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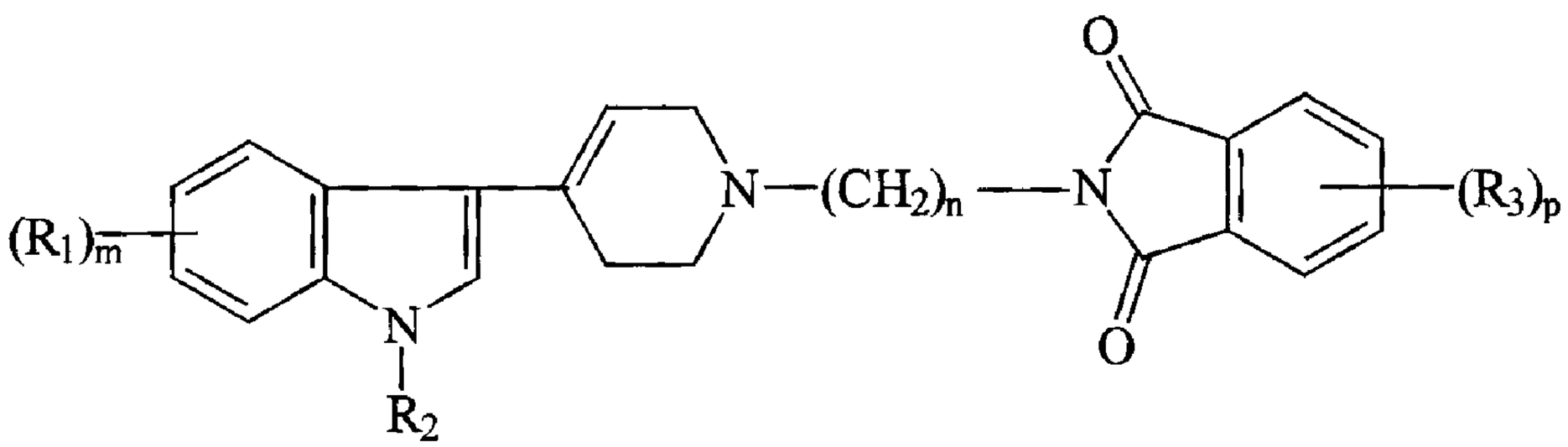
(54) Titre : 3-TETRAHYDROPYRIDIN-4-YL INDOLES POUR LE TRAITEMENT DES TROUBLES PSYCHOTIQUES
(54) Title: 3-TETRAHYDROPYRIDIN-4-YL INDOLES FOR TREATMENT OF PSYCHOTIC DISORDERS



(I)

(57) Abrégé/Abstract:
The invention relates to a novel group 3-tetrahydropyridin-4-yl indoles having interesting pharmacological properties. These compounds have general formula (I) wherein: R_1 is halogen, CF_3, alkyl (1-3C), alkoxy (1-3C), CN or SCH_3; m the value 0, 1 or 2; R_2 is H or alkyl (1-3C); n has the value 3, 4, 5 or 6; R_3 is halogen, alkyl (1-4C); or alkoxy (1-4C); p has the value 0, 1, or 2 and salts thereof.

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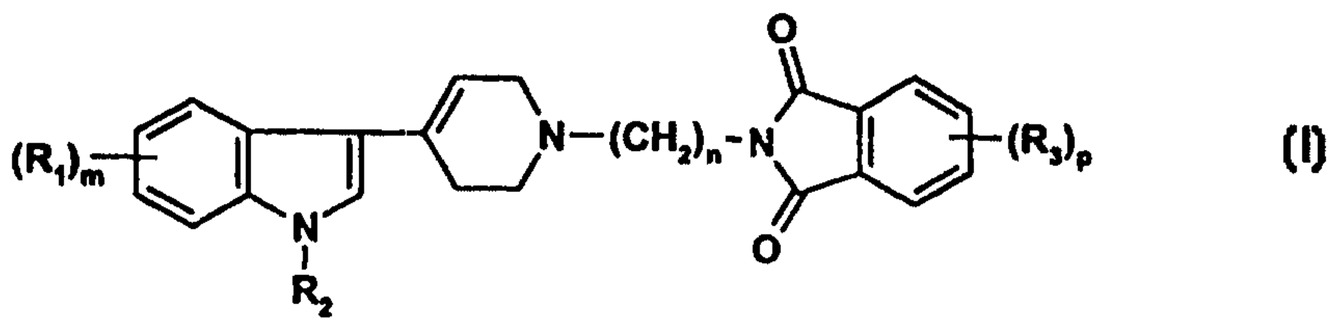
(54) Title: 3–TETRAHYDROPYRIDIN–4–YL INDOLES FOR TREATMENT OF PSYCHOTIC DISORDERS



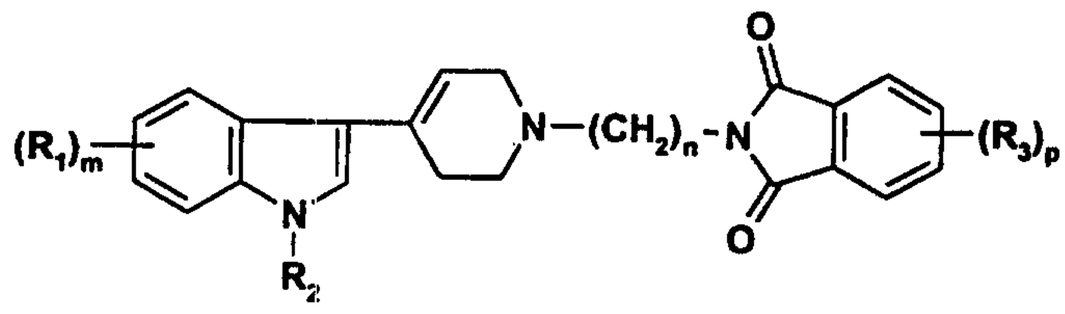
(I)

(57) Abstract

The invention relates to a novel group 3–tetrahydropyridin–4–yl indoles having interesting pharmacological properties. These compounds have general formula (I) wherein: R_1 is halogen, CF_3, alkyl (1–3C), alkoxy (1–3C), CN or SCH_3; m the value 0, 1 or 2; R_2 is H or alkyl (1–3C); n has the value 3, 4, 5 or 6; R_3 is halogen, alkyl (1–4C); or alkoxy (1–4C); p has the value 0, 1, or 2 and salts thereof.

3-TETRAHYDROPYRIDIN-4-YL INDOLES FOR TREATMENT OF PSYCHOTIC DISORDERS

The invention relates to a novel group of 3-tetrahydropyridin-4-yl indole derivatives of the formula (I):



(I)

wherein:

- R_1 is halogen, CF_3, alkyl (1-3C), alkoxy (1-3C), CN or SCH_3
- m the value 0, 1 or 2
- R_2 is H or alkyl (1-3C)
- n has the value 3, 4, 5 or 6
- R_3 is halogen, alkyl (1-4C) or alkoxy (1-4C)
- p has the value 0, 1, or 2

and salts thereof.

It has been found that the compounds having formula (I) show high affinity for the dopamine D_2-receptor and are good serotonin reuptake inhibitors (SRI's).

Preferred compounds of the invention are compounds having formula (I) wherein R_1 hydrogen (i.e. m=0) or F, Cl, CH_3 or CN, and m=1, R_2 is H or CH_3, n=4, R_3 is hydrogen (i.e. p=0), or F or alkyl (1-4C), p=1, and the salts thereof.
Especially preferred is the compound having formula (I)
wherein (R_1)m is F, R_2 is hydrogen, n=4 and p=0, and the salts thereof.

It has been found that the compounds according to the invention show high affinity for both the dopamine D_2 receptor and the serotonin reuptake site. This combination is useful for the treatment of schizophrenia and other psychotic disorders and might allow for a more complete treatment of all disease symptoms (e.g. positive symptoms and negative syrnptoms).

The compounds show activity as antagonists at dopamine D_2 receptors as they potentially antagonize apomorphine-induced climbing behaviour in mice. The compounds also show activity as inhibitors of serotonin reuptake, as they potentiate 5-HTP induced behaviour in mice.

The compounds are active in therapeutic models sensitive to clinically relevant antipsychotics (e.g. the conditioned avoidance response; Van der Heyden & Bradford, Behav. Brain Res., 1988, 31:61-67) and antidepressants or anxiolytics (e.g. suppression of stress-induced vocalization; van der Poel et al., Psychopharmacology, 1989, 97: 147-148).

In contrast to clinically relevant dopamine D_2 receptor antagonists the described compounds have a low propensity to induce catalepsy in rodents and as such are likely to induce less extrapyramidal side effects than existing antipsychotic agents.

The inhibitory activity of serotonin reuptake inherent in these compounds may be responsible for the therapeutic effects observed in behavioural models sensitive to either antidepressants or anxiolytics.

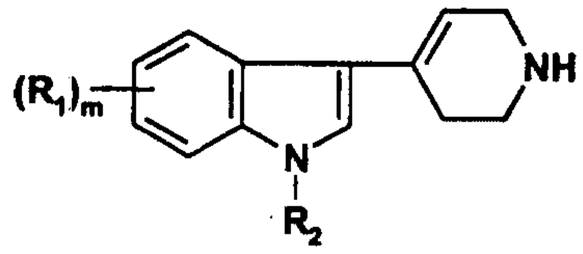
The compounds can be used for the treatment of affections or diseases of the central nervous system caused by disturbances in either the dopaminergic or serotonergic systems, for example: aggression, anxiety disorders, autism, vertigo, depression, disturbances of cognition or memory and in particular schizophrenia and other psychotic disorders.

Pharmacologically acceptable acids with which the compounds of the invention can form suitable acid addition salts are for example hydrochloric acid, sulphuric acid, phosphoric acid, nitric acid, and organic acids such as citric acid, fumaric acid, maleic acid, tartaric acid, acetic acid, benzoic acid, p-toluene sulphonic acid, methanesulphonic acid and naphthalene sulphonic acid.

The compounds are their acid addition salts can be brought into forms suitable for administration by means of suitable processes using auxiliary substances such as liquid and solid carrier materials.

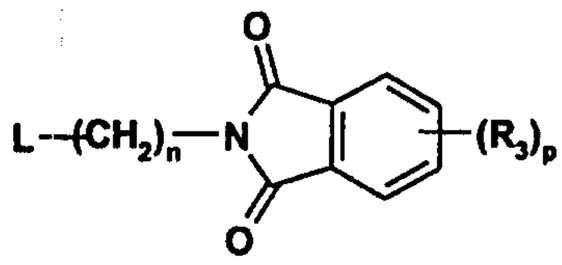
The compounds having formula (I) can be obtained as follows:

by reaction of a compound of formula (II)



(II)

with a compound of the formula (III)

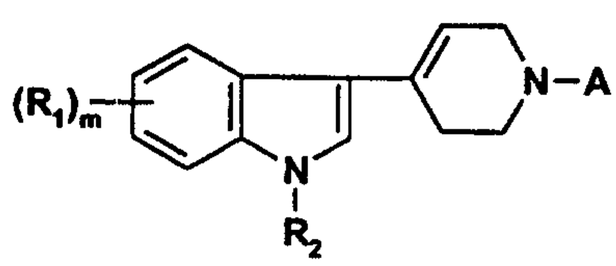


(III)

wherein the symbols have the above meanings and L is a so-called leaving group, for example bromo.

This reaction is carried out in a solvent such as acetonitrile in the presence of triethylamine or K_2CO_3 and KI at reflux temperature, or

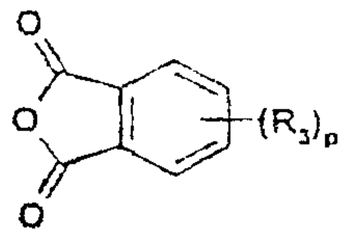
a) by (i) reduction of the cyano group in a compound of formula (IV)



(IV)

wherein A represents the group $-(CH_2)_{n-1}-CN$, to the corresponding group $-(CH_2)_n-NH_2$; and

(ii) reacting the obtained amine with an optionally substituted phthalic anhydride of the formula (V)



(V)

in which formula the symbols have the meanings give above.

Reaction step b (i) can be carried out for example with $LiAlH_4$ in an organic solvent such as tetrahydrofuran at reflux temperature.

Reaction step (ii) can be carried out for example in organic solvents such as tetrahydrofuran and toluene at reflux temperature.

The starting compounds as used in method a) of the formula (II) can be obtained in a manner known per se by reaching an optionally substituted indole derivate with 4-piperidone.

The starting compounds used in method b) having formula (IV) can be obtained by reaction of a compound having formula (II) with a bromoalkyl nitrile of the formula $Br-(CH_2)_{n-1}-CN$ in a manner known per se.

The invention provides use of a compound, salt or composition of the invention for the treatment of a CNS disorder, or for preparing a medicament for the treatment of a CNS disorder.

The invention provides a compound, salt or composition of the invention for use in the treatment of a CNS disorder, or for use in preparing a medicament for the treatment of a CNS disorder.

The invention provides a commercial package comprising a compound, salt or composition of the invention and associated therewith instructions for the use thereof in the treatment of a CNS disorder.

The preparation of the compounds having formula (I) will now be described in more detail in the following Examples.

Example I

Preparation of 1-methyl-3-(1,2,3,6-tetrahydropyridin-4-yl)indole.

To a solution of 4-piperidone.H_2O.HCl (50 g, 0.32 mol) in 100 ml of acetic acid and 150 ml of trifluoroacetic acid was added dropwise a solution of 1-methylindole (11.5 ml, 0.09 mol) in 100 ml of acetic acid at room temperature. After stirring for 1h the reaction mixture was concentrated (in vacuum, temp. ca. 30°C), water was added, the mixture was made basic with potassium carbonate and extracted with ethyl acetate. The organic layer was separated, dried and purified by silica gel column chromatography (dichloromethane/methanol/ammonium hydroxide = 84/15/1) to give

9 g (47%) of the title compound.

Example 2

Preparation of 5-fluoro-3-(1,2,3,6-tetrahydropyridin-4-yl)indole.

To a solution of sodium (60 g , 2.6 mol) in 1000 ml of methanol was added 5-fluoroindole (49 g, 0.36 mol) and 4-piperidone.H_2O.HCl (170 g , 1.11 mol). The mixture was heated under reflux for 18h , then concentrated , water was added and extracted with ethyl acetate. The combined organic layer was dried over sodium sulfate and then concentrated. The resulting solid was dissolved in methanol (about 200 ml) and then diluted with water (about 1000-1500 ml). The precipitate was collected , washed with water and petroleum ether and then dried in a vacuum oven at 60°C. Yield 74 g (95%) of a yellow solid.

Example 3

Preparation of N-[4-[4-[(5-fluoro-1H-indol-3-yl)-1,2,3,6-tetrahydropyridin-1-yl]butyl]-phthalimide.HCl **(compound 1)**

A solution of 5-fluoro-3-(1,2,3,6-tetrahydropyridin-4-yl)indole (7.5 g , 34.7 mmol) , N-(4-bromobutyl)phthalimide (10.8 g, 38.3 mmol) , triethylamine (4.5 ml) and potassium iodide (5.5 g) in 150 ml of acetonitrile was heated under reflux for 18h. The reaction mixture was concentrated and purified by silica gel column chromatografy (dichloromethane/methanol /ammonium hydroxide= 92/7.5/0.5) to give 8.3 g of the title compound as a free base. Mp. 186°C. The hydrochloride was prepared by dissolving the above mentioned free base in 20 ml of 1M HCl in ethanol. The solution was concentrated and the resulting solid was washed with ether. Yield 8.4 g (54%) of compound 1, mp. 224°C (dec.).

Example 4

Preparation of 5-fluoro-3-[1-(3-cyanopropyl)-1,2,3,6-tetrahydropyridin-4-yl]indole

A solution of 5-fluoro-3-(1,2,3,6-tetrahydropyridin-4-yl)indole (10 g , 46 mmol) , 4-bromobutyronitrile(5.6 ml , 56 mmol) , potassium carbonate (6.3 g) and potassium iodide (7.6 g) in 100 ml of acetonitrile was heated under reflux for 18h. The

mixture was filtered and the residue on the filter was washed with dichloromethane/methanol/ammonium hydroxide = 84/15/1. The organic layer was concentrated to give 10.9 g (83%) of the title compound. M.p 152°C.

Example 5

Preparation of 5-fluoro-3-[1-(4-aminobutyl)-1,2,3,6-tetrahydropyridin-4-yl]indole

To a solution of 5-fluoro-3-[1-(3-cyanopropyl)-1,2,3,6-tetrahydropyridin-4-yl]indole (10 g, 35 mmol) in 300 ml of dry THF was added slowly $LiAlH_4$ (2.0 g). The mixture was stirred and heated to reflux for 2h. Then the reaction mixture was cooled and water (1.9 ml) in THF (10 ml) was added slowly, followed by 2N sodium hydroxide (1.9 ml) . This mixture was heated to reflux for 0.25h , filtered over hyflo™ and concentrated to give 8.76 g (88%) of the title compound.

Example 6

Preparation of N-[4-[4-(5-fluoro-1H-indol-3-yl)-1,2,3,6-tetrahydropyridin-1-yl]butyl]-4-fluorophthalimide (compound 19)

To a solution of 5-fluoro-3-[1-(4-aminobutyl)-1,2,3,6-tetrahydropyridin-4-yl]indole (1.46 g, 5 mmol) in 20 ml of THF was added 4-fluorophthalic anhydride and 50 ml of toluene. The THF was removed by distillation and the resulting mixture was heated to reflux for 18h, with azeotropic removal of water (Dean and Stark apparatus). The reaction mixture was concentrated and purified by silica gel column chromatografy (dichloromethane/methanol/ammonium hydroxide =92/7.5/0.5) to give 1.52 g (69%) of the title compound 19. M.p. 197-199°C.

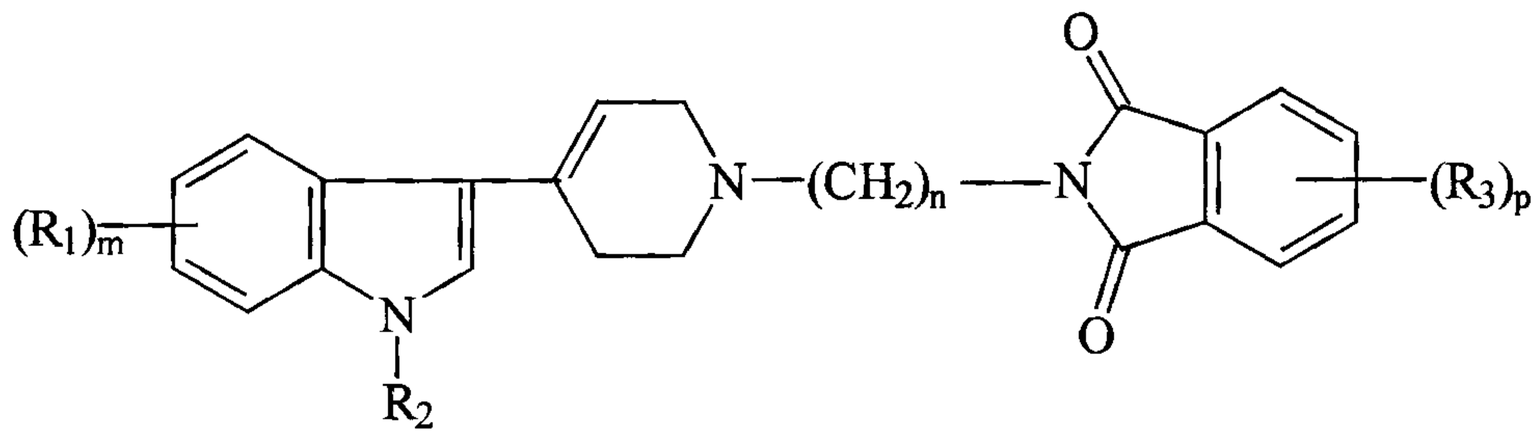
According to method a) as illustrated in Examples 1-3, or method b) as illustrated in Examples 4-6 the compounds listed in the following Table have been prepared:

Table

Comp.No	$(R_1)_m$	R_2	n	$(R_3)_p$	Salt/base	Melt. point °C
1	5-F	H	4	H	HCl	224(decomp.)
2	H	H	4	H	base	193-4
3	H	H	3	H	base	190-2
4	H	CH_3	4	H	HCl	230
5	7-CH_3	H	4	H	base	175-8
6	5-F	H	3	H	base	174-6
7	H	H	4	3-F	base	173-4
8	H	H	4	3-CH_3	base	184-5
9	H	H	4	4-CH_3	base	195-8
10	5-CN	H	3	H	base	amorph.
11	5-CN	H	4	H	base	amorph.
12	5-Cl	H	4	H	base	amorph.
13	H	H	4	4-F	base	197-8
14	H	H	4	4-t.C_4H_9	fumarate	243-5
15	5-F	H	4	4-t.C_4H_9	fumarate	193-5
16	5-F	H	4	3-CH_3	base	167-8
17	5-F	H	4	4-CH_3	base	199-200
18	5-F	H	4	3-F	base	188-190
19	5-F	H	4	4-F	base	197-9
20	H	H	6	H	base	196-7
21	5-F	H	6	H	base	170-2
22	5-F	H	4	4,5-diCl	base	216-8
23	H	H	4	4,5-diCl	base	217-8
24	5-F	H	5	H	base	194-8
25	5-F	H	4	4-Cl	base	186-8
26	H	H	4	4-Cl	base	209-215

CLAIMS:

1. A compound of the general formula (I):



(I)

wherein:

R_1 is H for m = 0, or a halogen atom, CF_3, alkyl (1-3C), alkoxy (1-3C), CN or SCH_3 for m > 0;

m has the value 0, 1 or 2;

R_2 is H or alkyl (1-3C);

n has the value 3, 4, 5 or 6;

R_3 is H for p = 0, or a halogen atom, alkyl (1-4C) or alkoxy (1-4C) for p > 0; and

p has the value 0, 1 or 2,

and a pharmacologically acceptable acid addition salt thereof.

2. A compound as claimed in claim 1, wherein:

$(R_1)_m$ is H for m = 0, or F, Cl, CH_3 or CN wherein m is 1;

R_2 is H or CH_3;

n is 4; and

$(R_3)_p$ is H for p = 0, or F or alkyl (1-4 C) wherein p is 1, and a pharmacologically acid addition salt thereof.

3. A compound as claimed in claim 1, wherein:

R_1 is F;

m is 1;

R_2 is H;

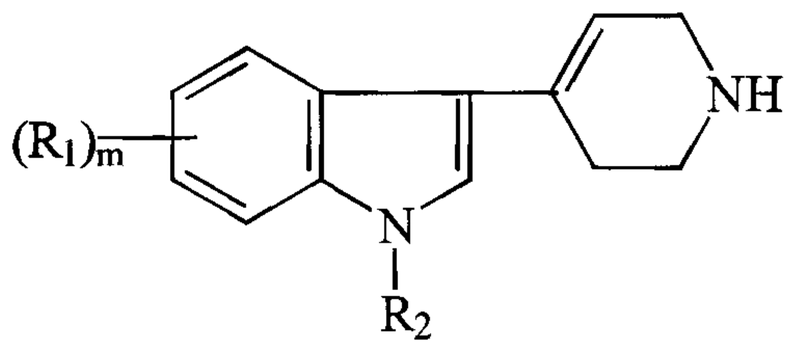
n is 4; and

p is 0,

and a pharmacologically acceptable acid addition salt thereof.

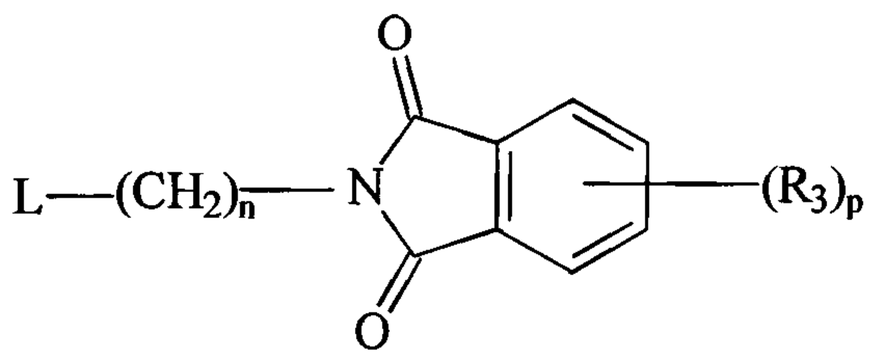
4. A method for preparing a compound as claimed in any one of claims 1 to 3, comprising:

(a) reacting a compound of the general formula (II):



(II)

wherein R_1, m and R_2 are as defined in any one of claims 1 to 3, with a compound of the general formula (III):



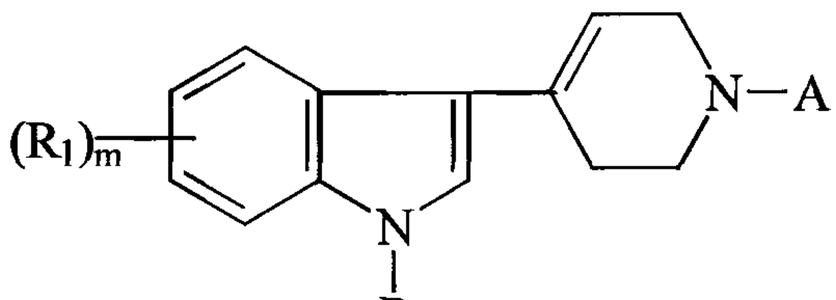
(III)

wherein:

n, R_3 and p are as defined in any one of claims 1 to 3, and

L is a leaving group; or

(b) (i) reducing a compound of the general formula (IV):



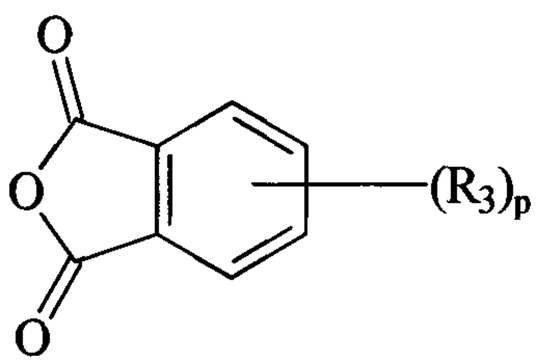
(IV)

wherein:

R_1, m and R_2 are as defined in any one of claims 1 to 3, and

A is the group $-(CH_2)_{n-1}-CN$, to the corresponding compound wherein A is the group $-(CH_2)_n-NH_2$, wherein n is as defined in claim 1 or 2, and

(ii) reacting the amine compound obtained from step (i) with a phthalic anhydride compound of the general formula (V):



(V)

wherein R_3 and p are as defined in any one of claims 1 to 3.

5. A pharmaceutical composition containing at least one compound as claimed in any one of claims 1 to 3, or a pharmaceutically acceptable salt thereof, as active component, and at least one auxiliary substance.

6. A method of preparing a composition as claimed in claim 5, wherein a compound as claimed in any one of claims 1 to 3, or a pharmaceutically acceptable salt thereof, is brought into a form suitable for administration.

7. Use of a compound as claimed in any one of claims 1 to 3, or a pharmaceutically acceptable salt thereof, or a composition as claimed in claim 5, for the treatment of a CNS disorder.

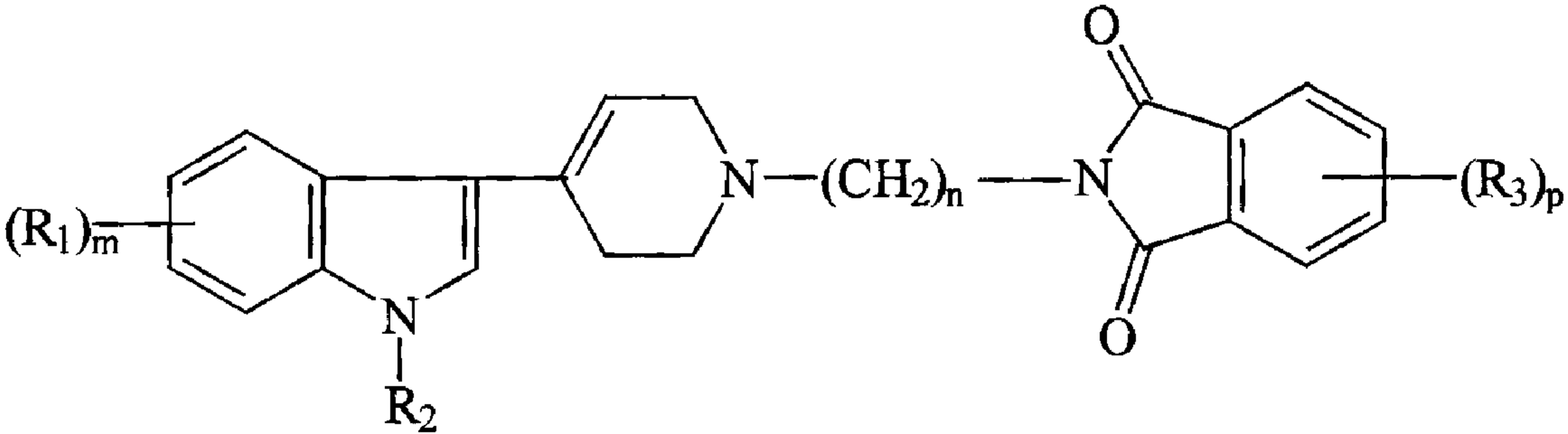
8. Use of a compound as claimed in any one of claims 1 to 3, or a pharmaceutically acceptable salt thereof, or a composition as claimed in claim 5, for preparing a medicament for the treatment of a CNS disorder.

9. A compound as claimed in any one of claims 1 to 3, or a pharmaceutically acceptable salt thereof, or a composition as claimed in claim 5, for use in the treatment of a CNS disorder.

10. A compound as claimed in any one of claims 1 to 3, or a pharmaceutically acceptable salt thereof, or a composition as claimed in claim 5, for use in preparing a medicament for the treatment of a CNS disorder.

11. A commercial package comprising a compound as claimed in any one of claims 1 to 3, or a pharmaceutically acceptable salt thereof, or a composition as claimed in claim 5, and associated therewith instructions for the use thereof in the treatment of a CNS disorder.

FETHERSTONHAUGH & CO.
OTTAWA, CANADA
PATENT AGENTS



(I)