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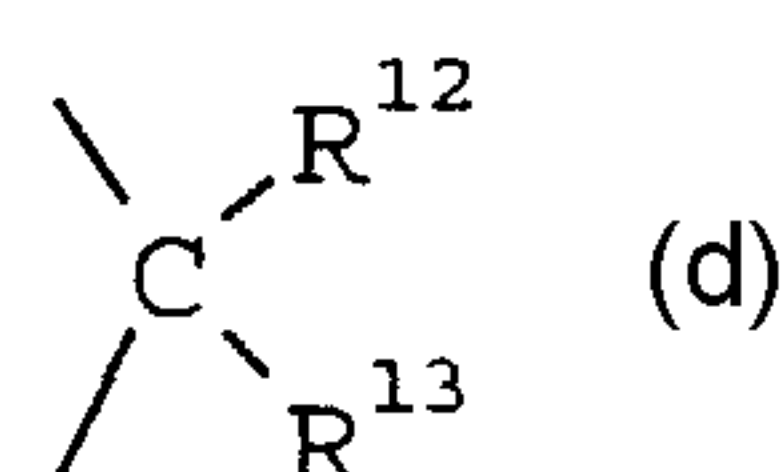
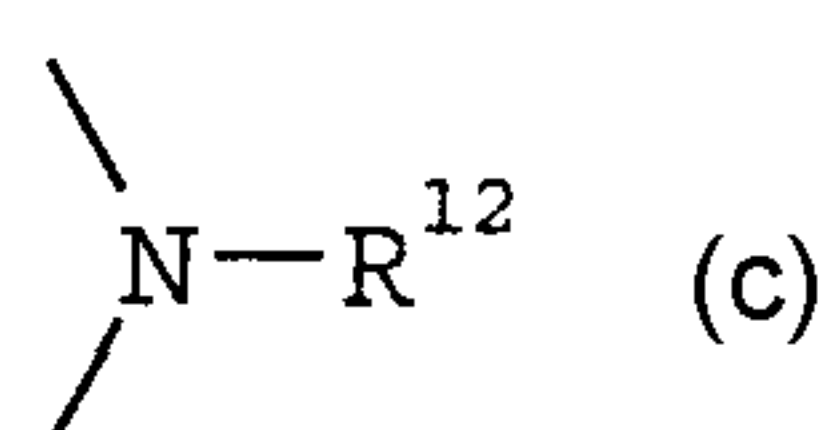
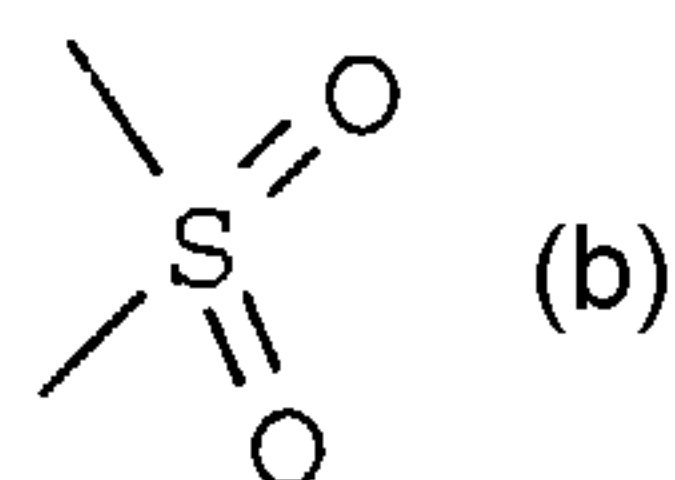
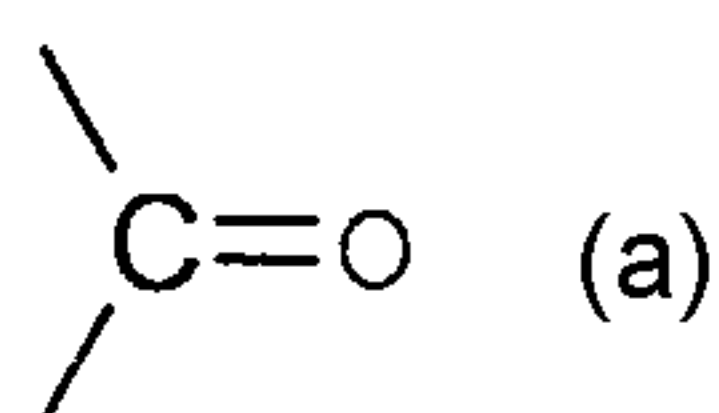
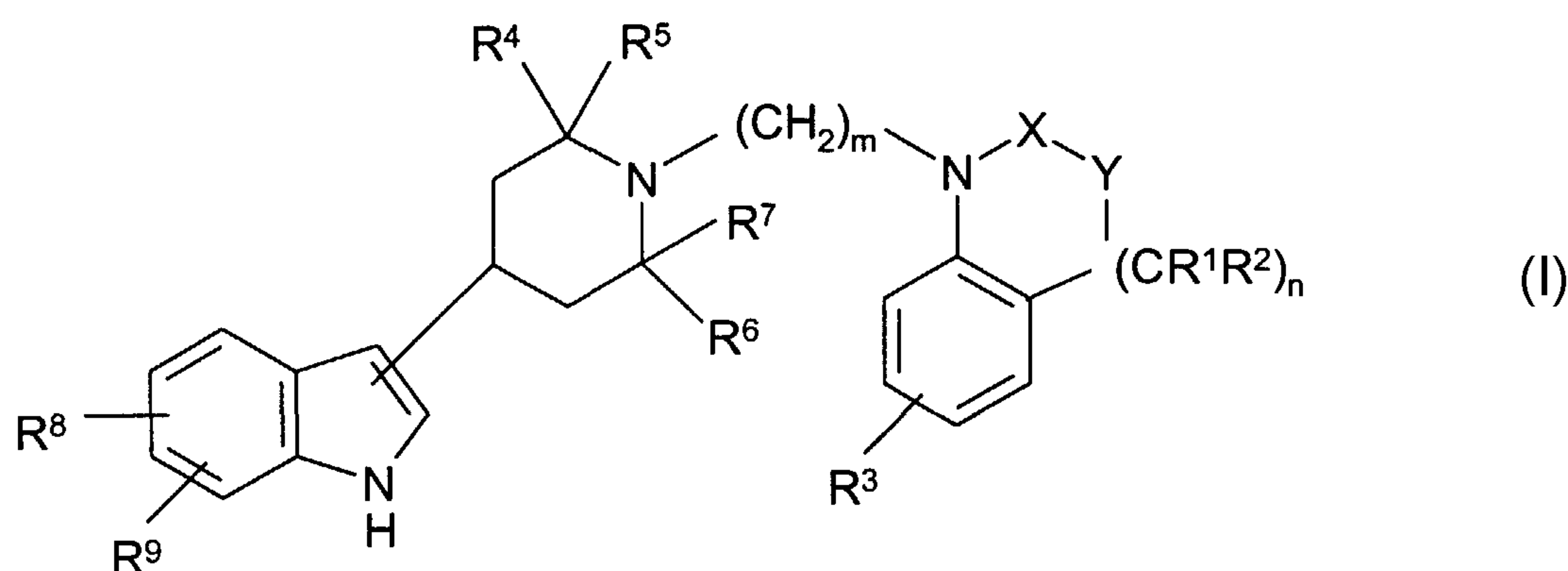
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(54) Titre : PIPERIDYINDOLES COMME LIGANDS DU RECEPTEUR DE LA SEROTONINE

(54) Title: PIPERIDYINDOLES AS SEROTONIN RECEPTOR LIGANDS



(57) **Abrégé/Abstract:**

A pharmaceutical compound of the formula (I) in which R¹ and R² are each hydrogen or C₁₋₆ alkyl, R³ is -SR¹⁰, -SOR¹⁰, -SO₂R¹⁰, -COR¹⁰, -CH₂OH or -CONHR¹¹, where R¹⁰ is C₁₋₆ alkyl and R¹¹ is hydrogen or C₁₋₆ alkyl, R⁴, R⁵, R⁶ and R⁷ are each hydrogen or C₁₋₆ alkyl, provided that at least one of R⁴, R⁵, R⁶ and R⁷ is C₁₋₆ alkyl, R⁸ and R⁹ are each hydrogen, halo, C₁₋₆ alkyl or cyano, n is 0 or 1 and m is 2 or 3, x is a (a) or (b), and y is (c) or (d), wherein R¹² and R¹³ are each hydrogen, C₁₋ alkyl, cyclopropyl or cyclopropyl-C₁₋₆ alkyl; and salts thereof.



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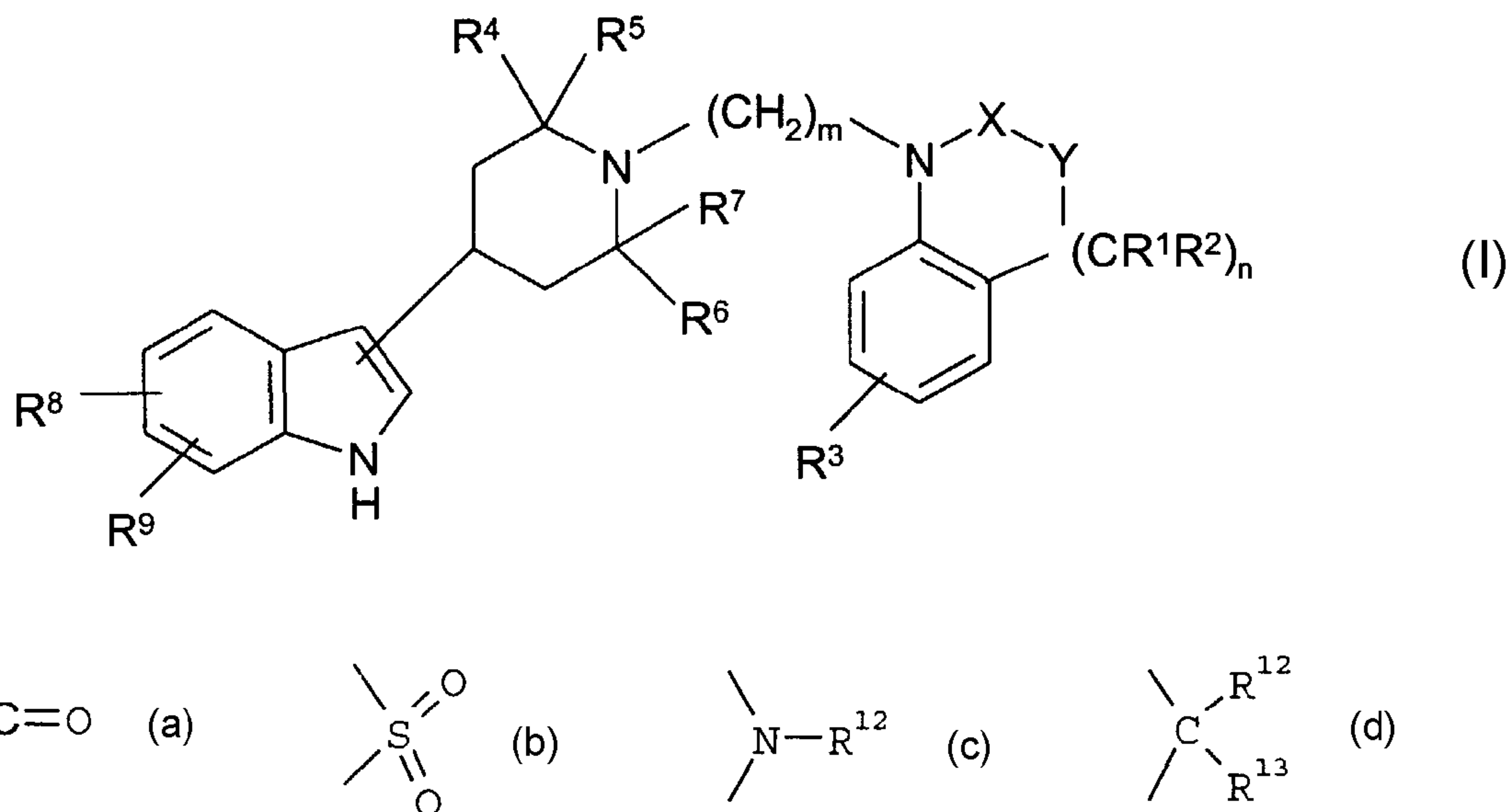
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(54) Title: PIPERIDYINDOLES AS SEROTONIN RECEPTOR LIGANDS



(57) Abstract: A pharmaceutical compound of the formula (I) in which R¹ and R² are each hydrogen or C₁₋₆ alkyl, R³ is -SR¹⁰, -SOR¹⁰, -SO₂R¹⁰, -COR¹⁰, -CH₂OH or -CONHR¹¹, where R¹⁰ is C₁₋₆ alkyl and R¹¹ is hydrogen or C₁₋₆ alkyl, R⁴, R⁵, R⁶ and R⁷ are each hydrogen or C₁₋₆ alkyl, provided that at least one of R⁴, R⁵, R⁶ and R⁷ is C₁₋₆ alkyl, R⁸ and R⁹ are each hydrogen, halo, C₁₋₆ alkyl or cyano, n is 0 or 1 and m is 2 or 3, x is a (a) or (b), and y is (c) or (d), wherein R¹² and R¹³ are each hydrogen, C₁₋ alkyl, cyclopropyl or cyclopropyl-C₁₋₆ alkyl; and salts thereof.

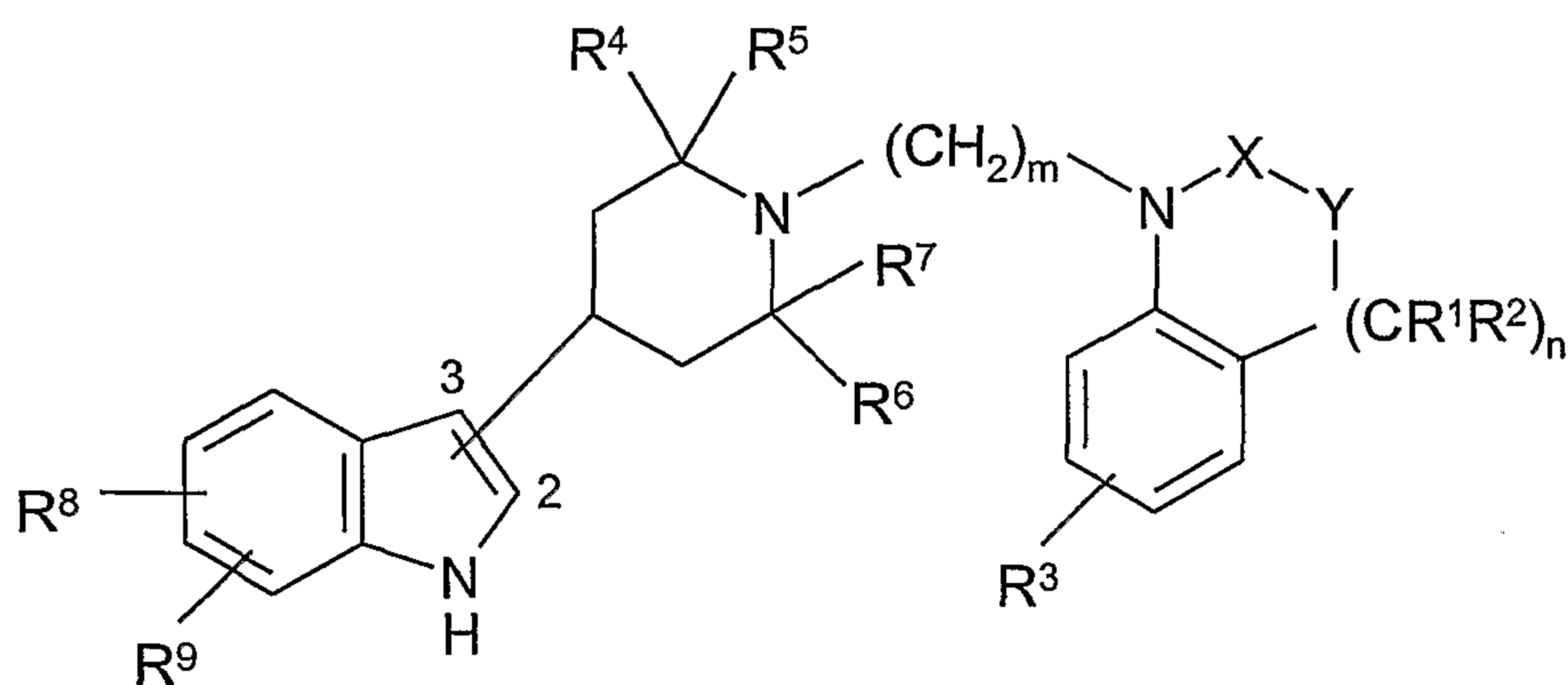
- 1 -

PIPERIDYINDOLES AS SEROTONIN RECEPTOR LIGANDS

This invention relates to pharmaceutical compounds and their use in the treatment of disorders of the central nervous system.

It is well known that compounds active at serotonin receptors have potential in the treatment of disorders of the central nervous system and, for example, certain halo-substituted indole compounds having serotonin antagonist properties are disclosed in WO 98/31686.

The compounds of the invention have the following formula:



(I)

in which R¹ and R² are each hydrogen or C₁₋₆ alkyl,

- 2 -

R^3 is $-SR^{10}$, $-SOR^{10}$, $-SO_2R^{10}$, $-COR^{10}$, $-CH_2OH$ or $-CONHR^{11}$, where R^{10} is C_{1-6} alkyl and R^{11} is hydrogen or C_{1-6} alkyl,

5 R^4 , R^5 , R^6 and R^7 are each hydrogen or C_{1-6} alkyl, provided that at least one of R^4 , R^5 , R^6 and R^7 is C_{1-6} alkyl,

R^8 and R^9 are each hydrogen, halo, C_{1-6} alkyl or cyano,
10 n is 0 or 1 and m is 2 or 3,

X is $\begin{array}{c} \diagup \\ \text{C}=\text{O} \\ \diagdown \end{array}$ or $\begin{array}{c} \diagup \\ \text{S}=\text{O} \\ \diagdown \\ \text{O} \end{array}$, and

Y is $\begin{array}{c} \diagup \\ \text{N}-\text{R}^{12} \\ \diagdown \end{array}$ or $\begin{array}{c} \diagup \\ \text{C}-\text{R}^{12} \\ \diagdown \\ \text{R}^{13} \end{array}$ wherein R^{12} and R^{13} are each

15 hydrogen, C_{1-6} alkyl, cyclopropyl or cyclopropyl- C_{1-6} alkyl;

and salts thereof.

20 The compounds of the invention and their pharmaceutically acceptable salts are indicated for use

- 3 -

in the treatment of disorders of the central nervous system.

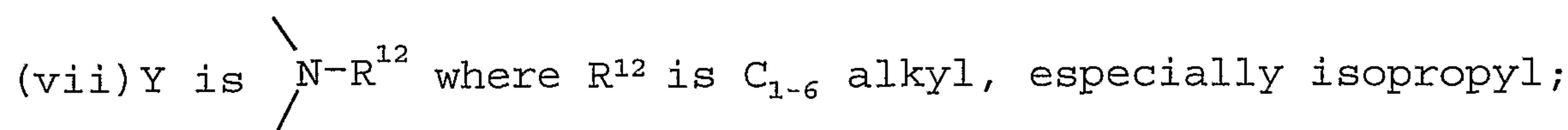
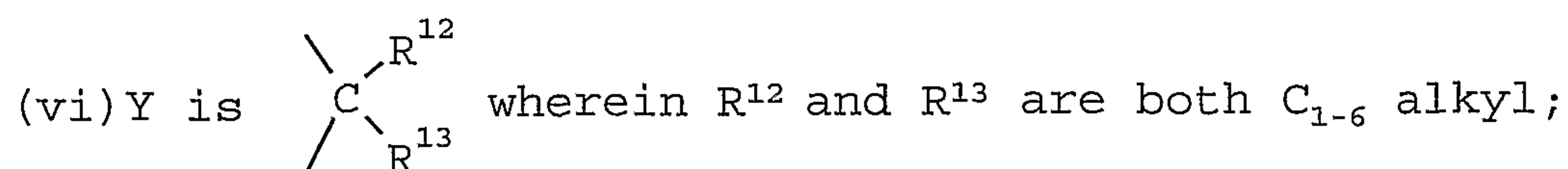
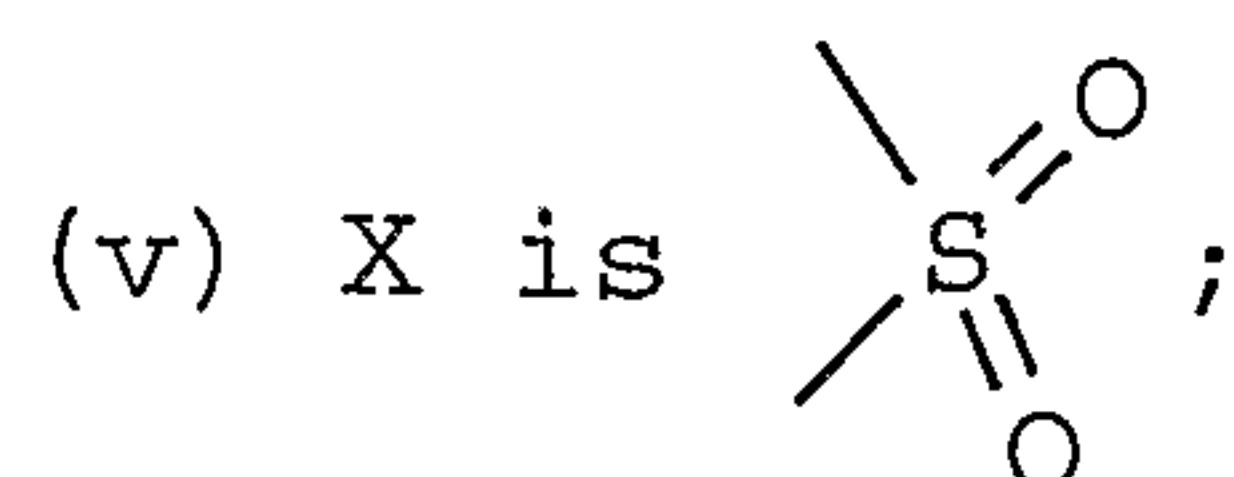
Accordingly, the present invention also provides the use
5 of a compound of the present invention in the preparation of a medicament for the treatment of a disorder of the central nervous system.

In the above formula (I), a halo atom is preferably
10 chloro, bromo or fluoro, and is especially fluoro. A C₁₋₆ alkyl group can be methyl, ethyl, propyl, butyl or pentyl or hexyl, and can be branched or unbranched including isopropyl and tert. butyl.

15 Preferred compounds are those which have one or more of the following features:

- (i) R⁸ and R⁹ are each hydrogen or halo;
- 20 (ii) R⁸ and R⁹ are each hydrogen or fluoro;
- (iii) R⁸ is fluoro and R⁹ is hydrogen;
- (iv) R⁸ is fluoro in the 6-position, and R⁹ is
25 hydrogen;

- 4 -



5

(viii) n is 1 and R¹ and R² are both hydrogen;

(ix) R³ is at the 6-position or the 7-position,
preferably at the 6-position;

10

(x) R³ is -SOR¹⁰, -SO₂R¹⁰ or -COR¹⁰;

(xi) R¹⁰ is methyl or ethyl, and especially methyl;

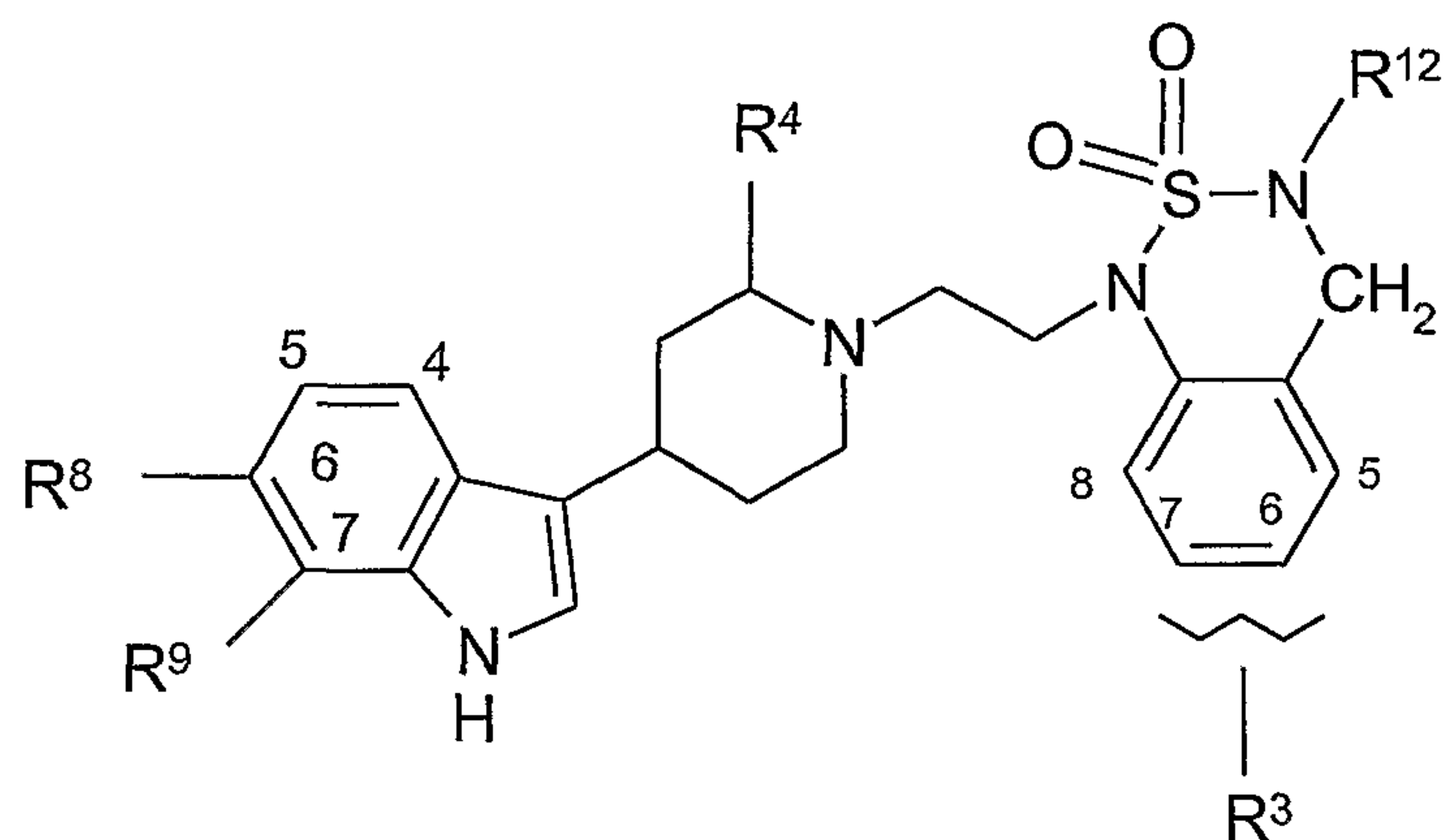
15 (xii) R³ is -SOCH₃ or -SO₂CH₃, at the 6-position or
the 7-position, preferably at the 6-position;

(xiii) the point of attachment of the piperidine group
is at the 3-position on the indole moiety;

20

(xiv) R⁴ is C₁₋₆ alkyl.

A preferred group of compounds is of the following formula:



5

in which

R^8 and R^9 are each hydrogen or halo, preferably fluoro,

R^3 is at the 6- or 7- position and is $-SOR^{10}$, $-SO_2R^{10}$ or

10 $-COR^{10}$, where R^{10} is C_{1-6} alkyl,

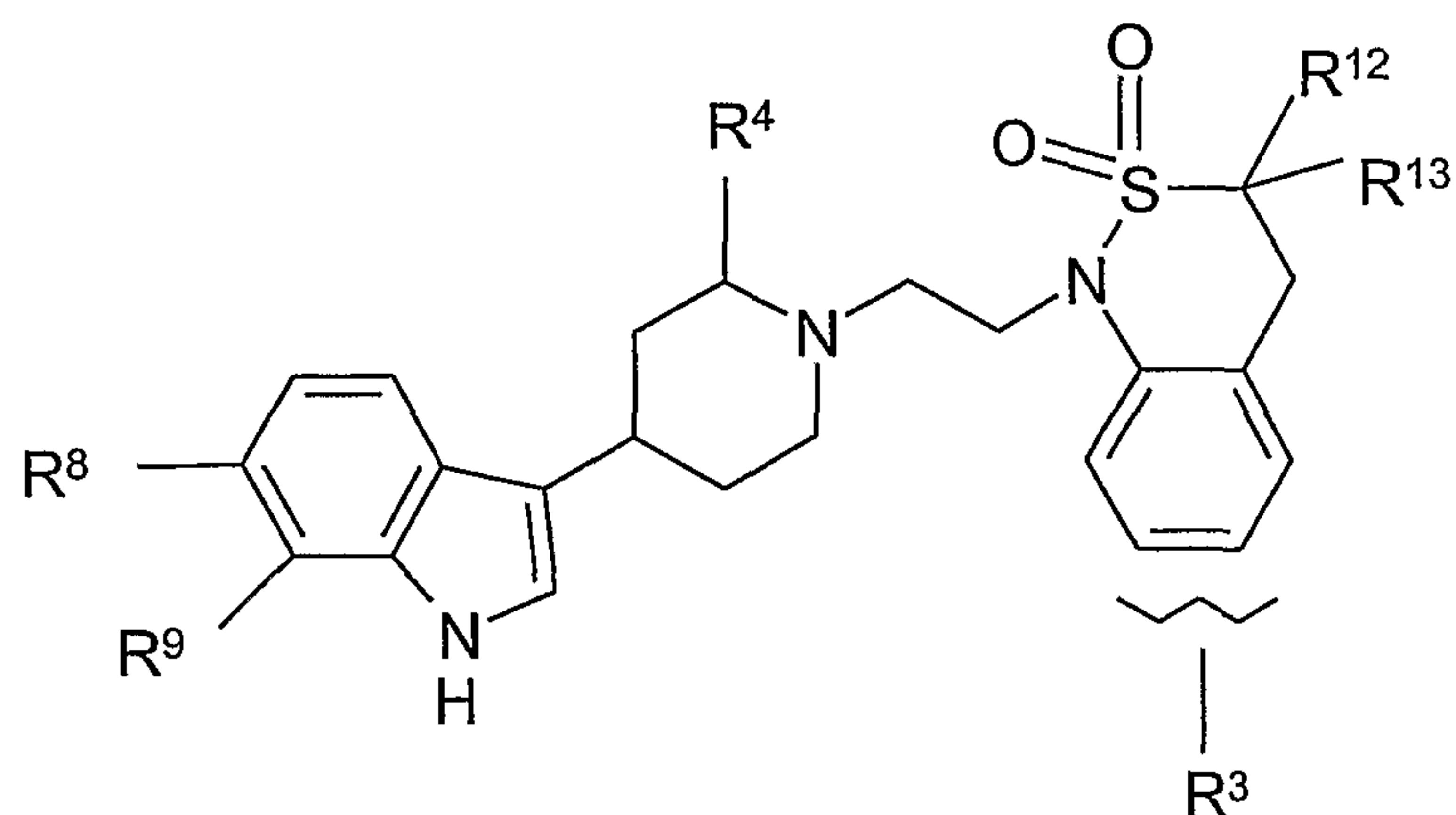
R^4 is C_{1-6} alkyl, and

R^{12} is C_{1-6} alkyl; and salts thereof.

A further preferred group of compounds is of the

15 following formula

- 6 -



in which

R^8 and R^9 are each hydrogen or halo, preferably fluoro,

5 R^3 is in the 6- or 7-position and is $-SOR^{10}$, $-SO_2R^{10}$ or $-COR^{10}$, where R^{10} is C_{1-6} alkyl,

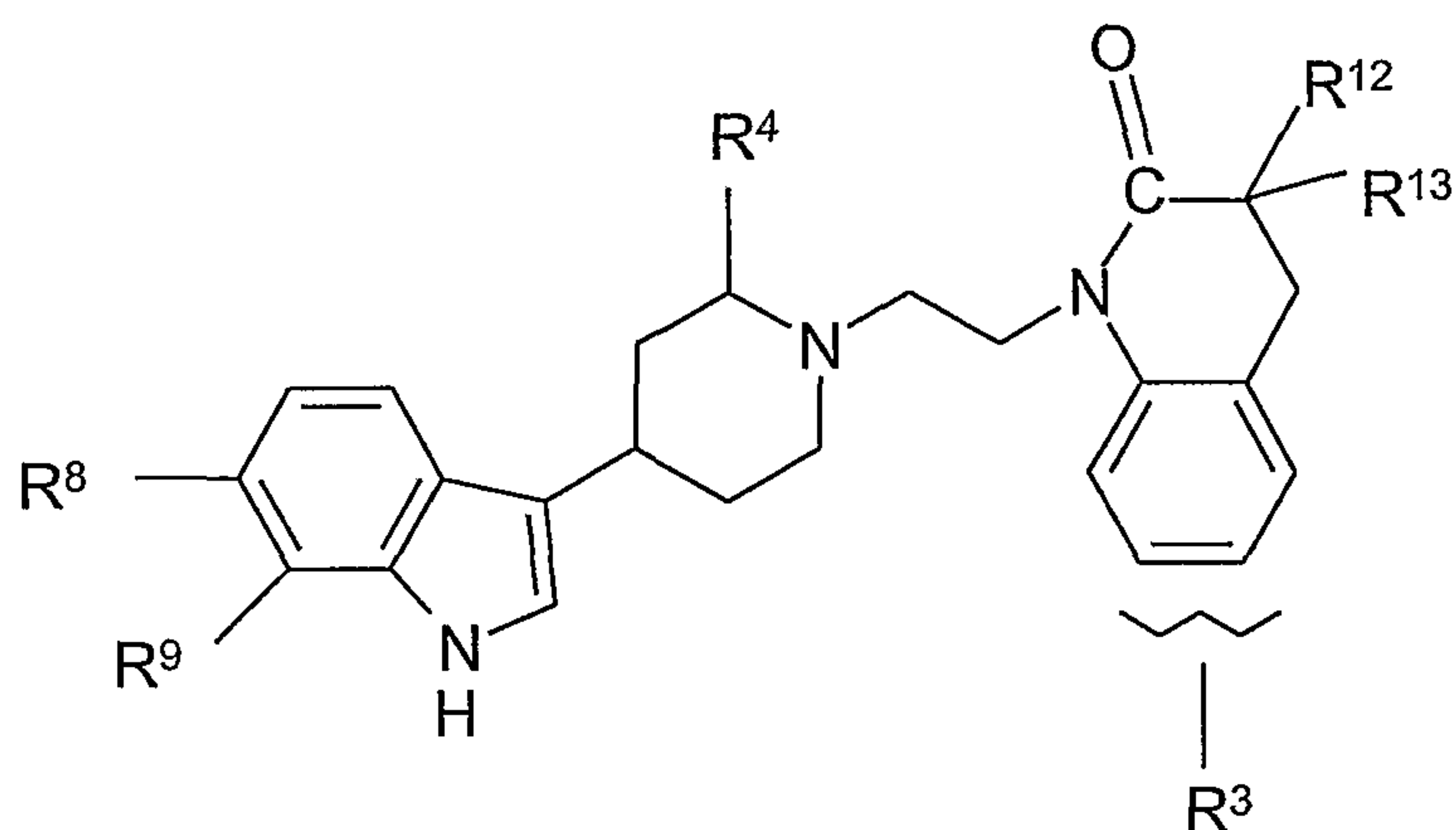
R^4 is C_{1-6} alkyl, and

R^{12} and R^{13} are each hydrogen or C_{1-6} alkyl; and salts thereof.

10

A further preferred group of compounds is of the following formula:

- 7 -



in which

R⁸ and R⁹ are each hydrogen or halo, preferably fluoro,

5 R³ is in the 6- or 7-position and is -SOR¹⁰, -SO₂R¹⁰ or
-COR¹⁰, where R¹⁰ is C₁₋₆ alkyl,

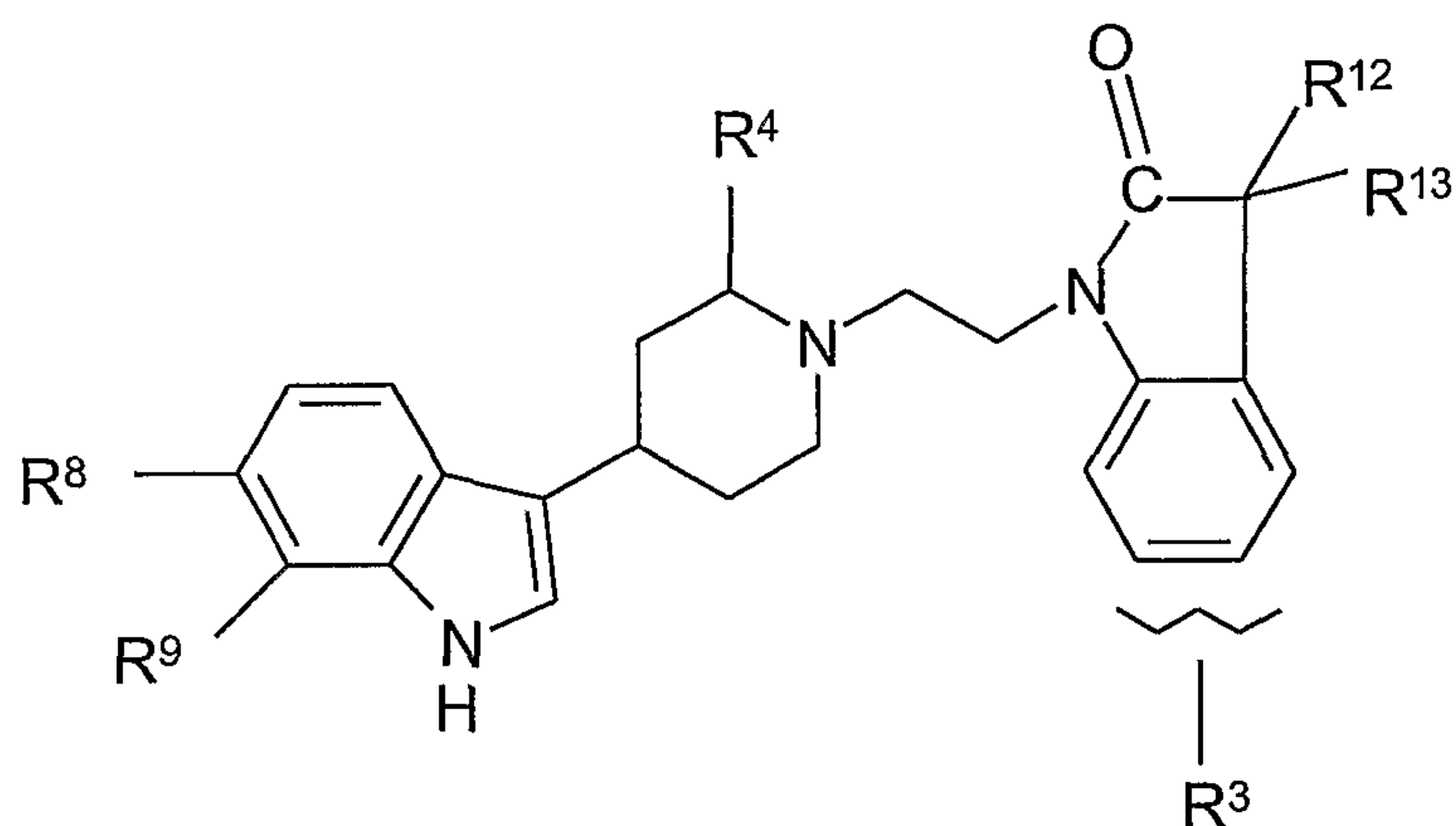
R⁴ is C₁₋₆ alkyl, and

R¹² and R¹³ are each hydrogen or C₁₋₆ alkyl; and salts
thereof.

10

A further preferred group of compounds is of the
following formula:

- 8 -



in which

R⁸ and R⁹ are each hydrogen or halo, preferably fluoro,

5 R³ is in the 6- or 7-position and is -SOR¹⁰, -SO₂R¹⁰ or
-COR¹⁰, where R¹⁰ is C₁₋₆ alkyl,

R⁴ is C₁₋₆ alkyl, and

R¹² and R¹³ are each hydrogen or C₁₋₆ alkyl; and salts
thereof.

10

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

- 9 -

hydroxymaleic, fumaric, malic, tartaric, citric,
salicyclic, o-acetoxybenzoic, or organic sulphonic,
2-hydroxyethane sulphonic, toluene-p-sulphonic,
naphthalene-2-sulphonic, bisethanesulphonic acid or
5 methanesulphonic acid. A preferred salt is the
tartrate.

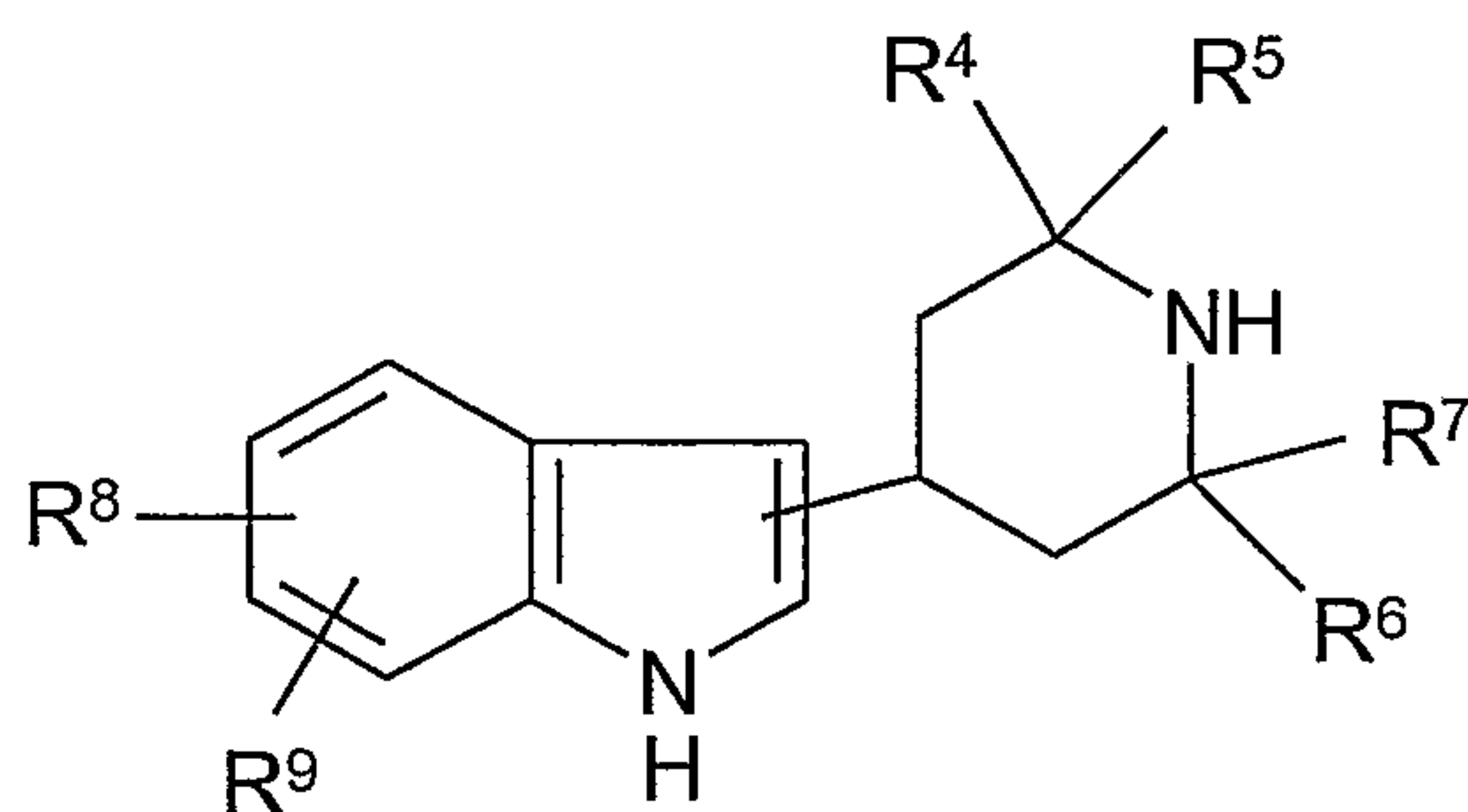
In addition to the pharmaceutically acceptable salts,
other salts are included in the invention. They may
10 serve as intermediates in the purification of compounds
or in the preparation of other, for example
pharmaceutically acceptable, acid addition salts, or are
useful for identification, characterisation or
purification.

15 Some of the compounds of the invention contain one or
more asymmetric carbon atoms which gives rise to
isomers. Moreover, compounds which are substituted by a
sulphonyl group (R^3 is $-SOR^{10}$) also exist in isomeric
20 forms. These compounds are normally prepared as racemic
mixtures and can conveniently be used as such, but
individual isomers can be isolated by conventional
techniques, if so desired. Such racemic mixtures and
individual optical isomers form part of the present
25 invention. It is preferred to use an enantiomerically
pure form.

- 10 -

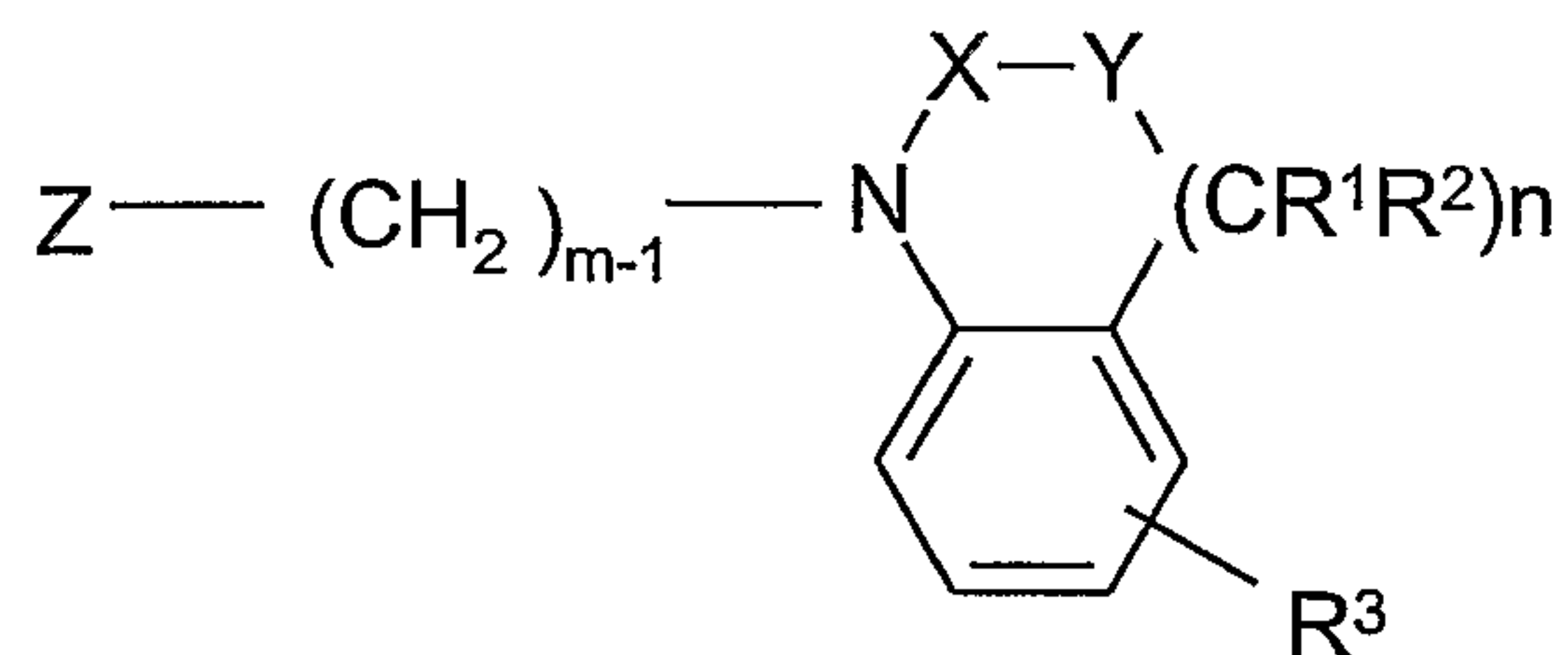
The invention also includes a process for producing a compound of formula (I) above, which comprises reacting a compound of the formula:

5



(III)

with a compound of the formula



(IV)

10

where n and m, and the substituents, have the values given above, and (i) Z is $-\text{CH}_2\text{W}$, where W is a leaving group such as, for example, a halo atom or a mesylate or tosylate, or (ii) Z is $-\text{CHO}$.

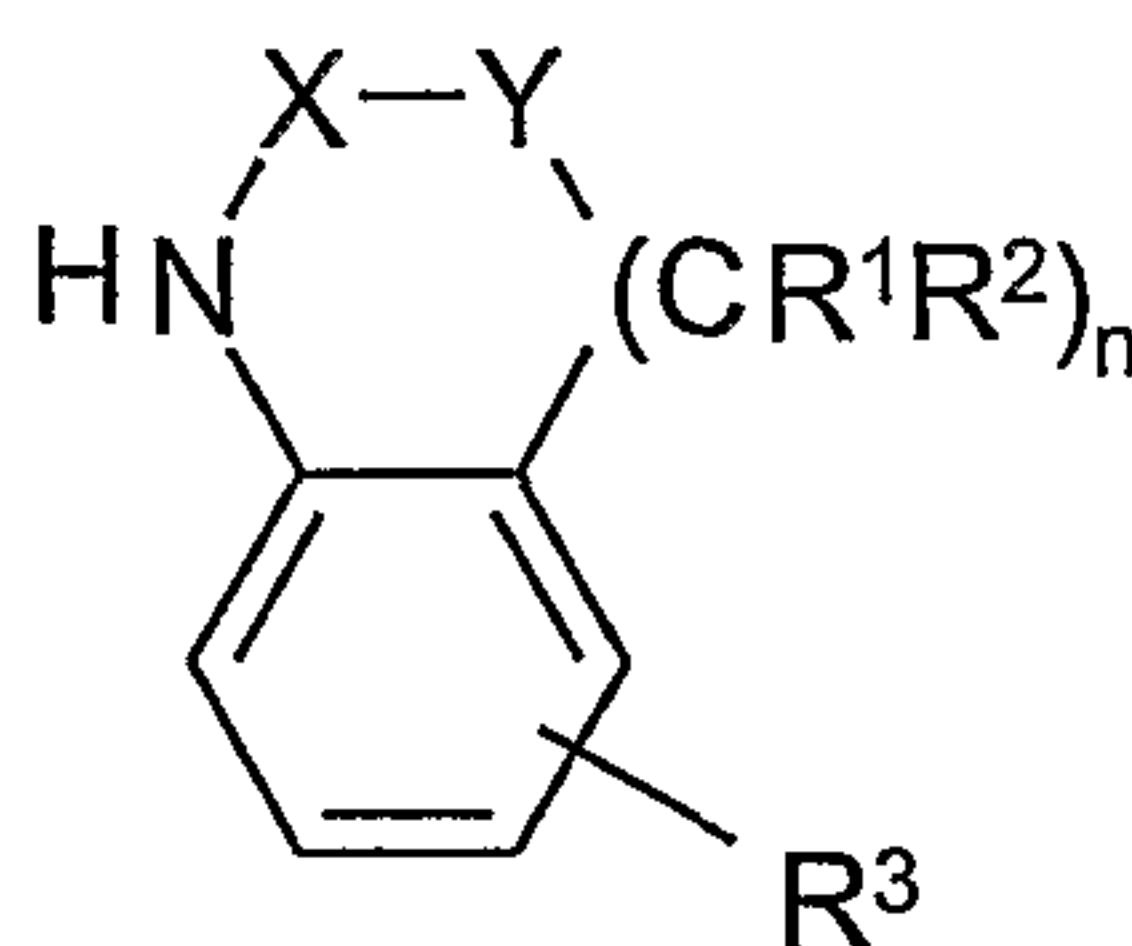
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- 11 -

The reaction is preferably carried out in a polar solvent such as, for example, acetonitrile or water, at a temperature of from 50°C. to 150°C., and in the presence of sodium iodide and a base such as, for example, sodium carbonate. When an aldehyde intermediate is employed, the reaction is one of reductive amination using, for example, sodium cyanoborohydride, borane in pyridine or triacetoxy borohydride in the presence of the compound of formula (III).

The intermediate compounds of formula (III) can be made by reacting an indole with the appropriate piperidinone.

Compounds of formula (VI) can be prepared by reacting an ethane derivative of the formula $V-(CH_2)_m-W$ (V), where V is halo, preferably bromo, with a compound of formula:



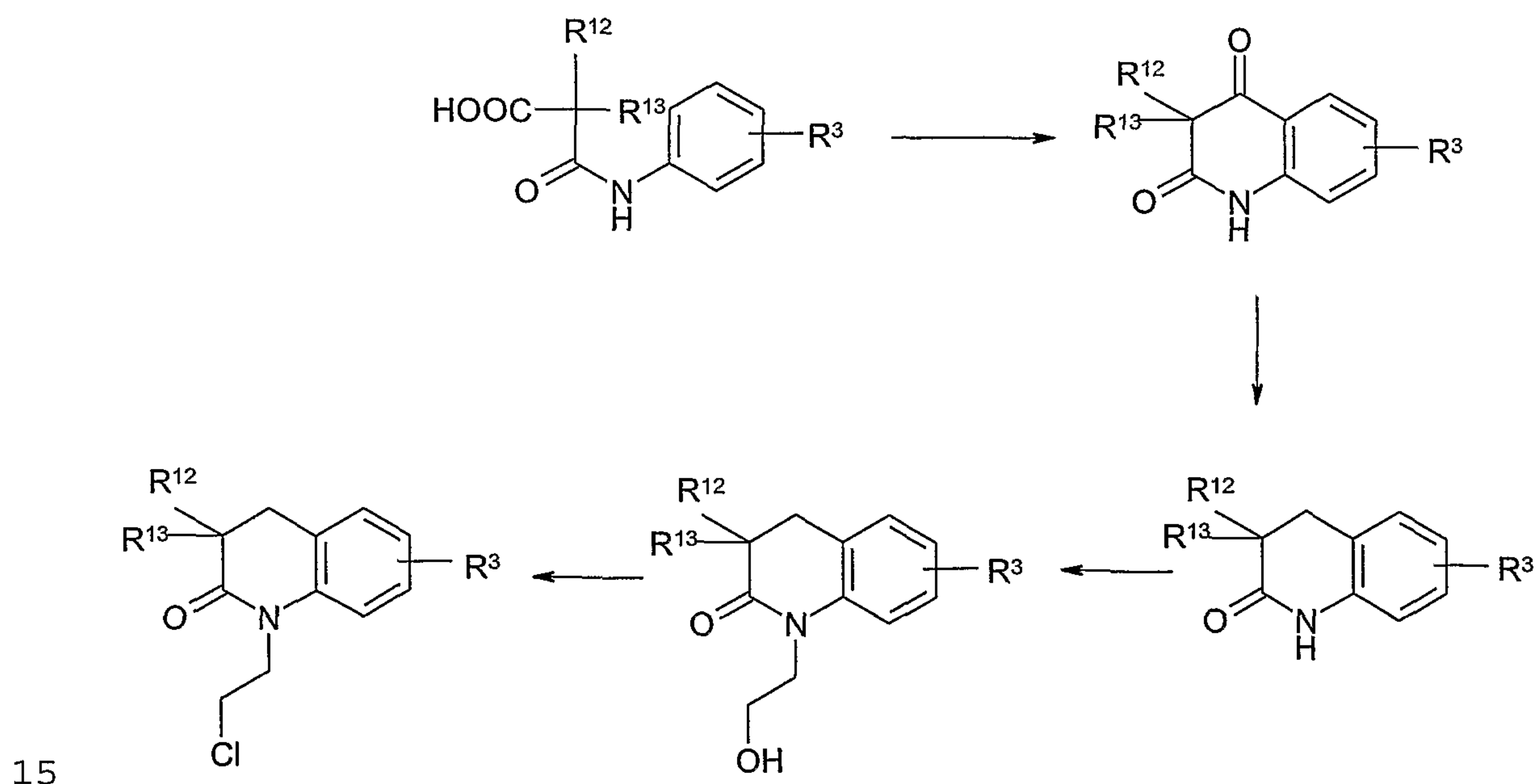
(VI)

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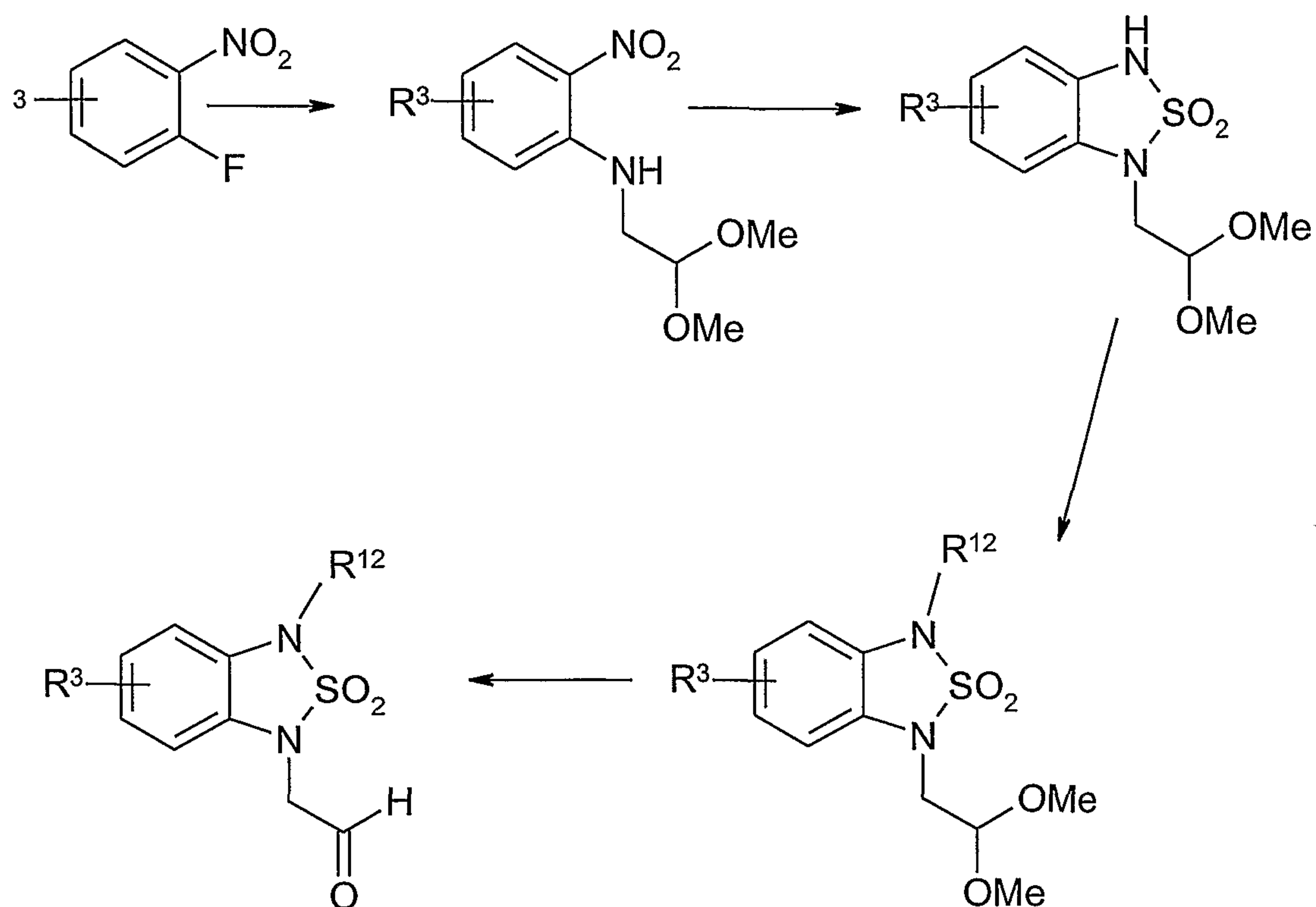
Preferred ethane derivatives of formula (V) are dihalo-ethanes, for instance bromo chloroethane, and the reaction is preferably carried out in an organic solvent such as, for example, dimethyl formamide, with a strong
 5 base such as sodium hydride, at a temperature of from 0 C. to 100 C., for instance room temperature.

Aldehyde intermediates of formula (IV) can be prepared from the appropriate alkene by oxidation employing, for
 10 example, ozone or osmium tetroxide.

Alternatively, compounds of formula (VI) can be prepared by a synthetic route, such as the following:

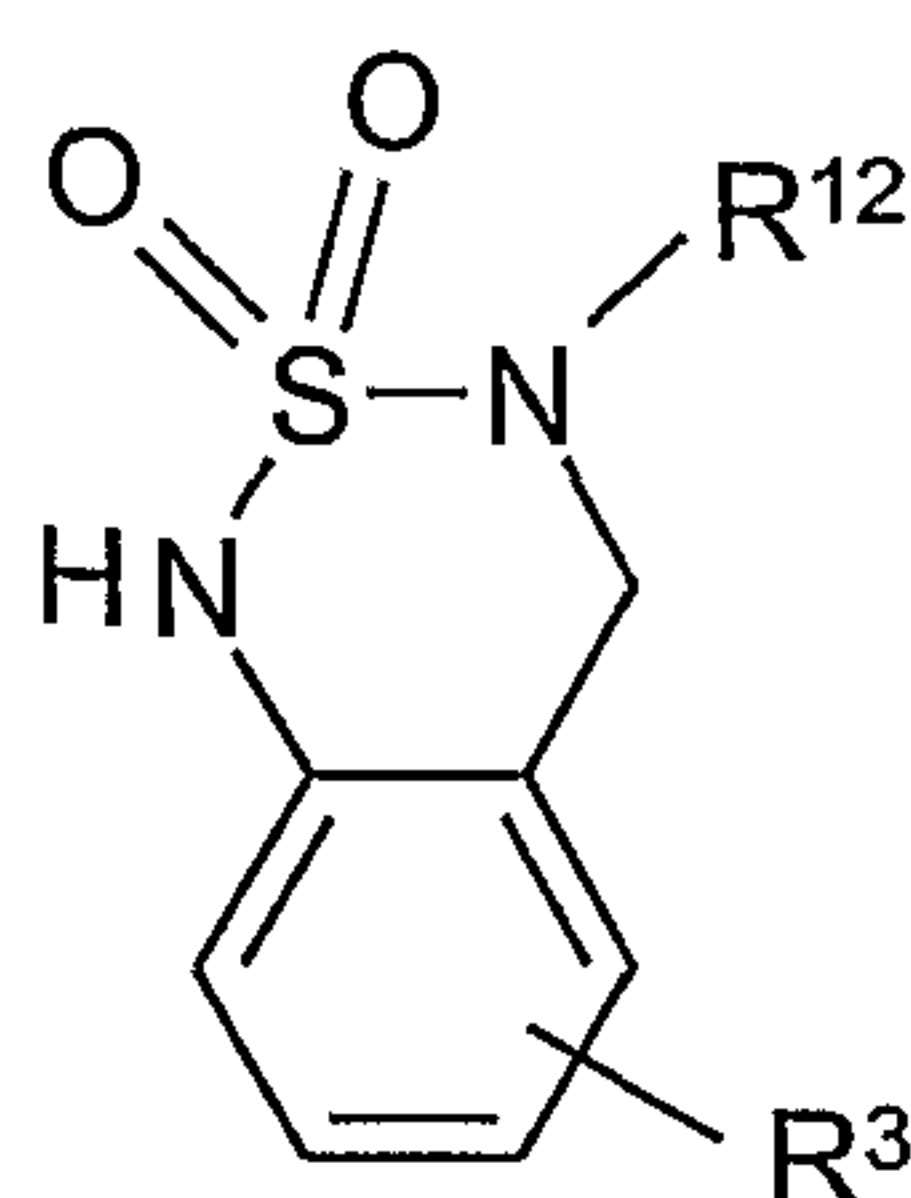


or by the following route:



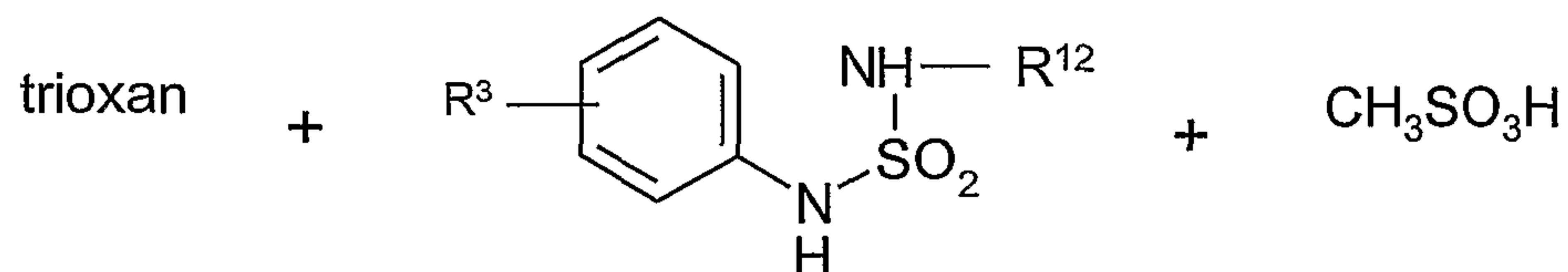
- 5 The intermediate compounds of formula (VI) are known in the literature, and they can readily be prepared by a variety of routes as, for example, in the case of compounds of formula (VI) having the following structure:

- 14 -



(VIII)

the principal route of synthesis is by means of a reaction between the appropriate sulfamoyl compound prepared from an aniline and sulfamoyl chloride and trioxan, in the presence of an acid, for example, an alkyl sulfonic acid:

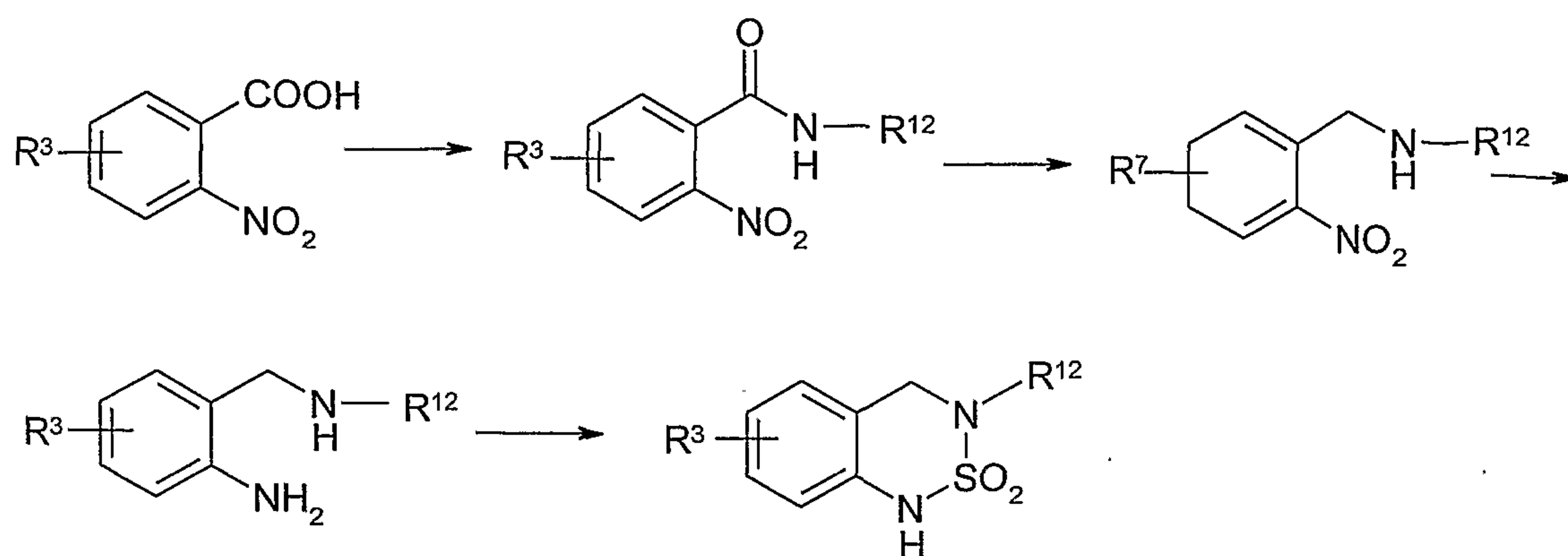


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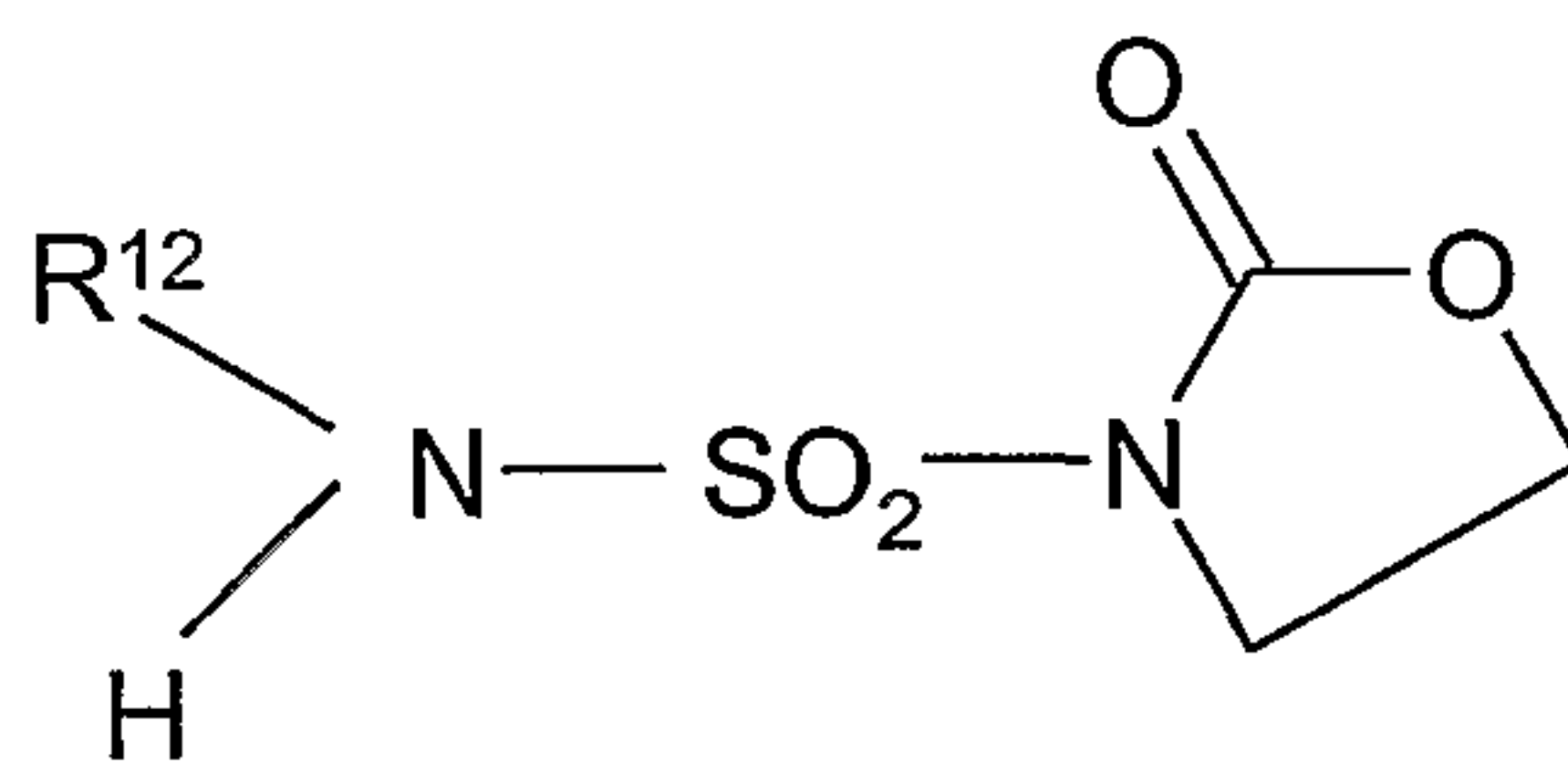
Alternatively, compounds of formula (VII) can be synthesised by reaction of sulfamide with an amino benzylamine in pyridine or diglyme. The amino benzylamine can be prepared in three steps from the appropriate nitrobenzoic acid via amide formation and a two step reduction as, for example:

15

- 15 -

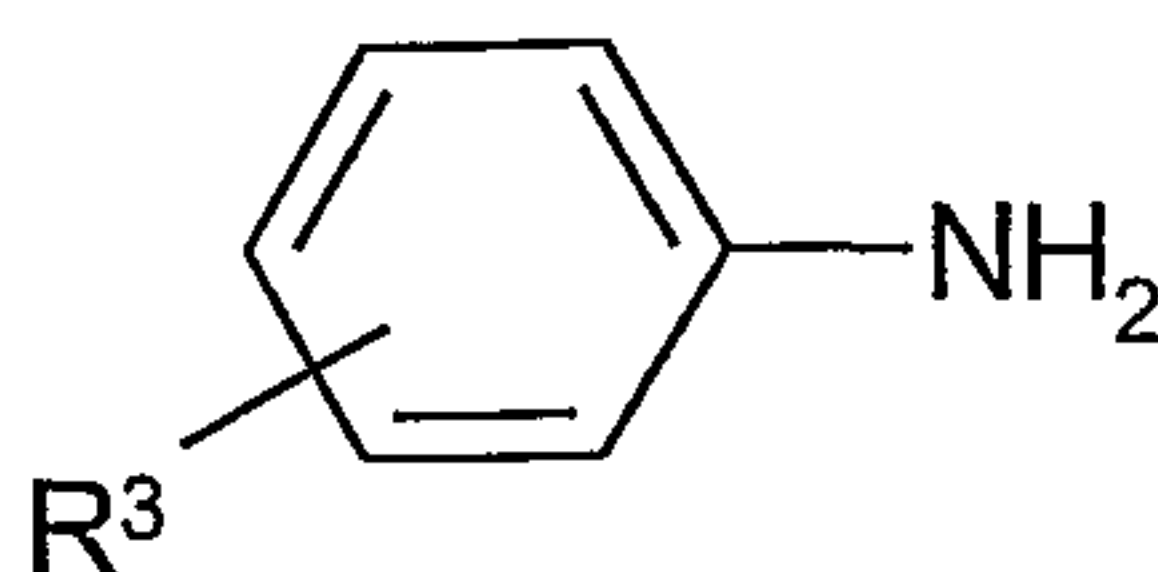


A further alternative route to compounds of
 5 formula (VII) involves the use of an appropriate
 N-sulfamoyloxazolidinone of formula:



10 which can be readily prepared by reacting
 chlorosulfonylisocyanate
 and amine with chloro- or bromo-ethanol. The
 N-sulfamoyloxazolidinone is then reacted with an aniline
 of formula

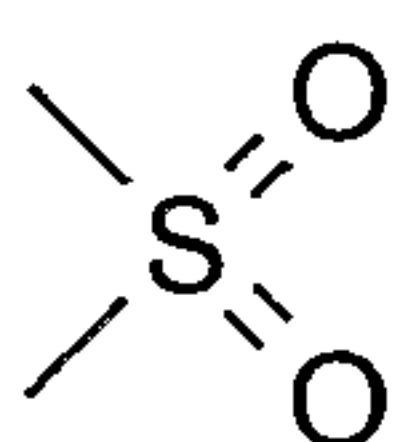
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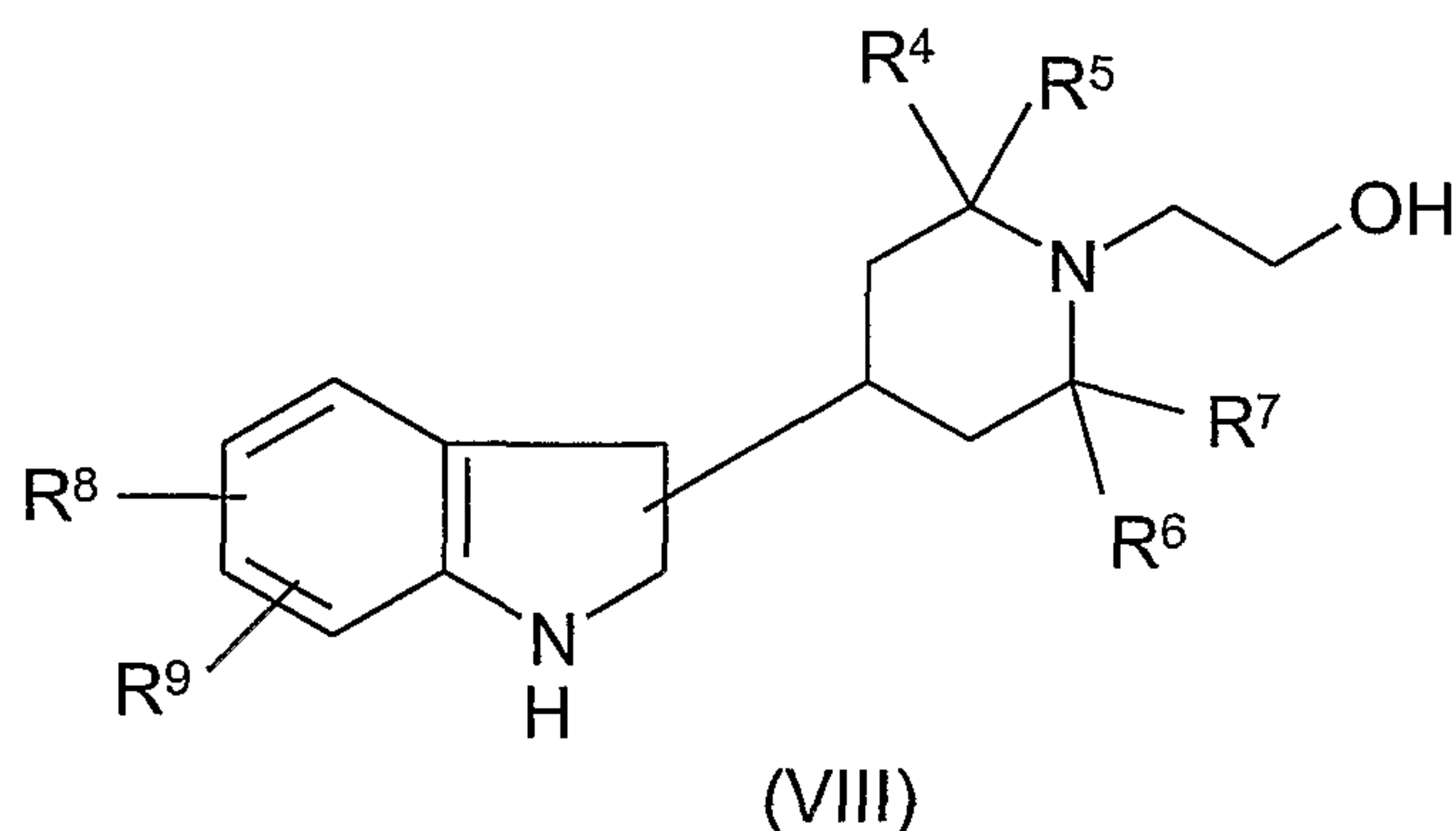
- 16 -

and the resulting sulfonyl urea reacted with trioxan, as described above, to give the compound of formula (VII).

An alternative route to the compounds of the invention
5 in which in formula (I) X is:



consists of an analogous, reverse, condensation of the
10 two principal components of the molecule as, for example, by reacting a compound of the formula:



15 with a compound of formula (VII) above, employing the Mitsunobu reaction. The reaction is carried out in an organic solvent such as tetrahydrofuran or dimethyl formamide, at a temperature of, for example, 0 C. to 5 C. employing a dialkylazodicarboxylate and
20 triphenylphosphine or tributylphosphine. Intermediate

- 17 -

compounds of formula (VIII) are novel and are included as part of the present invention.

It will be appreciated that in preparing compounds of formula (I) in which R^3 is $-SOR^{10}$ or $-SO_2R^{10}$, the appropriate intermediates as, for example, those of formula (VII), can be prepared by oxidation of the $-SR^{10}$ substituted compound, by the use of metachloro perbenzoic acid or Oxone® or sodium perborate or osmium tetroxide/sodium periodate.

As mentioned above, the compounds of the invention and their pharmaceutically acceptable salts have useful central nervous system activity. They have been shown to increase release of tritiated-5HT from guinea pig cortical slices in a test with the following procedure.

Cortical slices from the brains of male guinea pigs were incubated with 50 nM $[^3H]$ -5-HT for 30 minutes at 37°C. The slices were washed in basal buffer containing 1 μ M paroxetine and then transferred to baskets. The baskets were used to transfer the tissue between the washing and release buffers, all of which contained 1 μ M paroxetine.

- 18 -

In order to obtain a stable baseline release, the slices were incubated for 11 minutes in buffer and then transferred for 4 minutes to a second tube containing buffer. Following incubation they were again
5 transferred, for a further 4 minutes, to a buffer in which NaCl had been substituted, on an equimolar basis, to give a KCl concentration of 30 mM (release sample). The tritium in the tissue samples and in the buffers from the three incubation periods was estimated by
10 liquid scintillation spectroscopy. Test compound was present throughout the three incubation periods. The compounds of the invention enhanced release of 5-HT.

Compounds of the invention have been demonstrated to be
15 active at the serotonin 1B and 1D receptors. Their activity may be demonstrated in tests as described in Pullar, I. A. et al, European Journal of Pharmacology, 407, 39-46.

20 Compounds of the invention have also been demonstrated to be active at the serotonin, 5-HT_{2A}, receptor. Their binding activity has been demonstrated in a test described by Nelson, D. L. et al, J. Pharmacol. Exp. Ther., 265, 1272-1279, in which the affinity of the
25 compound for the human 2A receptor is measured by its ability to displace the ligand [³H]-ketanserin.

- 19 -

Compounds of the invention are also active serotonin reuptake inhibitors as measured by their displacement of [³H]-paroxetine at the reuptake site, Neuropharmacology Vol. 32 No. 8, 1993, pages 737-743.

5

Because of their ability to enhance 5-HT release as well as selective affinity for 5-HT receptors, the compounds of the present invention are indicated for use in treating a variety of conditions such as depression, 10 obesity, bulimia, alcoholism, pain, hypertension, ageing, memory loss, sexual dysfunction, anxiety, schizophrenia, gastrointestinal disorders, headache, cardiovascular disorders, smoking cessation, drug addiction, emesis, epilepsy, Alzheimer's and sleep 15 disorders. Compounds of the present invention may be particularly useful in the treatment of depression. Compounds of the invention may also be useful for the treatment of obsessive compulsive disorder.

20 The present invention also provides a method of treating a warm blooded mammal including a human suffering from or susceptible to a disorder of the central nervous system, which comprises administering to said human an effective amount of a compound of the present invention, 25 or a pharmaceutically acceptable salt thereof.

- 20 -

The present invention further provides a method of inhibiting the 5-HT_{2A} receptor which comprises administering to a warm blooded mammal including a human in need of such treatment a therapeutically effective
5 amount of a 5-HT_{2A} antagonist of formula I.

The present invention also provides a method of inhibiting the reuptake of serotonin, which comprises administering to a warm blooded mammal including a human
10 in need of such treatment a therapeutically effective amount of a serotonin reuptake inhibitor of formula I.

The compounds of the invention are effective over a wide dosage range, the actual dose administered being
15 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
20 humans, dosages of from 0.1 to 100 mg per day may be used, preferably from 2 to 20 mg per day as, for example, for the preferred compounds of formula (II) and (III).

25 The compounds of the invention will normally be administered orally or by injection and, for this

- 21 -

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
5 compound.

Accordingly the invention includes a pharmaceutical composition comprising as active ingredient a compound of formula (I) or a pharmaceutically acceptable salt or
10 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,
15 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. Some examples of suitable excipients are lactose, dextrose, sucrose, sorbitol, mannitol, starches, gum
20 acacia, calcium phosphate, alginates, tragacanth, gelatin syrup, methyl cellulose, methyl- and propyl-hydroxybenzoate, talc, magnesium stearate or oil. The compositions of the invention may, if desired, be formulated so as to provide quick, sustained or delayed
25 release of the active ingredient after administration to the patient.

- 22 -

Depending on the route of administration, the foregoing compositions may be formulated as tablets, capsules or suspensions for oral use and injection solutions or
5 suspensions for parenteral use or as suppositories. Preferably the compositions are formulated in a dosage unit form, each dosage containing from 0.1 to 100 mg, more usually 2 to 20 mg, of the active ingredient.

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

EXAMPLES

15

1-Dimethylamino-2-(4-fluoro-2-nitro)phenylethene

A mixture of 4-fluoro-2-nitrotoluene (50 g, 0.32 mol), dimethylformamide dimethylacetal
20 (76.77 g) and dimethylformamide (910 ml) were heated under reflux under nitrogen with stirring for 7 hr, cooled, allowed to stand for 16 hr, poured into ice-water (2 l), stirred for 15 mins and the resultant precipitate isolated by
25 filtration, washed with water (500 ml), dried to give a red solid. (Org. Synth. (1985), 63, 214-25)

- 23 -

6-Fluoro-1H-indole

A 40 litre Cook hydrogenator was charged under a nitrogen atmosphere with 10% palladium on charcoal (9 g) suspended in toluene (400 ml). To this suspension was added 1-dimethylamino-2-(4-fluoro-2-nitro) phenylethene (137.2 g, 0.653 mol) in toluene (1.4 l) and the mixture hydrogenated at 80 psi for 3.5 hr. The suspension was then filtered through a celite pad, which was washed through with toluene (2 x 200 ml) and the filtrate and washings evaporated under reduced pressure to give a brown oil which crystallised on standing to a yellow brown solid 93.65 g. This solid was dissolved in ethyl acetate-hexane (7:3) and filtered through a pad of flash silica. The required fractions were collected and evaporated under reduced pressure to give a pale brown solid. (Org. Synth. (1985), 63, 214-25)

Similarly prepared were:

6,7-Difluoro-1H-indole

δ (^1H NMR, CDCl_3 , ppm) : 6.50 (1H, m), 6.90 (1H, m), 7.30 (2H, m), 8.4 (1H, br).

- 24 -

6-Fluoro-7-methyl-1H-indole (J.Med.Chem., 1976
19(3) 391-5)

5 δ (^1H NMR, CDCl_3 , ppm) : 2.4 (3H, s), 6.50 (1H,),
6.90 (1H, t), 7.20 (1H, m), 7.4 (1H, m), .0 (1H,
s).

10 6-Fluoro-3-(6-methyl-1,2,3,6-tetrahydro-4-
pyridinyl)-1H-indole and 6-fluoro-3-(2-methyl-
1,2,3,6-tetrahydro-4-pyridinyl)-1H-indole

Powdered potassium hydroxide (4.01 g, 71.5 mmol) is
dissolved in a mixture of methanol (70 ml) and
water (1 ml), and stirred until no solid remains.
15 6-Fluoro indole (1.10g, 8.73 mmol) and 2-
methylpiperidone trifluoroacetic acid salt (4.18g,
18.4 mol) [2-methyl 4-piperidones can be
synthesised by known methods in the literature ,
for example Mistryukov, E. A.; Aronova, N. I.
20 Izv. Akad. Nauk SSSR, Ser. Khim. (1966), (12),
2171-6.] are added as single portions, and the
mixture is heated to reflux under a nitrogen
atmosphere for four hours, before being allowed to
cool to 50°C. Water (70 ml) is then added in a
25 dropwise manner over 20 mins, and. the mixture is
then stirred for a further 1 hour, during which

- 25 -

time the temperature falls to r.t. The yellow precipitate that forms is collected by vacuum filtration, rinsed with a small amount of cold water, then dried in vacuo at 60°C for 16 hours.

5 This affords 1.60g, (79.7%) of the title compound in a ratio of 2:1 for the regioisomers.

¹H NMR (CDCl₃), δ (ppm); 1.22-1.34 (2x d, 3H),
2.12-2.60 (m, 2.5 H), 2.92-3.8 (m, 2.5H), 3.68
(br.s 1H), 6.10 (s, 0.33H), 6.22 (s, 0.67H), 6.82-
10 6.98 (t, 1H), 7.00-7.10 (d, 1H), 7.14 (s, 1H), 7.74
(m, 1H), 8.34 (br.s, 1H); MS, reqd. 230.1; obs.
231.1 (M+1 ; FIAPOS); 229.1 (M-1 ; FIANEG)

15 Similarly prepared were

6,7-Difluoro-3-(6-methyl-1,2,3,6-tetrahydro-4-pyridinyl)-1H-indole and 6,7-difluoro-3-(2-methyl-1,2,3,6-tetrahydro-4-pyridinyl)-1H-indole

20 ¹H NMR (CD₃OD), (ppm); 1.40 (m, 3H), 2.32-2.84 (m, 2H),
3.06-3.32 (m, 1H), 3.34-3.58 (m, 1H), 3.64-3.88 (m, 1H),
6.22 (s, 0.28H), 6.40 (s, 0.72H), 7.04-7.20 (m, 1H),
7.50 (s, 1H), 7.70-7.78 (s, 1H); MS, reqd. 248.1; obs.
249.1 (M+1 ; FIAPOS); 247.1 (M-1 ; FIANEG).

25

- 26 -

6-Fluoro-7-methyl-3-(6-methyl-1,2,3,6-tetrahydro-4-pyridinyl)-1H-indole) and 6,7-difluoro-3-(2-methyl-1,2,3,6-tetrahydro-4-pyridinyl)-1H-indole

¹H NMR ((CD₃)₂SO), δ (ppm); 1.30-1.44 (m, 3H), 2.20-2.40

5 (m, 1H), 2.54 (s, 3H), 3.04-3.86 (m, 4H), 6.14-6.24 (m, 1H), 6.98-7.10 (m, 1H), 7.52-7.72 (s, 1H), 7.72-7.82 (m, 1H).

10 *tert*-Butyl 4-(6-fluoro-1H-indol-3-yl)-6-methyl-3,6-dihydro-1(2H)-pyridinecarboxylate and *tert*-butyl 4-(6-fluoro-1H-indol-3-yl)-2-methyl-3,6-dihydro-1(2H)-pyridinecarboxylate

15 Di-*tert* butyl dicarbonate (5.90g, 0.027 mol) is dissolved in THF at 0°C, and a mixture 6-fluoro-3-(6-methyl-1,2,3,6-tetrahydro-4-pyridinyl)-1H-indole and 6-fluoro-3-(2-methyl-1,2,3,6-tetrahydro-4-pyridinyl)-1H-indole (5.17g, 0.022 mol) is added portionwise over 5
20 minutes. The mixture is stirred at this temperature for 1 hour, then for 3 hours at room temperature, before 100 ml aqueous sodium bicarbonate (sat. solution) is added. This mixture is extracted with ethyl acetate (3 x 100 ml), then the combined organic layers are dried over
25 MgSO₄, before the solvent is removed in vacuo. The residual pale yellow oil is passed through a silica pad, eluted with dichloromethane, then 10% methanol, 90%

- 27 -

dichloromethane, to give 7.36g, 100% of the desired product after removal of the solvent. The ratio of regioisomers is 2:1.

¹H NMR (CDCl₃), δ (ppm); 1.18 (d, 3H), 1.50 (s, 9H),
5 2.20-2.30 (br. d, 1H), 2.76-2.90 (br. d, 1H), 3.72-3.82
(br. d, 1H), 4.30-4.54 (br d, 1H), 4.64 (m, 1H), 6.10
(br. s, 1H), 6.90 (t, 1H), 7.06 (d, 1H), 7.12 (s, 1H),
7.74 (m, 1H), 8.54 (m, 1H); MS, reqd. 330.1; obs. 331.1
(M+1 ; FIAPOS); 329.1 (M-1 ; FIANEG)

10

Similarly prepared were

tert-Butyl 4-(6,7-difluoro-1*H*-indol-3-yl)-6-methyl-3,6-
dihydro-1(2*H*)-pyridinecarboxylate and *tert*-butyl 4-(6,7-
15 difluoro-1*H*-indol-3-yl)-2-methyl-3,6-dihydro-1(2*H*)-
pyridinecarboxylate

¹H NMR (CDCl₃), (ppm); 1.20-1.28 (m, 3H), 1.44 (s, 9H),
1.84-2.10 (m, 1H), 2.12-2.58 (m, 1H), 2.60-3.16 (m, 1H),
3.62-3.84 (m, 1H), 4.22-4.82 (m, 1H), 6.08 (br. s, 1H),
20 6.88-7.00 (m, 1H), 7.00-7.12 (m, 1H), 7.38-7.60 (m, 1H);
MS, reqd. 348.1; obs. 347.1 (M-1 ; FIANEG).

tert-Butyl 4-(6-fluoro-7-methyl-1*H*-indol-3-yl)-6-methyl-
3,6-dihydro-1(2*H*)-pyridinecarboxylate and *tert*-butyl 4-
25 (6-fluoro-7-methyl-1*H*-indol-3-yl)-2-methyl-3,6-dihydro-
1(2*H*)-pyridinecarboxylate

- 28 -

¹H NMR (CDCl₃), δ (ppm); 1.18-1.32 (m, 3H), 1.50 (s, 9H),
2.20-2.70 (m, 4H), 2.78-3.14 (m, 1H), 3.60-3.86 (m, 1H),
4.04-4.72 (m, 2H), 6.02-6.12 (m, 1H), 6.82-6.94 (m, 1H),
5 7.10-7.12 (m, 1H), 7.54-7.62 (m, 1H), 7.96 (br. s, 1H).

tert-Butyl 4-(6-fluoro-1H-indol-3-yl)-(2S,4R)-2-methyl-
1-piperidinecarboxylate and tert-butyl 4-(6-fluoro-1H-
indol-3-yl)-(2R,4S)-2-methyl-1-piperidinecarboxylate

10

A mixture of of tert-butyl 4-(6-fluoro-1H-indol-3-yl)-6-
methyl-3,6-dihydro-1(2H)-pyridine carboxylate and tert-
butyl 4-(6-fluoro-1H-indol-3-yl)-2-methyl-3,6-dihydro-
1(2H)-pyridine carboxylate (2.06g, 6.24 mmol) is
15 dissolved in dry ethanol (40 ml), along with a
suspension of 10% palladium on carbon (0.50 g). This
mixture is agitated under 70 psi pressure of hydrogen
gas for 16 hours, before the catalyst is removed by
filtration through a celite plug. The solvent is removed
20 in vacuo, and the residue purified by column
chromatography, using 25% ethyl acetate, 75% hexane as
the eluent. After removal of the solvent, this affords
1.21g, 58 % yield of tert-butyl 4-(6-fluoro-1H-indol-3-
yl)-2-methyl-1-piperidinecarboxylate as a mixture of cis
25 and trans products. This mixture is subjected to

- 29 -

preparative HPLC, firstly using an achiral column
(Kromasil KR60-5SIL column, eluted with 89% hexane, 9%
dichloromethane, 2% ethanol and 0.1% dimethylamine) to
separate the *trans* and *cis* isomers (retention times =
5 11.6 and 12.2 min), then using a chiral stationary phase
column (Chiralcel-OJ column, eluted with 60% hexane, 40%
ethanol and 0.2% dmea) to resolve the two *trans*
enantiomers (retention times = 9.1 and 10.5 min). ¹H NMR
(CDCl₃), δ (ppm); 1.28 (d, 3H), 1.50 (s, 9H), 1.82-2.06
10 (m, 3H), 2.88-3.22 (m, 3H), 4.00-4.20 (br. m, 1H), 4.50-
4.66 (br. m, 1H), 6.88 (t, 1H), 6.92 (s, 1H), 7.04 (d,
1H), 7.52 (m, 1H), 8.20 (br. s, 1H); MS, reqd. 332; obs.
331.1 (M-1; FIANEG).

15 Similarly prepared were

**tert-Butyl 4-(6,7-difluoro-1H-indol-3-yl)-(2S,4R)-2-
methyl-1-piperidinecarboxylate and tert-butyl 4-(6,7-
difluoro-1H-indol-3-yl)-(2R,4S)-2-methyl-1-
20 piperidinecarboxylate**

¹H NMR (CDCl₃), (ppm); 1.16-1.34 (m, 3H), 1.52 (s, 9H),
1.60-1.92 (m, 2H), 1.94-2.36 (m, 2H), 2.96-3.38 (m, 2H),
3.80-4.32, (m, 1H), 4.36-4.74 (m, 1H), 6.82-7.00 (m,
2H), 7.18-7.30 (m, 1H); MS, reqd. 250.1; obs. 251.1 (M+1
25 ; FIAPOS); 249.1 (M-1 ; FIANEG).

- 30 -

tert-Butyl 4-(6-fluoro-7-methyl-1H-indol-3-yl) - (2S,4R) -
2-methyl-1-piperidinecarboxylate and tert-butyl 4-(6-
fluoro-7-methyl-1H-indol-3-yl) - (2R,4S) -2-methyl-1-
5 piperidinecarboxylate

¹H NMR (CDCl₃), δ (ppm); 1.24-1.32 (m, 3H), 1.48 (s, 9H),
1.56-1.70 (m, 1H), 1.78-1.96 (m, 2H), 1.98-2.10 (m, 1H),
2.38 (s, 3H), 2.96-3.24 (m, 2H), 4.08 (br. s, 1H), 4.52
(br. s, 1H), 6.82-6.96 (m, 2H), 7.34-7.40 (m, 1H), 7.82
10 (br. s, 1H).

6-Fluoro-3-[(2S,4R)-2-methylpiperidin-4-yl]-1H-indole and 6-
fluoro-3-[(2R,4S)-2-methylpiperidin-4-yl]-1H-indole

15

tert-Butyl (2S,4R)-4-(6-fluoro-1H-indol-3-yl)-2-methyl-
1-piperidinecarboxylate (1.21 g, 3.64 mmol) is dissolved
in trifluoroacetic acid (50 ml) and dichloromethane
(50ml) and the mixture stirred at room temperature under
20 nitrogen for 1 hour. The reaction is then quenched by
the cautious addition of saturated aqueous sodium
bicarbonate (500 ml), and the mixture extracted with
ethyl acetate (2 x 250 ml). The organic layers are
combined, dried over MgSO₄, then the solvent is removed
25 in vacuo. This affords the desired product as a clear
oil (0.84g, 100% yield). ¹H NMR (CD₃OD), δ (ppm); 1.06

- 31 -

(d, 3H), 1.60-1.70 (m, 1H), 1.72-1.98 (m, 3H), 2.72-2.90 (m, 2H), 2.92-3.12 (m, 1H), 3.14-3.24 (m, 2H), 6.6 (t, 1H), 6.9 (d, 1H), 6.94 (d, 1H), 7.34 (d.d, 1H); MS, reqd. 232.1; obs. 233.1 (M+1 ; FIAPOS); 231.1 (M-1 ; FIANEG) .

Similarly prepared were

6-Fluoro-7-methyl-3-[(2S,4R)-2-methylpiperidin-4-yl]-1H-indole and 6-fluoro-7-methyl-3-[(2R,4S)-2-methylpiperidin-4-yl]-1H-indole

¹H NMR ((CD₃)₂SO), δ (ppm); 1.02-1.10 (m, 3H), 1.50-1.92 (m, 4H), 2.34 (s, 3H), 2.66-2.88 (m, 2H), 2.94-3.08 (m, 1H), 3.18-3.28 (m, 1H), 6.70-6.84 (m, 1H), 7.08 (s, 1H), 7.24-7.36 (m, 1H) .

6,7-Difluoro-3-[(2S,4R)-2-methylpiperidin-4-yl]-1H-indole and 6,7-difluoro-3-[(2R,4S)-2-methylpiperidin-4-yl]-1H-indole (as a mixture)

The synthesis of the above compound was carried out in the same manner as that use to synthesise the 6-fluoro analogue. No HPLC was carried out, and instead, column chromatography (silica gel, eluted with 98% dichloromethane, 2% methanol and 0.2% aqueous ammonia)

- 32 -

afforded the trans isomers as a racemic mixture. ^1H NMR (CDCl₃), δ (ppm); 1.18 (d, 3H), 1.60-1.92 (m, 2H), 1.96-2.12 (d, 2H), 2.34 (br.s, 2H), 2.78-3.12 (m, 2H), 3.14-3.28 (m, 1H), 3.32-3.46 (m, 1H), 6.80-7.06 (m, 2H), 7.18-7.30 (m, 1H); MS, reqd. 250.1; obs. 251.1 (M+1 ; FIAPOS); 249.1 (M-1 ; FIANEG).

(1-Methylethyl)sulfamic acid

10 A 250 ml 3-necked round bottom flask equipped with a magnetic stirrer bar, pressure equalising dropping funnel, thermometer and nitrogen gas bleed was charged with nitromethane (75 ml) and fuming sulfuric acid
15 (30 g, i.e. oleum 12-17%). The mixture was cooled to 0°C. using an external cardice (solid CO₂)/acetone bath. Then isopropyl isocyanate (25 g, 0.294 mol) was added dropwise to the mixture, stirred under nitrogen, keeping the temperature below 30°C. during the addition. The
20 stirred suspension was then heated under reflux for 30 mins, then allowed to cool to room temperature and stirred overnight. Diethyl ether (100 ml) was added to the mixture, which was then filtered. The filter pad was washed with more ether (3 x 100 ml) and then dried
25 in an air stream at room temperature to give a pale

- 33 -

yellow crystalline solid, (1-methyl ethyl)sulfamic acid.
(JOC 1976 41 (25) 4028-9)

(1-Methylethyl)sulfamoyl chloride

5

A 500 ml 3-necked round bottom flask equipped with a water condenser, thermometer and magnetic stirrer bar was charged with (1-methyl ethyl)sulfamic acid (34.8 g, 0.25 mol), phosphorus pentachloride (52.06 g, 0.25 mol) and toluene (400 ml). The mixture was warmed under reflux for 1 hr, then cooled back down to room temperature. The solvent was removed *in vacuo* to give a pale brown oil which was then purified by distillation under reduced pressure (approximately 15 mm Hg and 110°C.) to give a clear, colourless liquid, (1-methyl ethyl)sulfamoyl chloride (JOC 1976 41 (25) 4028-9)

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20

N-(4-Methylthiophenyl)-2,2-dimethylmalonamic acid

25

Thionyl chloride (8.15 g, 5 ml, 0.069 mol) was added to a stirred solution of 2,2-dimethylmalonic acid (7.26 g, 0.055 mol) in dry THF (55 ml). The mixture was heated under reflux for 3 hr. The reaction mixture was

- 34 -

cooled to room temperature and 4-methylthioaniline (15.3 g, 0.11 mol) in THF (30 ml) was then added dropwise over 30 mins to the solution. The mixture was stirred at
5 room temperature for 2 hr. The reaction mixture was then concentrated *in vacuo* and then treated with hydrochloric acid (2N, 100 ml). The product was extracted with ethyl acetate (2 x 100 ml). The organic extracts
10 were combined, then washed with water (100 ml) and saturated sodium hydrogen carbonate solution (5 x 80 ml). The organic layer was then acidified with hydrochloric acid (5N, 250 ml) and the resultant white crystalline
15 precipitate was collected by filtration to afford N-(4-methylthiophenyl)-2,2-dimethylmalonamic acid. mp 130-132°C.

N-(4-Methylthiophenyl)-N'-(1-methylethyl)sulfamide

20

(1-Methylethyl)sulfamoyl chloride (6.63 g, 0.034 mol) was added dropwise to a solution of 4-(methylthio) aniline (4.48 g, 0.032 mol) and triethylamine (4.87 ml, 0.035 mol) in dry
25 dichloromethane (100 ml) at 0°C. under a nitrogen atmosphere. After addition, the resultant mixture

- 35 -

was allowed to warm to room temperature and was stirred for 6 hr. The reaction mixture was further extracted with dichloromethane and the organic extracts washed with water (2 x 50 ml), dried (MgSO₄) and concentrated *in vacuo* to yield N-(4-methylthiophenyl)-N'-(1-methylethyl)sulfamide as a white solid. δ (1H NMR, DMSO, ppm) : 0.8 (6H, d), 2.3 (3H, s), 3.2 (1H, m), 3.35 (1H, s), 6.9-7.1 (4H, m), 9.5 (1H, s). M.P. 65-68°C.

10

**3,4-Dihydro-3-(1-methylethyl)-6-methylthio-1H-
2,1,3-benzothiadiazine-2,2-dioxide**

15 N-(4-Methylthiophenyl)-N'-(1-methylethyl)sulfamide (4.35 g, 0.016 mol) was dissolved in dry dichloromethane (150 ml) and methanesulphonic acid (18.87 ml, 0.303 mol). The solution was cooled at 0°C. before the addition of trioxan (0.480 g, 0.005
20 mol) in dichloromethane (15 ml). After stirring at 0°C. for 1 hr, the reaction mixture was poured onto ice-water (250 ml), the layers separated, dried (MgSO₄) and concentrated *in vacuo* to yield 3,4-dihydro-6-(ethylsulfonyl)-3-(1-methylethyl)-1H-
25 2,1,3-benzothiadiazine-2,2-dioxide as a white

- 36 -

solid. δ (^1H NMR, DMSO, ppm) : 0.9 (6H, d), 2.3 (3H, s), 3.9 (1H, m), 4.5 (2H, s), 6.6 (1H, d), 7.0 (2H, m), 10.1 (1H, s)

5

3,4-Dihydro-3-(1-methylethyl)-6-(methylsulfonyl)-1H-2,1,3-benzothiadiazine-2,2-dioxide

A solution of OXONE[®] (potassium peroxymonosulfate) (5.65 g, 0.0092 mol) in water was added to a solution of 3,4-dihydro-3-(1-methylethyl)-6-(methylthio)-1H-2,1,3-benzothiadiazine-2,2-dioxide (1 g, 0.0037 mol) in acetone/water (25 ml/2.5 ml) stirring at room temperature. After 30 mins, water (25 ml) and ethyl acetate (50 ml) were added to the mixture. The two layers were separated and the organic layer was then dried (MgSO_4) and concentrated *in vacuo* to afford 3,4-dihydro-3-(1-methylethyl)-6-(methylsulfonyl)-1H-2,1,3-benzothiadiazine-2,2-dioxide as a pale yellow solid. δ (^1H NMR, CDCl_3 , 300MHz, ppm) : 1.0 (3H, d), 2.9 (3H, s), 4.1 (1H, m), 4.6 (2H, s), 6.8 (1H, d), 7.6 (2H, m), 9.9 (1H, s).

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- 37 -

**3,3-Dimethyl-6-methylthio-2,4-(1H,3H) -
quinolinedione**

Phosphorus pentoxide (4.49 g, 0.032 mol) was added
5 to a stirred solution of N-(4-methylthiophenyl)-
2,2-dimethylmalonamic acid (5.0 g, 0.020 mol) in
methanesulfonic acid (35 ml). The reaction mixture
was warmed to 70°C. and stirred for 90 mins. The
product mixture was then cooled to room temperature
10 and poured over ice. The product was extracted
with ethyl acetate (2 x 200 ml). The organic
extracts were combined, washed with water (200 ml),
saturated sodium hydrogen carbonate solution (200
ml), dried (MgSO₄) and concentrated *in vacuo* to give
15 3,3-dimethyl-6-methylthio-2,4(1H,3H)-quinolinedione
as a yellow solid. Mp 152°C.

**3,4-Dihydro-3,3-dimethyl-6-methylthio-2(1H) -
quinolinone**

20

Triethylsilane (34.75 ml, 49.1 g, 0.042 mol) was
added dropwise to a stirred solution of 3,3-
dimethyl-6-methylthio-2,4(1H,3H)-quinolinedione
(12.79 g, 0.054 mol) in trifluoroacetic acid (520
25 ml) under nitrogen at 60°C. The reaction was then

- 38 -

allowed to cool slowly to room temperature and was stirred for 16 hr. The solvent was then evaporated *in vacuo* to afford a yellow residue. The residue was then poured into saturated potassium carbonate solution (200 ml). The product was extracted with ethyl acetate (3 x 150 ml). The organic extracts were combined, washed with water (200 ml), dried and concentrated *in vacuo* to afford 3,4-dihydro-3,3-dimethyl-6-methylthio-2(1H)-quinolinone as a yellow solid. Mp 154°C.

3,4-Dihydro-3-(1-methylethyl)-6-methylthio-1-(prop-2-en-1-yl)-1H-2,1,3-benzothiadiazine-2,2-dioxide.

3,4-Dihydro-3-(1-methylethyl)-6-methylthio-1H-2,1,3-benzothiadiazine-2,2-dioxide (10 g, 0.0367 mol) was added to a suspension of sodium hydride (1.61g, 60% dispersion) in dry dimethylformamide (200 ml) at room temperature under a nitrogen atmosphere. The pale grey suspension was stirred for ten mins, and then allyl bromide (3.49 ml, 0.0404 mol) was added in one portion. The reaction mixture was stirred at 80°C. for 3 hr. The mixture was then concentrated *in vacuo* to yield a brown residue. The residue was dissolved in ethyl

- 39 -

acetate (50 ml) and washed with water (2 x 50 ml).

The organic layer was then dried (MgSO₄) and

concentrated *in vacuo* to afford 3,4-dihydro-3-(1-

methylethyl)-6-methylthio-1-(prop-2-en-1-yl)-1H-

5 2,1,3-benzothiadiazone-2,2-dioxide. δ (¹H NMR, DMSO,

ppm) : 1.1 (6H, d), 2.5 (3H, s), 4.1 (1H, m), 4.5

(2H, d), 4.7 (2H, s), 5.3 (1H, dd), 5.4 (1H, dd),

6.0 (1H, m), 7.0 (1H, d), 7.3 (2H, m).

10 Similarly prepared was

3,3-Dimethyl-5-methanesulphonyl-1-(prop-2-en-1-yl)-

1,3 dihydro-2H-indol-2-one

from 3,3-dimethyl-5-methanesulphonyl-1,3 dihydro-

15 2H-indol-2-one [Lit. Ref. EP 0780388]:

δ (¹H NMR, CDCl₃, ppm); 1.45 (6H, s), 3.05 (3H, s),

4.35 (2H, d), 5.15-5.3 (2H, m), 5.75-5.9 (1H, m),

6.9 (1H, d), 7.75 (1H, s), 7.85 (1H, m)

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- 40 -

[3,4-Dihydro-2,2-dioxido-3-(1-methylethyl)-6-methylsulfonyl-1H-2,1,3-benzothiadiazin-1-yl]ethanal.

5

3,4-Dihydro-3-(1-methylethyl)-6-methylthio-1-(prop-2-en-1-yl)-1H-2,1,3-benzothiadiazine-2,2-dioxide (10 g, 0.032 mol) was dissolved in dioxan (100 ml) and water (20 ml). Osmium tetroxide (2 crystals) was added to the solution and the mixture was stirred for five mins at room temperature, before the addition of sodium periodate (34.28g, 0.160 mol) dissolved in water (25 ml). After stirring at ambient temperature for 14 hr, the reaction mixture was filtered through celite. The filtrate was then concentrated *in vacuo* to yield an oil. The oil was dissolved in ethyl acetate (100 ml) and washed with water (2 x 50 ml). The organic layer was then dried and concentrated *in vacuo* to afford [3,4-dihydro-2,2-dioxide-3-(1-methylethyl)-6-methylsulfonyl-1H-2,1,3-benzothiadiazin-1-yl]ethanal as a yellow solid. δ (^1H NMR, DMSO, ppm) : 1.1 (6H, d), 3.2 (3H, s), 4.0 (1H, m), 4.8 (2H, s), 4.9 (2H, s), 7.0 (1H, d), 7.7 (1H, dd), 7.8 (1H, d), 9.6 (1H, s).

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- 41 -

Similarly prepared was

3,3-Dimethyl-5-methanesulphonyl-1,3 dihydro-2H-indol-1-yl-2-one ethanal

from 3,4-dihydro-3-(1-methylethyl)-6-methylthio-1-(prop-2-en-1-yl)-1H-2,1,3-benzothiadiazone-2,2-dioxide

δ (^1H NMR, CDCl_3 , ppm); 1.45 (6H, s), 3.05 (3H, s), 4.9 (2H, s), 6.9 (1H, d), 7.7 (1H, s), 7.9 (1H, m), 9.6 (1H, s).

1-(2-Chloroethyl)-3,4-dihydro-3-(1-methylethyl)-6-methylthio-1H-2,1,3-benzothiadiazone-2,2-dioxide.

To a 250 ml 3 necked flask equipped thermometer, pressure equalised dropping funnel, nitrogen bubbler and magnetic stirrer bar was added 60% sodium hydride (1.77 g, 1.062 g, 0.04425 mol,) hexane washed, to dry DMF (75 ml). To this stirred suspension was added dropwise a solution of 3,4-dihydro-3-(1-methylethyl)-6-methylthio-1H-2,1,3-benzothiadiazone-2,2-dioxide (10.0 g, 0.0368mol) in dry DMF (75 ml) (slight exotherm). The suspension was stirred under nitrogen for 2 hr until hydrogen

- 42 -

evolution ceased. 1-Bromo-2-chloroethane (6.33 g, 3.77 ml, 0.04425 mol) was added dropwise and the reaction mixture allowed to stir at room temperature under nitrogen overnight. The reaction mixture was poured onto ice-water (800 ml) with stirring for 1 hr, filtered and washed with water (200 ml) to leave a white solid which was dried *in vacuo* at 50°C. to give a solid. Mp 74-75°C.

10 **5-Methylthio-2-nitrobenzoic acid.**

5-Chloro-2-nitrobenzoic acid (25.2 g, 0.125 mol) was stirred in water. To this was added sufficient sodium hydroxide solution (2M, 42 ml, 0.084 mol) to dissolve the acid completely. A solution of sodium sulfide nonahydrate (33.0 g, 0.1375 mol) in water (75 ml) was added and the solution was stirred at 60 °C for 2.5 hr. This resultant red solution was added to a solution of sodium hydroxide (50% 10 ml, 0.125 mol) in water (15 ml), dimethyl sulfate (24 ml, 0.25 mol) was added and the solution heated under reflux for 1 hour. The solution was cooled and acidified with hydrochloric acid (5M, 32 ml, 0.16 mol). The precipitated yellow solid was filtered off, washed with water, dried at 60°C.

- 43 -

under vacuum, mp 173°C. (lit. J. Heterocyclic
Chemistry 1981 18 117). Mp 175-178°C.)

Methyl 4-methylthio-2-nitro benzoate

5

To a suspension of 4-methylthio-2-nitro benzoic acid
(10g; 0.047mol) [Lit. Ref. DE 2421541] in dry
dimethylformamide (300mL) was added potassium carbonate
(8.43g; 0.061mol) and iodomethane (6.41mL; 0.103mol) and
10 the solution stirred at room temperature for 24hrs. The
reaction was poured into water and extracted with ether
(3x500mL). The combined organic extracts were washed
with water, dried over anhydrous magnesium sulphate,
filtered and the solvent removed under vacuum to yield a
15 yellow solid. This was dried at 50°C under vacuum.
(10.4g; 97.5%)

¹H NMR (CDCl₃), δ (ppm); 2.5 (s, 3H), 3.85 (s, 3H), 7.25-
7.3 (m, 2H), 7.85 (d, 1H)

20

Methyl 2-amino-4-methylthio benzoate

Methyl 4-methylthio-2-nitro benzoate (10.4g; 0.046mol)
25 was dissolved in ethanol and Raney nickel added as an
aqueous suspension. The solution was hydrogenated at
60psi on a Parr hydrogenator for 6 hrs. The catalyst

- 44 -

was filtered off through celite, washed with ethanol to give the product which was used directly in the next step. (8.9g; 98%)

5 ^1H NMR (CDCl_3), δ (ppm); 2.4 (s, 3H), 3.9 (s, 3H), 5.75 (br s, 2H), 6.6 (d, 1H), 7.3 (dd, 1H), 7.9 (d, 1H)

Methyl 2-methylsulphonylamino-4-methylthio benzoate

10

To a stirred solution of methyl 2-amino-4-methylthio benzoate (11.53g; 0.0585mol) in dry pyridine (60mL) was added slowly over a 5 minute period methane sulphonyl chloride (4.98mL; 0.0643mol). An exotherm was produced taking the internal temperature to 35°C. After stirring overnight at room temperature, the pyridine was removed under vaccuo and water (150mL) was added. Concentrated hydrochloric acid was added to pH2 and the product was extracted with ethyl acetate (3x100mL). The organic extracts were washed with water (2x100mL), 2N HCl (2x100mL) and water (2x100mL). After drying with anhydrous magnesium sulphate, filtering and removing the solvent, the product was isolated as a red oil which solidified on standing. (15.6g; 97%)

25

- 45 -

^1H NMR (CDCl_3), δ (ppm); 2.5 (s, 3H), 3.05 (s, 3H), 3.95 (s, 3H), 7.47 (dd, 1H), 7.7 (d, 1H), 7.95 (d, 1H), 10.25 (s, 1H)

5

Methyl 2-(N-(prop-2-en-1-yl)-N-methylsulphonyl)amino-4-methylthio benzoate

To a solution of methyl 2-methylsulphonylamino-4-methylthio benzoate (6.9g; 0.025mol) in dry dimethylformamide (120mL) was added anhydrous potassium carbonate (34.4g; 0.25mol) and tetrabutylammonium bromide (0.81g; 2.51mmol). Allyl bromide (20 equivalents) was added in one portion and the solution was stirred overnight at room temperature. The reaction was poured into water and the product extracted with ethyl acetate. The organic extracts were washed with water, dried over anhydrous magnesium sulphate, filtered and the solvent removed to give an oil. Column chromatography eluting with 20%-50% ethyl acetate-hexane gave a clear oil (7.2g; 92%).

^1H NMR (CDCl_3), δ (ppm); 2.5 (s, 3H), 3.05 (s, 3H), 3.9 (s, 3H), 4.65 (d, 2H), 5.25-5.4 (m, 2H), 5.8-6.0 (m, 1H), 7.26 (d, 1H), 7.35 (m, 1H), 7.75 (d, 1H)

25

- 46 -

6-Methylthio-1-(prop-2-en-1-yl) -1H-2,1-benzothiazine-4-(3H)-one 2,2-dioxide

5

To a solution of sodium hydride (1.32g; 0.0552m of 50 % dispersion in paraffin oil) in dry dimethylformamide (60mL) was slowly added under nitrogen at 0°C a solution of methyl 2-(N-(prop-2-en-1-yl)-N-methylsulphonyl)amino-10 4-methylthio benzoate (7.2g;0.023mol) in dry dimethylformamide (15ml). After stirring overnight at room temperature the reaction was poured into ice water and the product extracted with ethyl acetate, washed repeatedly with water and dried over magnesium sulphate. 15 After filtering and removal of the solvent, the oil was chromatographed on silica eluting with 20% ethyl acetate to give the product, 4.2g; 65%)

¹H NMR (CDCl₃), δ (ppm); 2.53 (s, 3H), 4.3 (s, 2H), 4.55 20 (m, 2H), 5.3-5.47 (m, 2H), 5.85-6.0 (m, 1H), 7.25 (d, 1H), 7.5 (dd, 1H), 7.95 (d, 1H)

3,3-Dimethyl-6-methylthio-1-prop-2-en-1-yl -1H-2,1-benzothiazine-4-(3H)-one 2,2-dioxide. 25

- 47 -

1-(Prop-2-en-1-yl)-6-methylthio-benzothiazine-4-one 2,2-dioxide (2.07g; 0.0067mol) was dissolved in dry dimethylformamide (50mL) and potassium carbonate (2.03g; 5 0.0147mol) added followed by iodomethane (1.25mL; 0.02mol). The reaction was stirred overnight at room temperature and water was added. The product was extracted with ethyl acetate and, after washing with water and drying over magnesium sulphate the product was 10 isolated as a solid (2.0g; 89%)

^1H NMR (CDCl_3), δ (ppm); 1.65 (s, 6H), 2.5 (s, 3H), 4.55 (d, 2H), 5.3-5.5 (m, 2H), 5.9-6.1 (m, 1H), 7.05 (d, 1H), 7.45 (dd, 1H), 8.0 (d, 1H)

15

3,3-Dimethyl-6-methylthio-1-(prop-2-en-1-yl) -1H-2,1-benzothiazine 2,2-dioxide

20 1-(Prop-2-en-1-yl)-3,3-dimethyl-6-methylthio-1H-2,1-benzothiazine-4-(3H)-one 2,2-dioxide (2g; 0.006mol) was dissolved in methanol (40mL) and sodium borohydride (0.45g; 0.012mol) was added in one portion. After the initial effervescence, the reaction was left stirring 25 overnight. The solvent was removed under vacuo, water

- 48 -

added and the product extracted with chloroform. After washing the organic extracts with water, drying over magnesium sulphate and filtering, the product was isolated as a white solid (1.8g; 90%) of 3,4-dihydro-
5 3,3-dimethyl-6-methylthio-1-(prop-2-en-1-yl) -1H-2,1-benzothiazin-4-ol 2,2-dioxide, used immediately in the next step.

¹H NMR (CDCl₃), δ (ppm); 1.4 (s, 3H), 1.6 (s, 3H), 2.5
10 (s, 3H), 3.35 (dd, 1H), 4.25-4.55 (m, 2H), 4.6-4.7 (dd, 1H), 5.3-5.5 (m, 1H), 6.9 (d, 1H), 7.22 (dd, 1H), 7.4 (d, 1H)

15 3,4-Dihydro-1-(prop-2-en-1-yl) -3,3-dimethyl-6-methylthio-1H-2,1-benzothiazin-4-ol 2,2-dioxide (1.8g; 0.0053m) was dissolved in trifluoroacetic acid (30mL) and triethylsilane (15mL) was added in one portion. After stirring for 4hrs, the reaction was reduced to an
20 oil under vacuo and after the addition of saturated sodium bicarbonate, the product extracted with dichloromethane, dried, filtered and isolated as a colourless solid. (1.6g; 93%)

- 49 -

^1H NMR (CDCl_3), δ (ppm); 1.45 (s, 6H), 2.4 (s, 3H), 4.4 (d, 2H), 5.25-5.5 (m, 2H), 5.9-6.03 (m, 1H), 6.85 (d, 1H), 7.05 (d, 1H), 7.15 (dd, 1H)

5

3,4-Dihydro-3,3-dimethyl-1-(prop-2-en-1-yl)-6-sulphonylmethyl-1H-2,1-benzothiazine 2,2-dioxide

3,4-Dihydro-3,3-dimethyl-6-methylthio-1-(prop-2-en-1-yl)-1H-2,1-benzothiazine 2,2-dioxide (1.6g; 0.00539mol) was dissolved in acetone (50mL) and oxone (7.29g; 0.01185mol) in water (20mL) was added. The solution went opaque and was stirred for 30min at room temperature. The acetone was removed on the rotary and water and ethyl acetate were added. The product was extracted with ethyl acetate (2x100mL) and the organic extracts washed with water (2x100mL). After drying, filtering and removal of solvent, a solid was isolated (1.2g; 68%)

20

^1H NMR (CDCl_3), δ (ppm); 1.5 (s, 6H), 3.05 (s, 3H), 3.35 (d, 2H), 4.57 (m, 2H), 5.35-5.55 (m, 2H), 5.87-6.0 (m, 1H), 7.05 (d, 1H), 7.68 (dd, 1H), 7.75 (dd, 1H)

25

- 50 -

[3,4-Dihydro-3,3-dimethyl-6-sulphonylmethyl-1H-2,1-benzothiazin-1-yl 2,2-dioxide] ethanal

To 3,4-dihydro-3,3-dimethyl-1-(prop-2-en-1-yl)-6-sulphonylmethyl-1H-2,1-benzothiazine 2,2-dioxide (1.2g; 0.00365mol) dissolved in tetrahydrofuran (100ml) was added sodium periodate (1.56g; 0.0073mol) dissolved in water (20ml) with warming . A crystal of osmium tetroxide was added and the solution stirred at room temperature overnight. Water was added and the product was extracted with ethyl acetate (3x100ml). The organic extracts were collected, washed with water, dried over anhydrous magnesium sulphate, filtered and the solvent removed in vacuo to give a gum. (1.0g; 83%)

15

^1H NMR (CDCl_3), δ (ppm); 1.53 (s, 6H), 3.05 (s, 3H), 3.38 (d, 2H), 4.73 (s, 2H), 6.7 (dd, 1H), 7.7-7.8 (m, 2H), 9.75 (s, 1H)

20

1-(2-Chloroethyl)-3,4-dihydro-3-(1-methylethyl)-6-methylsulfonyl-1H-2,1,3-benzothiadiazine-2,2-dioxide.

25

A 500 mL 3 necked flask equipped thermometer, pressure equalised dropping funnel, nitrogen

- 51 -

bubbler and magnetic stirrer bar was charged with
1-(2-chloroethyl)-3,4-dihydro-3-(1-methylethyl)-6-
methylthio-1H-2,1,3-benzothiadiazine-2,2-dioxide
(10.0 g, 0.0299 mol) and chloroform (200 ml). To
5 this solution was added in one portion m-
chloroperbenzoic acid (20.6 g, ~4 equivalents,
nominal purity 56-86 %), this resulted in an
exotherm which raised the temperature from 20°C. to
50°C. This solution was then stirred for 15 mins,
10 water (100 ml) was added then 2M sodium hydroxide
(100 ml). The organic layer was separated, washed
again with 2M sodium hydroxide (100 ml), then water
(100 ml) dried (MgSO₄), filtered and the filtrate
evaporated under reduced pressure to leave a white-
15 cream foam, which was dried at 45°C. *in vacuo* to
yield the product.

δ (¹H NMR, CDCl₃, ppm) : 7.8 (1H, d), 7.7 (1H, s),
7.1 (1H, d), 4.7 (2H, s), 4.2 (1H, m), 4.2 (2H, t),
3.0 (3H, s), 1.1 (6H, d).

20

**1-(2-Chloroethyl)-3,4-dihydro-3,3-dimethyl-6-
methylsulfonyl-2(1H)-quinolinone.**

(Prepared from 1-(2-chloroethyl)-3,4-dihydro-3,3-
25 dimethyl-6-methylthio-2(1H)-quinolinone.

- 52 -

δ (^1H NMR, CDCl_3 , ppm) : 7.8 (1H, dd), 7.7 (1H, d), 7.1 (1H, d), 4.2 (2H, t), 3.6 (2H, t), 3.0 (3H, s), 2.8 (2H, s), 1.1 (6H, s).

5

3,3-Dimethyl-1-{2-[(2*R*,4*S*)-4-(6-fluoro-1*H*-indol-3-yl)-2-methylpiperidinyl]ethyl}-6-(methylsulfonyl)-3,4-dihydro-1*H*-2,1-benzothiazine 2,2-dioxide

- 10 To a stirred solution of 6-fluoro-3-[(2*R*,4*S*)-2-methylpiperidin-4-yl]-1*H*-indole (0.71g; 0.0033mol) and [3,3-dimethyl-6-sulphonylmethyl-1*H*-2,1-benzothiazin-1-yl 2,2-dioxide] ethanal in dry tetrachloroethane (70ml) was added glacial acetic acid (6 drops). The solution was
- 15 stirred for 10mins at room temperature and sodium triacetoxyborohydride (0.76g; 0.0036mol) was added in one portion and the solution stirred rapidly at room temperature overnight. The reaction was poured into water and the product extracted with dichloromethane.
- 20 The organic extracts were washed with water(2x100ml) and dried over anhydrous magnesium sulphate. After filtration, the solvent was removed in vacuo to give a yellow oil. Flash chromatography on silica eluting with 75%-90% ethyl acetate-hexane mixtures gave product as a
- 25 yellow solid. (1.0g; 62.5%)

- 53 -

¹H NMR (CDCl₃), δ (ppm); 1.5 (s, 6H), 2.6 (m, 2H), 2.85
 (m, 4H), 3.05 (s, 3H), 3.3 (m, 4H), 4.1 (m, 2H), 6.15
 (s, 1H), 6.9 (dt, 1H), 7.05 (dd, 1H), 7.15 (d, 1H)
 5 7.25 (d, 1H), 7.7 (d, 1H), 7.8 (m, 2H), 8.2 (s, 1H)

Similarly prepared were

3,3-Dimethyl-1-{2-[(2S,4R)-4-(6-fluoro-1H-indol-3-yl)-2-
 10 methylpiperidinyl]ethyl}-6-(methylsulfonyl)-3,4-dihydro-
 1H-2,1-benzothiazine 2,2-dioxide

from 6-fluoro-3-[(2S,4R)-2-methylpiperidin-4-yl]-1H-
 indole

15 3,3-Dimethyl-1-{2-[(2S,4R)-4-(6-fluoro-7-methyl-1H-
 indol-3-yl)-2-methylpiperidinyl]ethyl}-5-
 methylsulphonyl-1,3-dihydro-2H-indol-2-one

from 6-fluoro-3-[(2S,4R)-2-methylpiperidin-4-yl]-1H-
 indole

20

¹H NMR ((CD₃)₂SO), δ (ppm); 1.02-1.10 (m, 3H), 1.45 (6H,
 s), 1.50-1.92 (m, 4H), 2.34 (s, 3H), 2.66-2.88 (m, 2H),
 2.94-3.08 (m, 1H), 3.05 (3H, s), 3.05-3.3 (m, 3H), 4.05-
 25 4.15 (m, 2H), 6.70-7.1 (m, 3H), 7.24-7.36 (m, 1H), 7.65
 (1H, s), 7.8 (1H, m)

- 54 -

- 3,3-Dimethyl-1-{2-[(2R,4S)-4-(6-fluoro-7-methyl-1H-indol-3-yl)-2-methylpiperidinyl]ethyl}-5-methylsulphonyl-1,3-dihydro-2H-indol-2-one
- from 6-fluoro-3-[(2R,4S)-2-methylpiperidin-4-yl]-1H-indole
- 1- {2-[(2R,4S)-4-(6-Fluoro-1H-indol-3-yl)-2-methylpiperidinyl]ethyl}-3-isopropyl-6-(methylsulfonyl)-3,4-dihydro-1H-2,1,3-benzothiadiazine 2,2-dioxide and 1-{2-[(2S,4R)-4-(6-Fluoro-1H-indol-3-yl)-2-methylpiperidinyl]ethyl}-3-isopropyl-6-(methylsulfonyl)-3,4-dihydro-1H-2,1,3-benzothiadiazine 2,2-dioxide

A racemic mixture of 6-fluoro-3-[(2S,4R)-2-methylpiperidin-4-yl]-1H-indole and 6-fluoro-3-[(2R,4S)-2-methylpiperidin-4-yl]-1H-indole (0.34g, 1.46 mmol), 1-(2-chloroethyl)-3-isopropyl-6-(methylsulfonyl)-3,4-dihydro-1H-2,1,3-benzothiadiazine 2,2-dioxide (0.64g, 1.74 mmol), sodium iodide (0.26g, 1.75 mmol) and sodium carbonate (0.90g, 8.49 mmol) are suspended in a mixture of water (50 ml) and acetonitrile (5 ml), and stirred at reflux under nitrogen for 72 hours. The mixture is

- 55 -

then cooled to room temperature, water is added (100 ml), and the off white gum that has formed is extracted with ethyl acetate (2 x 100 ml). The combined organic layers are combined, dried over magnesium sulfate, and the solvent evaporated under reduced pressure. Column chromatography, using hexane (60%) and ethyl acetate (40%) as the eluent affords 0.45g of the desired product (54.8% yield) as mixture of *trans* enantiomers. The enantiomers are subjected to chiral stationary phase HPLC (Chiralpak-AD column, eluted with 60% hexane, 40% isopropanol and 0.2% dmea, F/R: 1.0 ml/min) to resolve the two *trans* enantiomers (retention times = 9.9 and 10.7 min). ¹H NMR (CDCl₃), δ (ppm); 1.02-1.22 (m, 9H), 1.68-2.12 (m, 4H), 2.70-2.92 (m, 4H), 3.0 (s, 3H), 3.06-3.26 (m, 2H), 3.94-4.04 (m, 2H), 4.14-4.24 (m, 1H), 5.68 (br. s, 2H), 6.82-6.92 (t, 1H), 6.94 (s, 1H), 7.00-7.08 (d, 1H), 7.50-7.60 (m, 1H), 7.72 (br. s, 1H), 7.80-7.90 (d, 2H), 8.12-8.26 (br. s, 1H). MS, reqd. 562.2; obs. 563.2 (M+1 ; FIAPOS); 561.2 (M-1 ; FIANEG).

20

1-{2-[(2*R*,4*S*)-4-(6,7-Difluoro-1*H*-indol-3-yl)-2-methylpiperidinyl]ethyl}-3-isopropyl-6-(methylsulfonyl)-3,4-dihydro-1*H*-2,1,3-benzothiadiazine 2,2-dioxide and 1-{2-[(2*S*,4*R*)-4-(6,7-difluoro-1*H*-indol-3-yl)-2-

25

- 56 -

**methylpiperidinyl]ethyl}-3-isopropyl-6-(methylsulfonyl)-
3,4-dihydro-1H-2,1,3-benzothiadiazine 2,2-dioxide**

A racemic mixture of 6,7-difluoro-3-[(2S,4R)-2-methylpiperidinyl]-1H-indole and 6,7-difluoro-3-[(2R,4S)-2-methylpiperidin-4-yl]-1H-indole (0.73g, 2.92 mmol), 1-(2-chloroethyl)-3-isopropyl-6-(methylsulfonyl)-3,4-dihydro-1H-2,1,3-benzothiadiazine 2,2-dioxide (1.28g, 3.49 mmol), sodium iodide (0.52g, 3.48 mmol) and sodium carbonate (1.80g, 17.0 mmol) are suspended in a mixture of water (70 ml) and acetonitrile (7 ml), and stirred at reflux under nitrogen for 24 hours. The mixture is then cooled to room temperature, water is added (100 ml), and the off white gum that has formed is extracted with ethyl acetate (2 x 100 ml). The combined organic layers are combined, dried over magnesium sulfate, and the solvent evaporated under reduced pressure. Column chromatography, using hexane (50%) and ethyl acetate (50%) as the eluent affords 0.42g of the desired product (20.8% yield) as mixture of *trans* enantiomers. The enantiomers are subjected to chiral stationary phase HPLC (Chiralpak AD eluted with 60% Ethanol, 40% Heptane and 0.2% dmea, F/R: 1.0 ml/min) to resolve the two *trans* enantiomers (retention times = 14.7 and 16.4 min). ¹H NMR (CDCl₃), δ (ppm); 1.02-1.18

- 57 -

(m, 3H), 1.36-1.52 (d, 6H), 1.86-2.00 (m, 1H), 2.00-2.10 (d, 1H), 2.12-2.20 (d, 1H), 2.34-2.44 (m, 1H), 2.50-2.62 (m, 1H), 2.70 (s, 1H), 3.06-3.14 (m, 3H), 3.18-3.30 (m, 2H), 3.32-3.50 (m, 1H), 3.90-3.98 (s, 1H), 4.10-4.12 (m, 1H), 4.54-4.78 (m, 4H), 6.92-7.00 (m, 1H), 7.12 (s, 1H), 7.30-7.36 (m, 1H), 7.70 (s, 1H), 7.92-7.98 (m, 1H), 8.56 (s, 1H); MS, reqd. 580.2; obs. 581.2 (M+1 ; FIAPOS).

10 Similarly prepared were

1-{2-[(2*R*,4*S*)-4-(6-Fluoro-1*H*-indol-3-yl)-2-methylpiperidinyl]ethyl}-3,3-dimethyl-6-(methylsulfonyl)-3,4-dihydro-2(1*H*)-quinolinone and 1-{2-[(2*S*,4*R*)-4-(6-Fluoro-1*H*-indol-3-yl)-2-methylpiperidinyl]ethyl}-3,3-dimethyl-6-(methylsulfonyl)-3,4-dihydro-2(1*H*)-quinolinone

¹H NMR ((CD₃)₂SO), (ppm); 1.08-1.20 (m, 3H), 1.56-2.00 (m, 4H), 2.56 (s, 6H), 2.66-2.82 (m, 2H), 2.94 (s, 2H), 3.06-3.18 (m, 2H), 3.28 (s, 3H), 4.00-4.22 (m, 2H), 6.84-6.92 (t, 1H), 7.08-7.18 (m, 2H), 7.46-7.60 (m, 2H), 7.82-7.92 (m, 2H); MS, reqd. 511.3; obs. 512.3 (M+1 ; FIAPOS).

25

- 58 -

1-{2-[(2*R*,4*S*)-4-(6,7-Difluoro-1*H*-indol-3-yl)-2-methylpiperidinyl]ethyl}-3,3-dimethyl-6-(methylsulfonyl)-3,4-dihydro-2(1*H*)-quinolinone

5 from 4-(6,7-difluoro-1*H*-indol-3-yl)-(2*R*,4*S*)-2-methylpiperidine.

¹H NMR (CDCl₃), δ (ppm); 1.05-1.20 (m, 3H), 1.6-2.00 (m, 4H), 2.55 (s, 6H), 2.58-2.80 (m, 2H), 2.94 (s, 2H), 3.06-3.18 (m, 2H), 3.3 (s, 3H), 4.00-4.20 (m, 2H), 6.80-
10 7.06 (m, 2H), 7.1-7.3 (m, 2H), 7.6-7.8 (m, 2H)

1-{2-[(2*S*,4*R*)-4-(6,7-Difluoro-1*H*-indol-3-yl)-2-methylpiperidinyl]ethyl}-3,3-dimethyl-6-(methylsulfonyl)-3,4-dihydro-2(1*H*)-quinolinone

15 from 4-(6,7-difluoro-1*H*-indol-3-yl)-(2*S*,4*R*)-2-methylpiperidine.

The following Examples illustrate formulations
20 comprising an active ingredient according to the invention.

EXAMPLE 2

- 59 -

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

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

EXAMPLE 3

Capsules each containing 20 mg of active ingredient are made as follows:

- 60 -

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

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

EXAMPLE 4

15

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

	Active ingredient	20 mg
20	Lactose	171 mg
	Sodium lauryl sulphate	2 mg
	Sodium starch glycollate	6 mg
	Magnesium stearate	1 mg

25		200 mg

- 61 -

The active ingredient, lactose, sodium lauryl sulphate and sodium starch glycollate are mixed thoroughly. The blend is mixed with the magnesium stearate and filled
5 into hard gelatine capsules in 200 mg quantities.

EXAMPLE 5

Tablets each containing 20 mg and medicaments are made
10 as follows:

	Active ingredient	20 mg
	Lactose	103 mg
	Microcrystalline cellulose	150 mg
15	Hydroxypropylmethylcellulose	15 mg
	Sodium starch glycollate	9 mg
	Magnesium stearate	3 mg

		300 mg
20		_____

The active ingredient, lactose, microcrystalline cellulose, sodium starch glycollate and hydroxypropylmethylcellulose are passed through a sieve
25 and blended together. Water is added to the blended powders to form a damp mass. The damp mass is passed

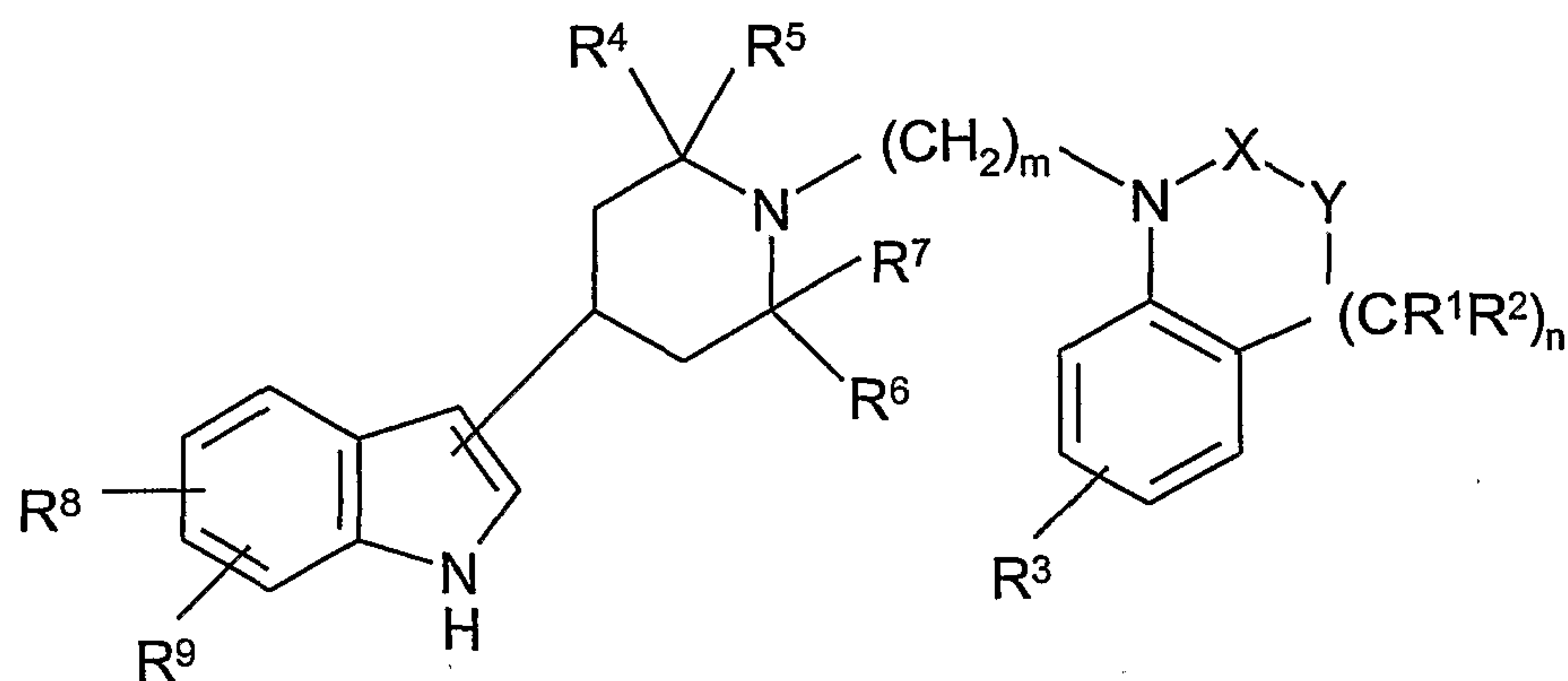
- 62 -

through a coarse screen, dried, then re-screened. The dried granules are mixed with the magnesium stearate and compressed into tablets of 300 mg weight.

- 63 -

CLAIMS

1. A compound of the formula:



5

in which R^1 and R^2 are each hydrogen or C_{1-6} alkyl,

R^3 is $-SR^{10}$, $-SOR^{10}$, $-SO_2R^{10}$, $-COR^{10}$, $-CH_2OH$ or

10 $-CONHR^{11}$, where R^{10} is C_{1-6} alkyl and R^{11} is

hydrogen or C_{1-6} alkyl,

R^4 , R^5 , R^6 and R^7 are each hydrogen or C_{1-6} alkyl,

provided that at least one of R^4 , R^5 , R^6 and R^7 is

15 C_{1-6} alkyl,

R^8 and R^9 are each hydrogen, halo, C_{1-6} alkyl or

cyano,

- 64 -

n is 0 or 1 and m is 2 or 3,

X is $\begin{array}{c} \diagup \\ \text{C}=\text{O} \\ \diagdown \end{array}$ or $\begin{array}{c} \diagup \\ \text{S}=\text{O} \\ \diagdown \\ \text{O} \end{array}$, and

Y is $\begin{array}{c} \diagup \\ \text{N}-\text{R}^{12} \\ \diagdown \end{array}$ or $\begin{array}{c} \diagup \\ \text{C}-\text{R}^{12} \\ \diagdown \\ \text{R}^{13} \end{array}$ wherein R^{12} and R^{13} are each

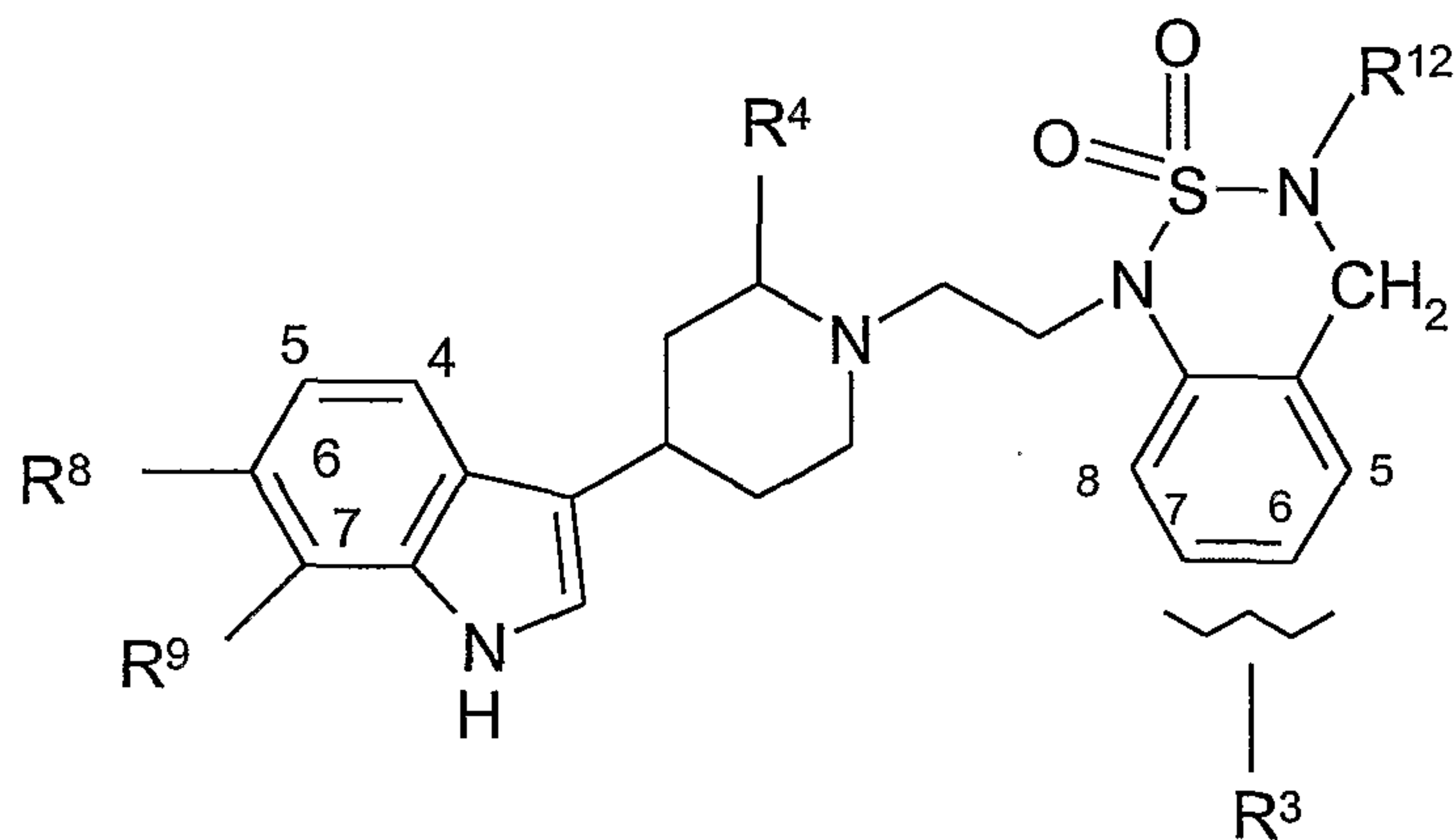
hydrogen, C_{1-6} alkyl, cyclopropyl or cyclopropyl-

5 C_{1-6} alkyl;

and salts thereof.

2. A compound according to Claim 1 of the formula:

10

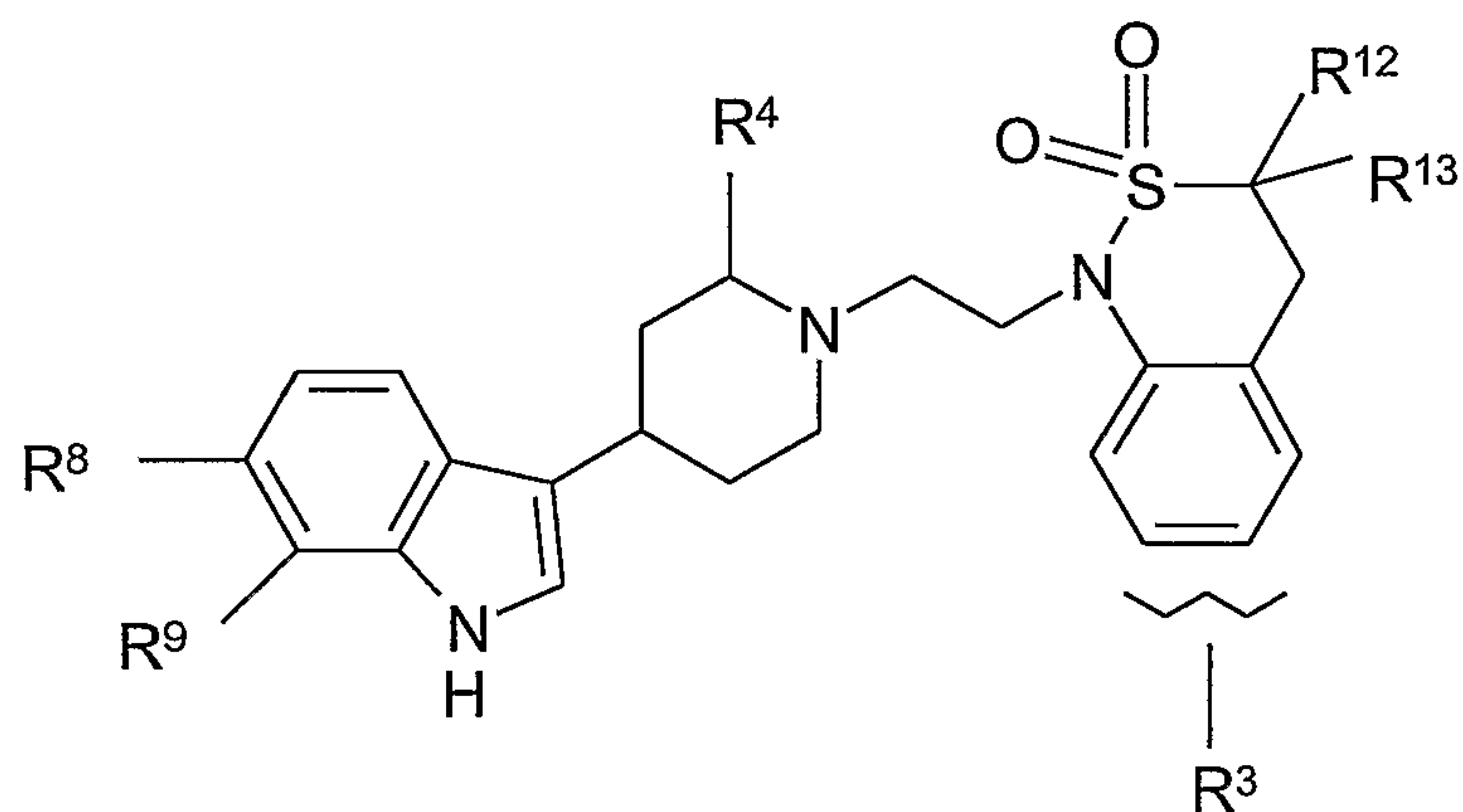


in which R^8 and R^9 are each hydrogen or fluoro,

- 65 -

R^3 is at the 6- or 7- position and is $-\text{SOR}^{10}$, $-\text{SO}_2\text{R}^{10}$ or $-\text{COR}^{10}$, where R^{10} is C_{1-6} alkyl, R^4 is C_{1-6} alkyl; and salts thereof.

5 3. A compound according to Claim 1 of the formula



in which R^8 and R^9 are each hydrogen or fluoro,

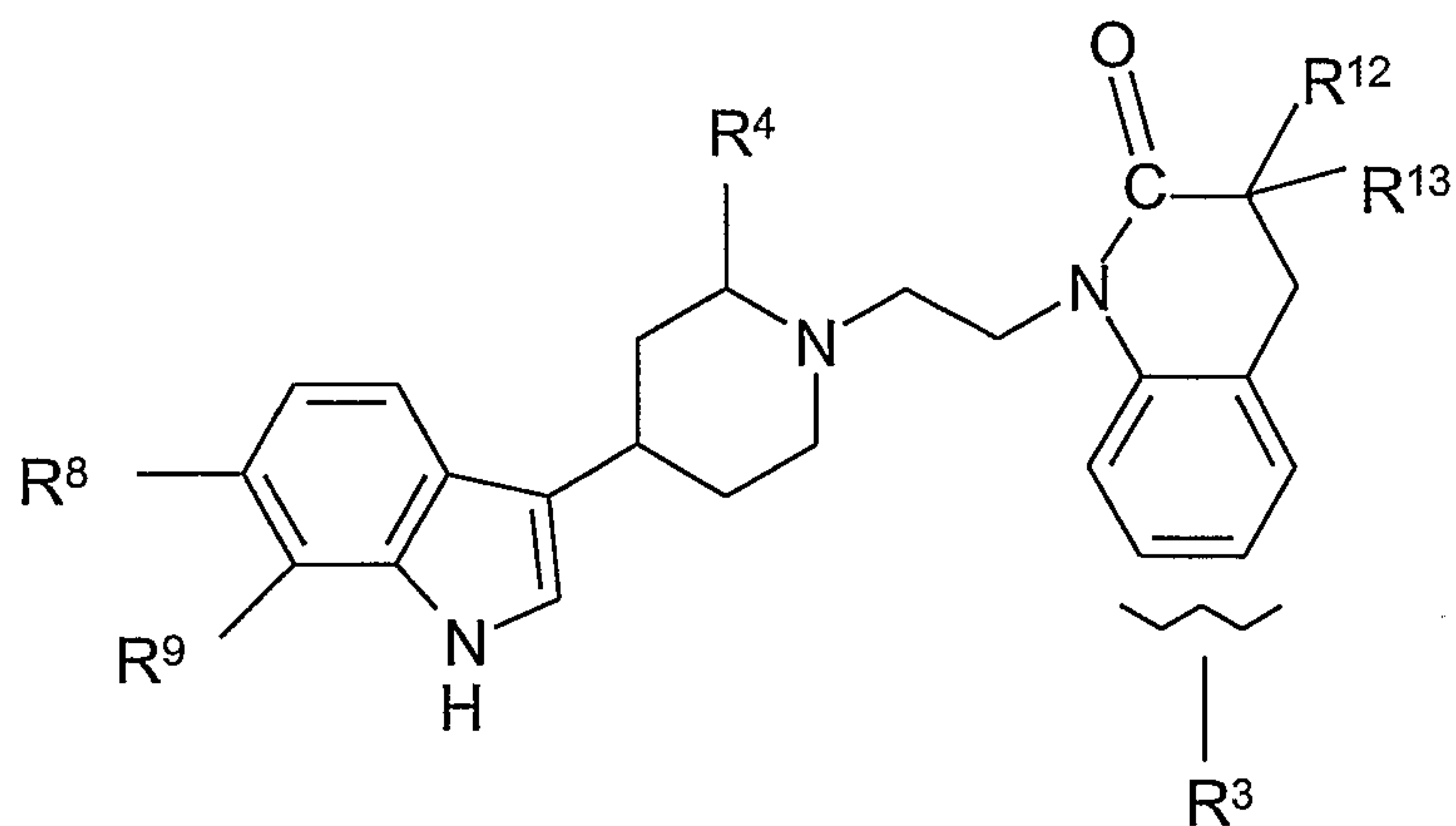
10

R^3 is in the 6- or 7-position and is $-\text{SOR}^{10}$, $-\text{SO}_2\text{R}^{10}$ or $-\text{COR}^{10}$, where R^{10} is C_{1-6} alkyl, R^4 is C_{1-6} alkyl, and R^{12} and R^{13} are each hydrogen or C_{1-6} alkyl; and salts thereof.

15

4. A compound according to Claim 1 of the formula:

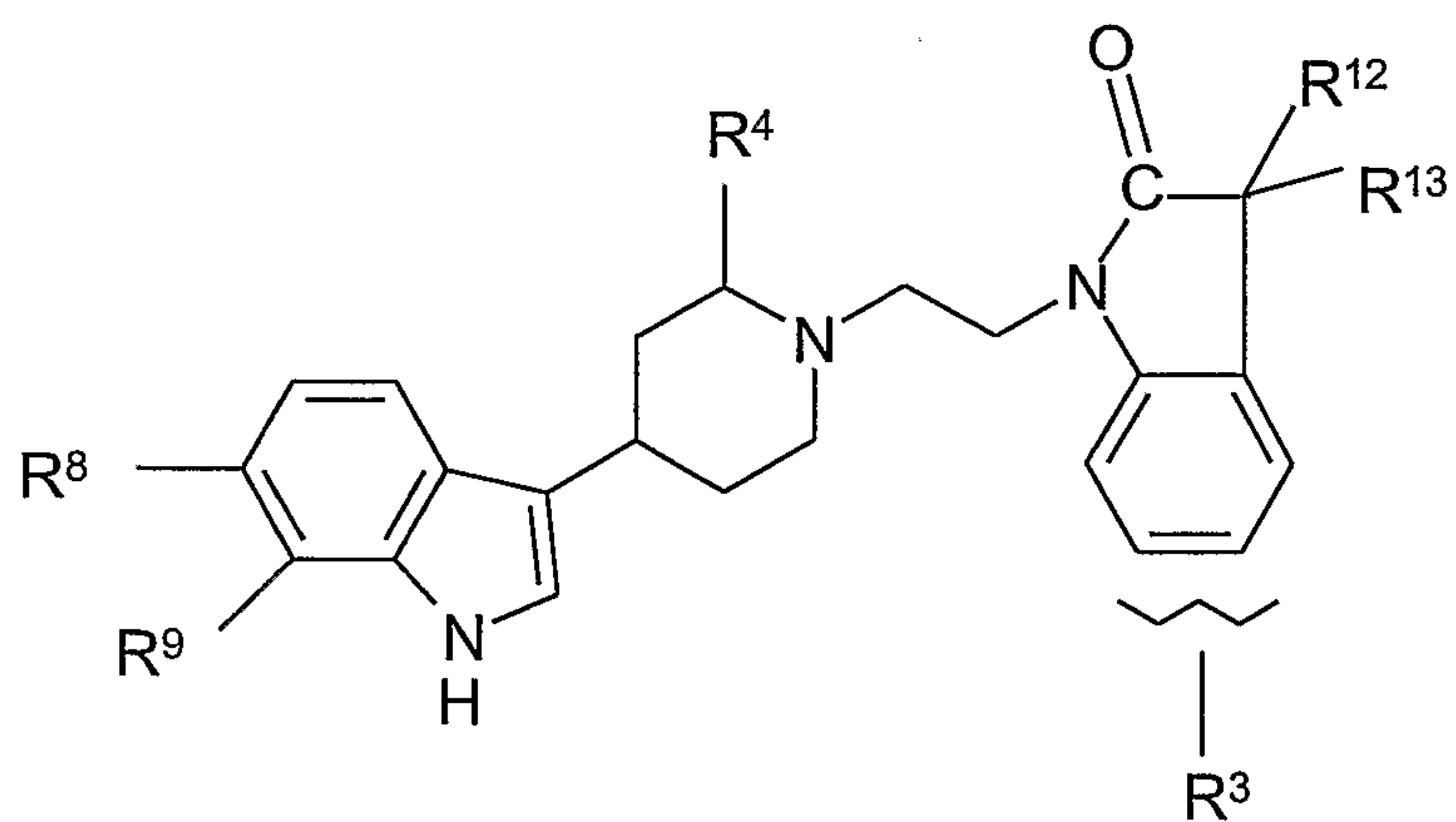
- 66 -



in which R^8 and R^9 are each hydrogen or fluoro, R^3 is in the 6- or 7-position and is $-SOR^{10}$, $-SO_2R^{10}$ or $-COR^{10}$, where R^{10} is C_{1-6} alkyl, R^4 is C_{1-6} alkyl, and R^{12} and R^{13} are each hydrogen or C_{1-6} alkyl; and salts thereof.

5. A compound according to Claim 1 of the formula:

10

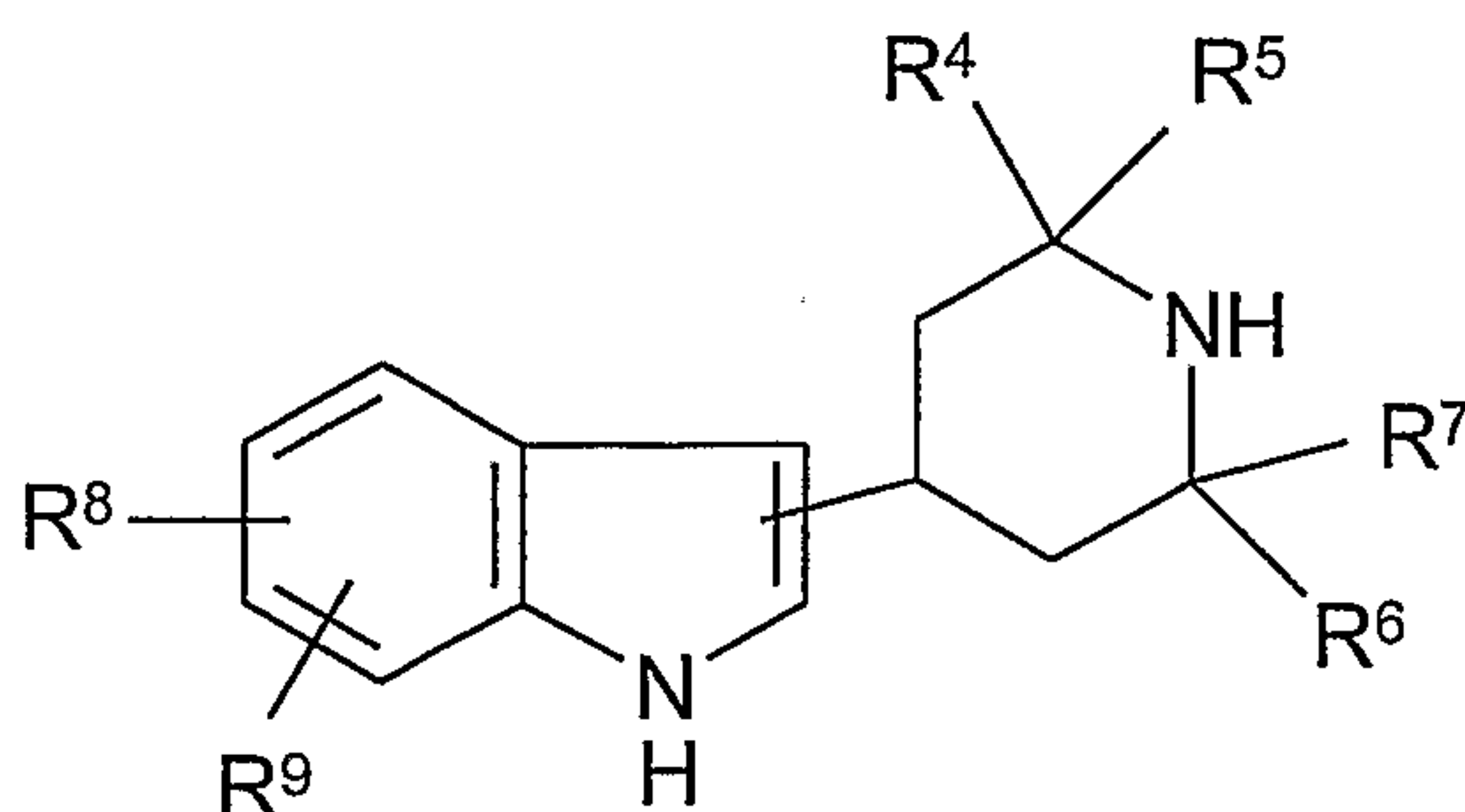


- 67 -

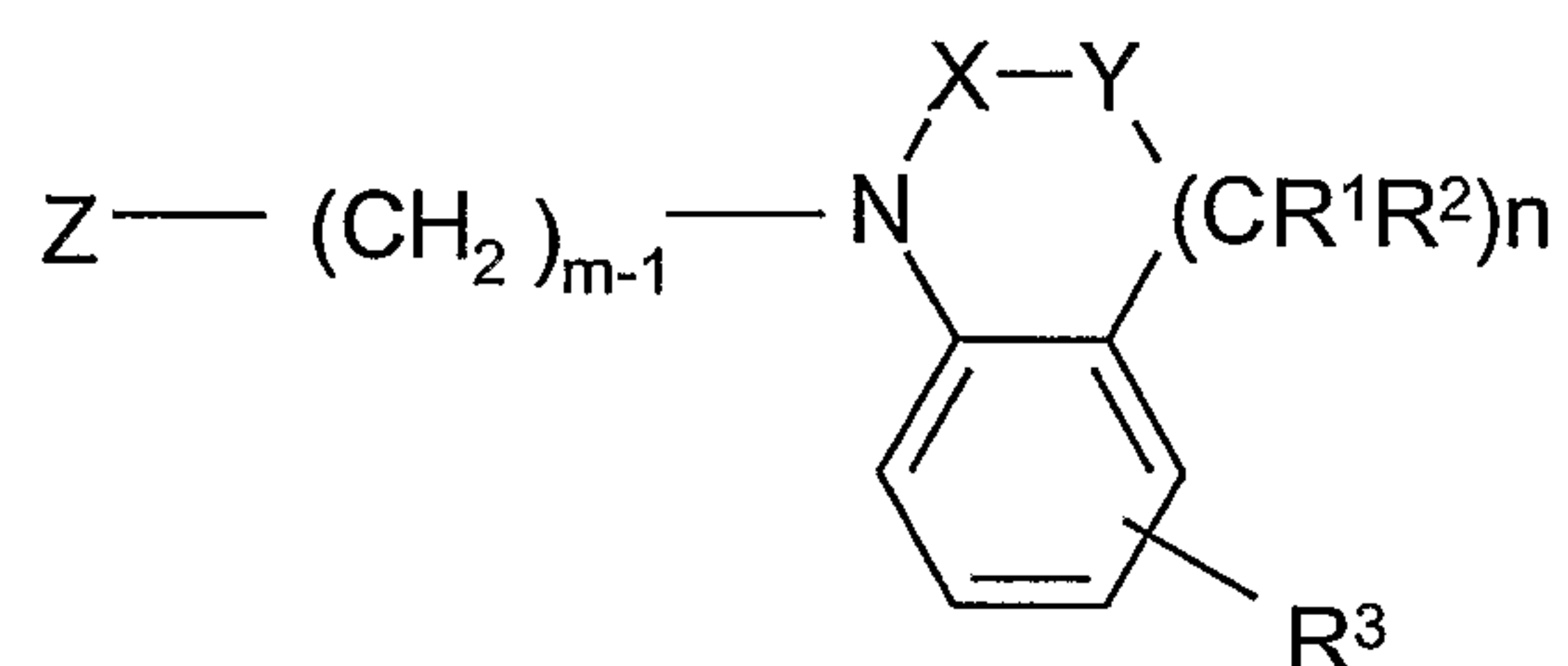
in which R^8 and R^9 are each hydrogen or fluoro, R^3 is in the 6- or 7-position and is $-SOR^{10}$, $-SO_2R^{10}$ or $-COR^{10}$, where R^{10} is C_{1-6} alkyl, R^4 is C_{1-6} alkyl, and R^{12} and R^{13} are each hydrogen or C_{1-6} alkyl; and salts thereof.

6. A pharmaceutical formulation comprising a compound according to any one of Claims 1 to 5, or a pharmaceutically acceptable salt thereof, together with a pharmaceutically acceptable diluent or carrier therefor.
7. A compound according to any one of Claims 1 to 5, or a pharmaceutically acceptable salt thereof, for use as a pharmaceutical.
8. The use of a compound according to any one of Claims 1 to 5, or a pharmaceutically acceptable salt thereof, in the preparation of a medicament for treating a disorder of the central nervous system.
9. A method of preparing a compound according to any one of Claims 1 to 5, which comprises reacting a compound of the formula

- 68 -



5 with a compound of the formula



where (i) Z is $-\text{CH}_2\text{W}$, where W is a leaving group,
 10 or (ii) Z is $-\text{CHO}$.

10. A method of treating a human suffering from or
 susceptible to a disorder of the central nervous
 system, which comprises administering to said human
 15 an effective amount of a compound of formula I
 according to anyone of claims 1 to 5, or a
 pharmaceutically acceptable salt thereof.

- 69 -

11. A method of inhibiting the 5-HT_{2A} receptor which comprises administering to a human in need of such treatment a therapeutically effective amount of a 5-HT_{2A} antagonist of formula I as claimed in any
5 one of Claims 1 to 5, or a pharmaceutically acceptable salt thereof.

12. A method of inhibiting the reuptake of serotonin, which comprises administering to a human in need of
10 such treatment a therapeutically effective amount of a serotonin reuptake inhibitor of formula I as claimed in any one of Claims 1 to 5, or a pharmaceutically acceptable salt thereof.

15

