by liquid scintillation counting. The binding isotherms are analysed by non-linear regression to determine the IC₅₀ values. The latter are converted into a
- 15 dissociation constant (K_i) using the Cheng-Prusoff equation:

$$K_i = IC_{50} / \{(L / K_d) - 1\}$$

wherein L is the concentration of [³H]-paroxetine and K_d is the dissociation constant (0.13nM).

Results:

- 20 The compounds of the invention appear to have a very high affinity for serotonin-reuptake sites (5-HT_u) and cloned-human serotonin-reuptake sites (5-HT_{uh}) (see Table 1).

Table 1:

Compounds of example	1	2	3	4	5	6
pK _{i(5-HT_u)}	8.34	8.85	8.15	8.89	9.34	-
pK _{i(5-HT_{uh})}	-	8.84	-	-	-	9.31

25

Compounds of example	8	9	10	12	13	14
pK _{i(5-HT_u)}	-	-	-	-	-	-
pK _{i(5-HT_{uh})}	8.60	8.20	6.50	7.75	8.85	7.60

By way of example, the affinity of the compound of Example 6 is 4.10⁻¹⁰M.

EXAMPLE B: Marble-burying test in mice**Materials and Method:**

This test enables evaluation of the capacity of pharmacological agents to inhibit the spontaneous marble-burying behaviour of mice, the inhibition being predictive of antidepressant and/or anti-impulsive action. Male mice of the NMRI strain weighing from 20 to 25 g on the day of the experiment are placed individually in Macrolon boxes (30x18x19 cm) containing 5 cm of sawdust and covered with a perforated plexiglass plate. Twenty four "tiger's eye" glass marbles are evenly distributed on the sawdust at the periphery of the box. At the end of 30 minutes free exploration, the animals are removed from the box and the number of buried marbles is counted.

Results: it appears that compounds of the invention inhibit the spontaneous marble-burying behaviour of mice.

Table 2:

Compounds of example	6	7	13	14
ED ₅₀ (mg/Kg)	3.9	1.5	0.63	3.5

The compounds of the present invention have pharmacological properties which allow their use in the treatment of disorders of the central nervous system.

By way of Example, compounds of examples 6 and 7 possess an ED₅₀ (Efficacy dose 50) of 3.8 mg/kg and 1.5 mg/kg, respectively.

EXAMPLE C: Pharmaceutical composition

Formulation for the preparation of 1000 tablets each containing 10 mg of active ingredient:

Compound of Example 6	10 g
Hydroxypropyl cellulose	2 g
Wheat starch	10 g
Lactose	100 g
Magnesium stearate	3 g
Talc	3 g

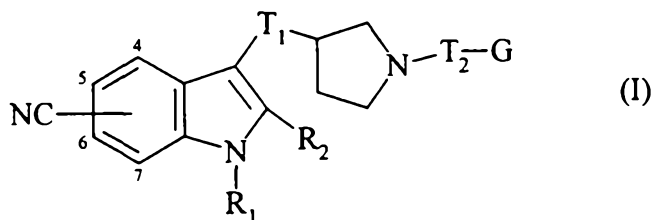
Comprises/comprising and grammatical variations thereof when used in this specification are to be taken to specify the presence of stated features, integers, steps or components or groups thereof, but do not preclude the presence or addition of one or more other features, integers, steps, components

5 or groups thereof.

CLAIMS

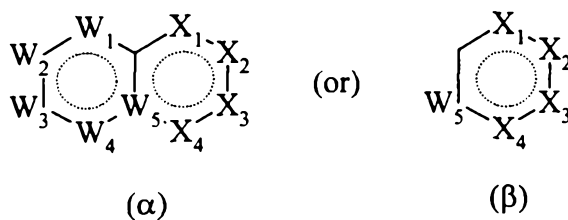
THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:

1. Compounds of formula (I) :



wherein :

- R_1 and R_2 each independently of the other represents a hydrogen atom or a linear or branched (C_1 - C_6)alkyl group,
- T_1 and T_2 each independently of the other represents a linear or branched (C_1 - C_6)-alkylene group,
- G represents a heterocyclic group of formula (α) or (β) :



wherein :

W_1 to W_5 and X_1 to X_4 are so selected as to form a chemically stable group and are defined as follows :

- W_1 , W_2 and W_3 each independently of the others represents a nitrogen atom or a group CR_5 , NR_4 or CO ,
- W_4 represents a nitrogen atom or a group CR_3 , NR_4 or CO ,
- W_5 represents a carbon atom or a nitrogen atom,

- X_1 represents a bond, a nitrogen atom or a group CR_3 or NR_4 ,
- X_2 to X_4 each independently of the others represents a group CR_3 , NR_4 , CO , SR_4 or SO_2 or an oxygen, sulphur or nitrogen atom,
- R_3 represents a hydrogen or halogen atom or a linear or branched (C_1 - C_6)alkyl group, hydroxy group, linear or branched (C_1 - C_6)perhaloalkyl group, nitro group, or amino group (optionally substituted by one or two groups selected from linear or branched (C_1 - C_6)alkyl, or benzyl),
- R_4 represents a hydrogen atom or a linear or branched (C_1 - C_6)alkyl group, optionally substituted aryl group or optionally substituted arylalkyl group,
- R_5 represents a group R_3 , or two adjacent groups R_5 form, together with the carbon atoms carrying them, a saturated, partially unsaturated or unsaturated mono- or bi-cyclic group optionally containing from 1 to 5 hetero atoms selected from nitrogen, oxygen and sulphur, the said group being optionally substituted by one or more groups selected from R_3 or oxo,

it being understood that, in formulae (α) and (β), at least one heteroatom is present, the dotted lines indicate that the groups in question may contain an unsaturated bond or a plurality of conjugated or unconjugated unsaturated bonds and that, if there is no unsaturated bond, the remaining valences are occupied by hydrogen atoms, the groups (α) and (β) being linked to T_2 by any one of their ring junctions,

their enantiomers and diastereoisomers, and addition salts thereof with a pharmaceutically acceptable acid or base.

2. Compounds of formula (I) according to claim 1, wherein the cyano group is attached in the 5-position of the indole ring system, their enantiomers and diastereoisomers, and addition salts thereof with a pharmaceutically acceptable acid or base.

3. Compounds of formula (I) according to claim 1, wherein the cyano group is attached in the 6-position of the indole ring system, their enantiomers and diastereoisomers, and addition salts thereof with a pharmaceutically acceptable acid or base.

4. Compounds of formula (I) according to claim 1, wherein R_1 and R_2 each represents a hydrogen atom, their enantiomers and diastereoisomers, and addition salts thereof with a pharmaceutically acceptable acid or base.
5. Compounds of formula (I) according to claim 1, wherein T_1 represents a methylene group, their enantiomers and diastereoisomers, and addition salts thereof with a pharmaceutically acceptable acid or base.
6. Compounds of formula (I) according to claim 1, wherein G is selected from the groups:
2-furyl; 2,4-dioxo-1,4-dihydro-3(2*H*)-quinazolinyl; 3-oxo-[1,2,4]triazolo[4,3-*a*]-pyridin-2(3*H*)-yl; 1-oxo-2(1*H*)-phthalazinyl; 7-methyl-5-oxo-5*H*-[1,3]thiazolo-[3,2-*a*]pyrimidin-6-yl; 6-chloro-2-oxo-2,3-dihydro-1*H*-indol-5-yl; 2-oxo-2,3-dihydro-1*H*-indol-5-yl; 2-oxo-1,2,3,4-tetrahydro-6-quinolinyl; 3-benzyl-5-methyl-2,6-dioxo-3,6-dihydro-1(2*H*)-pyrimidinyl; 1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl; 1,1,3-trioxo-1,3-dihydro-2*H*-1,2-benzisothiazol-2-yl; 1,3-dioxo-3,6-dihydropyrrolo-3,4-*c*]carbazol-2(1*H*)-yl; 1,3-dioxo-1,3-dihydro-2*H*-benzo[*c*]isoindol-2-yl; 3,5-dimethyl-2,6-dioxo-3,6-dihydro-1(2*H*)-pyrimidinyl,
their enantiomers and diastereoisomers, and addition salts thereof with a pharmaceutically acceptable acid or base.
7. Compounds of formula (I) according to claim 1, wherein R_1 and R_2 each represents a hydrogen atom, T_1 represents a methylene group, T_2 represents an alkylene group and G is selected from the groups 2-furyl; 2,4-dioxo-1,4-dihydro-3(2*H*)-quinazolinyl; 3-oxo-[1,2,4]triazolo[4,3-*a*]pyridin-2(3*H*)-yl; 1-oxo-2(1*H*)-phthalazinyl; 7-methyl-5-oxo-5*H*-[1,3]thiazolo[3,2-*a*]pyrimidin-6-yl; 6-chloro-2-oxo-2,3-dihydro-1*H*-indol-5-yl; 2-oxo-2,3-dihydro-1*H*-indol-5-yl; 2-oxo-1,2,3,4-tetrahydro-6-quinolinyl; 3-benzyl-5-methyl-2,6-dioxo-3,6-dihydro-1(2*H*)-pyrimidinyl; 1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl; 1,1,3-trioxo-1,3-dihydro-2*H*-1,2-benzisothiazol-2-yl; 1,3-dioxo-3,6-dihydropyrrolo[3,4-*c*]carbazol-2(1*H*)-yl; 1,3-dioxo-1,3-dihydro-2*H*-benzo[*c*]isoindol-2-yl; 3,5-dimethyl-2,6-dioxo-3,6-dihydro-1(2*H*)-pyrimidinyl,

their enantiomers and diastereoisomers, and addition salts thereof with a pharmaceutically acceptable acid or base.

8. Compounds of formula (I) according to claim 7, wherein the cyano group is attached in the 5-position of the indole ring system, their enantiomers and diastereoisomers, and addition salts thereof with a pharmaceutically acceptable acid or base.

9. Compounds of formula (I) according to claim 7, wherein the cyano group is attached in the 6-position of the indole ring system, their enantiomers and diastereoisomers, and addition salts thereof with a pharmaceutically acceptable acid or base.

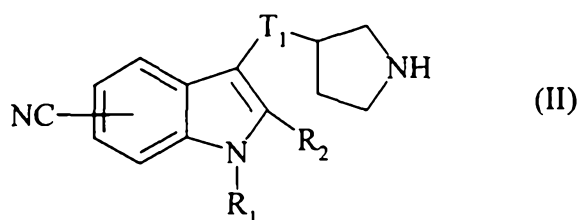
10. Compound of formula (I) according to claim 1 that is :

- 3-({1-[2-(7-methyl-5-oxo-5*H*)-[1,3]thiazolo[3,2-*a*]pyrimidin-6-yl)ethyl]-3-pyrrolidinyl)methyl)-1*H*-indole-5-carbonitrile hydrochloride.

11. Compound of formula (I) according to claim 1 that is :

- 3-({1-[2-(6-chloro-2-oxo-2,3-dihydro-1*H*-indol-5-yl)ethyl]-3-pyrrolidinyl)methyl)-1*H*-indole-5-carbonitrile hydrochloride.

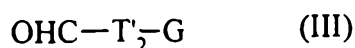
12. Process for the preparation of compounds of formula (I) according to claim 1, characterised in that there is used as starting material a compound of formula (II) :



wherein R_1 , R_2 and T_1 are as defined for formula (I),

which is subjected :

➔ either to the action, in a reducing medium, of an aldehyde of formula (III) :



wherein G is as defined for formula (I) and T'_2 represents a bond or a linear or branched ($\text{C}_1\text{-C}_5$)alkylene group,

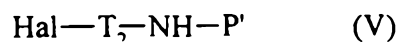
or to the action, in a basic medium, of a halogenated compound of formula (IV) :



wherein T_2 is as defined for formula (I) and Hal represents a halogen atom,

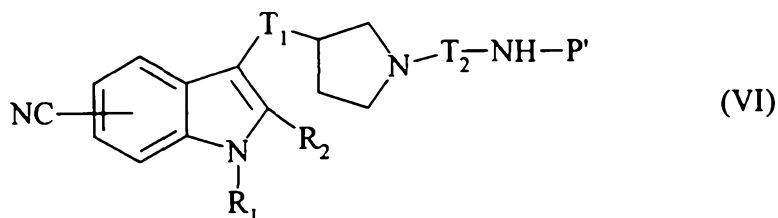
to yield a compound of formula (I),

or which is subjected to the action, in a basic medium, of a compound of formula (V) :



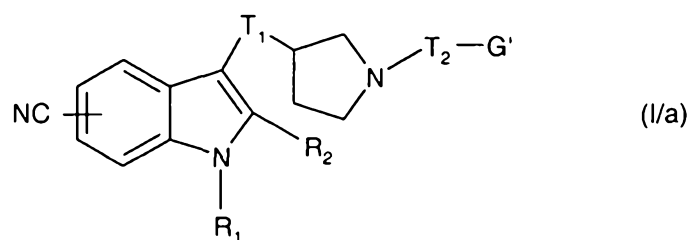
wherein T_2 is as defined for formula (I), Hal represents a halogen atom and P' is a protecting group for the amine,

to yield a compound of formula (VI),



wherein R_1 , R_2 , T_1 , T_2 and P' are as defined hereinbefore,

which compound of formula (VI), after deprotection of the primary amine group, is condensed with a cyclic group that is a precursor of group G defined for formula (I) to yield a compound of formula (I/a) :



a particular case of the compounds of formula (I) wherein R_1 , R_2 , T_1 and T_2 are as defined hereinbefore and G' represents a group as defined for G in formula (I), it being understood that G' is attached to T_2 by a nitrogen atom,

which compounds of formulae (I/a) and (I),

- may be purified, if necessary, according to a conventional purification technique,
- are separated, where appropriate, into their isomers according to a conventional separation technique,
- are converted, if desired, into addition salts thereof with a pharmaceutically acceptable acid or base.

13. Pharmaceutical compositions comprising at least one compound of the formula I as claimed in any one of claims 1 to 11, alone or in combination with one or more inert, non-toxic pharmaceutically acceptable excipients or carriers.

14. Pharmaceutical compositions according to claim 13 comprising at least one compound of the formula (I) as claimed in any one of claims 1 to 11 for use in the manufacture of medicaments for use as serotonin-reuptake inhibitors to treat disorders mediated by serotonin-reuptake including depression; obsessive-compulsive disorders; phobias; impulsive disorders associated with drug abuse; bulimia nervosa; or anxiety.

15. The use of a compound of the formula (I) as claimed in any one of claims 1 to 11 for the production of a medicament for use as serotonin-reuptake inhibitors to treat disorders mediated by serotonin-reuptake including depression;

obsessive-compulsive disorders; phobias; impulsive disorders associated with drug abuse; bulimia nervosa; or anxiety.

16. A method of treatment of disorders mediated by serotonin-reuptake including depression; obsessive-compulsive disorders; phobias; impulsive disorders associated with drug abuse; bulimia nervosa; or anxiety; comprising administering to a person in need to such treatment an effective amount of a compound of the formula (I) as claimed in any one of claims 1 to 11 and/or its physiologically tolerable salt.

17. A compound of the formula (I) substantially as hereinbefore described with reference to the examples.

18. A process for the preparation of a compound of the formula I substantially as hereinbefore described with reference to the examples.

DATED this 29th day of January 2004

LES LABORATOIRES SERVIER

WATERMARK PATENT & TRADE MARK ATTORNEYS
290 BURWOOD ROAD
HAWTHORN VICTORIA 3122
AUSTRALIA

P18290AU00 CJH/TAP/VRH