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(54) Titre : MATRICE ADHERANT A LA MUQUEUSE NASALE
(54) Title: MATRIX ADHERING TO NASAL MUCOSA

(57) **Abrégé/Abstract:**

This invention provides a matrix adhering to the nasal mucosa which allows improved transfer into the brain of a drug exerting its effect in the brain and is capable of continuously supplying the drug into the brain. This matrix contains a polyglycerol fatty acid ester, the drug exerting its effect in the brain, and a viscogenic substance.



ABSTRACT

This invention provides a matrix adhering to the nasal mucosa which allows improved transfer into the brain of a drug exerting its effect in the brain and is capable of continuously supplying the drug into the brain. This matrix contains a polyglycerol fatty acid ester, the drug exerting its effect in the brain, and a viscogenic substance.

MATRIX ADHERING TO NASAL MUCOSA

Technical Field

The present invention relates to a matrix adhering to
5 the nasal mucosa, which allows improved transfer, into the
brain, of a drug exerting its effect in the brain and is
capable of continuously supplying the drug into the brain.

Background Art

10 As those literatures that disclose pharmaceutical
compositions adsorbed into mucosae, the followings are
known.

- 1) WO-A 98/42323 describes "A pharmaceutical composition
comprising an unease inhibitor and an oil base material",
15 and there is an example of an agent adhering to mucosae on
digestive tracts.
- 2) JP-A 5-132416 describes "A matrix adhering to mucosae on
digestive tracts and being solid at ordinary temperature,
wherein a material rendered viscous with water is dispersed
20 in the vicinity of at least surface layers of matrix
particles containing a polyglycerol fatty acid ester or
lipid and an active ingredient".
- 3) JP-A 10-324643 describes "A pharmaceutical composition
adhering to mucosae on digestive tracts, which comprises a
25 swelling agent for a material rendered viscous with water".

On the other hand, as those literatures that disclose pharmaceutical compositions adhering to the nasal mucosa, the followings are known.

4) JP-A 56-100714 describes "A preparation adhering to
5 mucosae on the oral or nasal cavity, wherein a drug layer comprising an ointment base material containing a drug and a surfactant is unevenly distributed in a mucosa-adhesive coating layer consisting of a cellulose ether and/or an acrylate polymer or a pharmaceutically acceptable salt
10 thereof."

5) JP-A 7-316038 describes "A pharmaceutical composition for administration into mucosae, which comprises a) an acrylic acid-alkyl (meth)acrylate copolymer or a salt thereof, b) an alkali metal salt and/or an alkaline earth
15 metal salt, c) a drug and d) water as essential ingredients."

6) JP-A 7-215843 discloses "A sustained release pharmacological composition adhering to biological tissues, which comprises a large number of micro-units containing at
20 least one active ingredient and a means of regulating release of said active ingredient, wherein the micro-units do substantially not show biological adhesion before coating thereof, the respective micro-units are coated with a biologically adhering polymeric coating, the coating
25 contains one or more physically acceptable polymers, at

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least one of the polymers is a biologically adhering polymer, and said coating endows the micro-units with an ability to adhere to biological tissues."

7) USP 5723143 describes "A solid therapeutic or hygienic composition adhering to mucosae, which is used in administration into oral or nasal mucosae."

8) WO-A 95/5163 describes "An emulsion adhering to the living body, which is useful as a pharmaceutical composition with enhanced transfer of a drug into mucosae on the living body."

When a drug exerting its action on the brain is administered into the living body, transfer of the drug into the brain is significantly restricted by the blood-brain barrier. Accordingly, there is demand for a preparation capable of allowing a drug exerting its effect in the brain to exert the effect sufficiently in the brain.

Disclosure of the Invention

The present inventors made extensive study for allowing a drug exerting its effect in the brain to exert the effect sufficiently in the brain, and as a result, they unexpectedly found for the first time that when a matrix comprising a polyglycerol fatty acid ester, the drug and a viscogenic substance was created, the matrix had excellent properties as a pharmaceutical preparation, for example

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excellent adhesion to the nasal mucosa, improved transfer of the drug into the brain, sustained supply of the drug into the brain, etc., and on the basis of this finding, this invention was completed.

5 That is, this invention relates to:

- 10 (1) a matrix adhering to the nasal mucosa which allows improved transfer into the brain of a drug exerting its effect in the brain, which comprises a polyglycerol fatty acid ester, the drug exerting its effect in the brain, and a viscogenic substance;
- 15 (2) the matrix according to the above-mentioned (1), wherein the polyglycerol fatty acid ester is an ester of a polyglycerol having a polymerization degree of 2 to 20 with a fatty acid having 12 to 22 carbon atoms;
- 20 (3) the matrix according to the above-mentioned (1), wherein the HLB of the polyglycerol fatty acid ester is 1 to 9;
- (4) the matrix according to the above-mentioned (1), which comprises about 40 to about 95 % by weight of the polyglycerol fatty acid ester;
- (5) the matrix according to the above-mentioned (1), wherein the viscogenic substance is an acrylate type polymer or a salt thereof;
- 25 (6) the matrix according to the above-mentioned (5), wherein the molecular weight of the acrylate type polymer

or a salt thereof is 1,000,000 to 6,000,000;

(7) the matrix according to the above-mentioned (1), which comprises about 4 to about 30 % by weight of the viscogenic substance;

5 (8) the matrix according to the above-mentioned (1), which further comprises a swelling agent for the viscogenic substance;

(9) the matrix according to the above-mentioned (8), wherein the swelling agent for the viscogenic substance is
10 curdlan and/or low-substituted hydroxypropylmethyl cellulose;

(10) the matrix according to the above-mentioned (1), which further comprises lipid;

(11) the matrix according to the above-mentioned (1),
15 wherein the drug exerting its effect in the brain is a drug hardly transferring into the brain;

(12) the matrix according to the above-mentioned (1), wherein the drug exerting its effect in the brain is a sedative-hypnotic agent, an anti-anxiety agent, an
20 antidepressant agent or an agent for treating Alzheimer's disease;

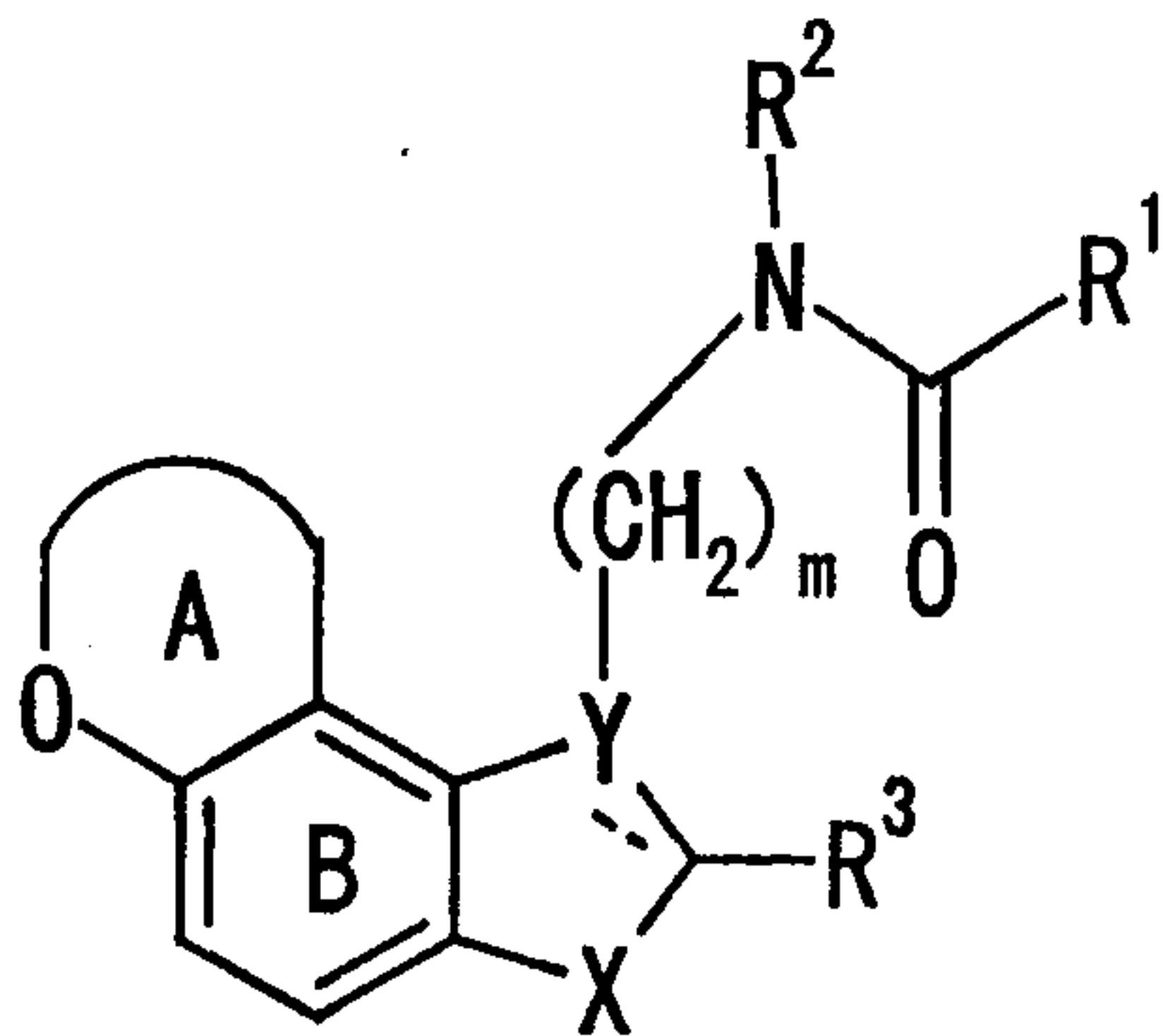
(13) the matrix according to the above-mentioned (1), wherein the drug exerting its effect in the brain is a compound having a melatonin receptor antagonist action;

25 (14) the matrix according to the above-mentioned (1),

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wherein the drug exerting its effect in the brain is a compound represented by the formula:



wherein R^1 is a hydrocarbon group which may have a
 5 substituent group, an amino group which may have a
 substituent group or a heterocyclic group which may have a
 substituent group,

R^2 is a hydrogen atom or a hydrocarbon group which may
 have a substituent group,

10 R^3 is a hydrogen atom or a hydrocarbon group which may
 have a substituent group or a heterocyclic group which may
 have a substituent group,

X is CHR^4 , NR^4 , O or S whereupon R^4 represents a
 hydrogen atom or a hydrocarbon group which may have a
 15 substituent group,

Y is C , CH or N provided that when X represents CH_2 , Y
 is C or CH ,

— is a single or double bond,

ring A is a 5- to 7-membered, oxygen atom-containing
 20 heterocyclic ring which may have a substituent group,

ring B is a benzene ring which may have a substituent group, and

m is an integer of 1 to 4; or

a salt thereof;

5 (15) the matrix according to the above-mentioned (1),
wherein the drug exerting its effect in the brain is (S)-N-
[2-(1,6,7,8-tetrahydro-2H-indeno [5,4-b]furan-8-yl)ethyl]
propionamide;

(16) the matrix according to the above-mentioned (1),
10 wherein the drug exerting its effect in the brain is (S)-N-
[2-(1,6,7,8-tetrahydro-2H-indeno [5,4-b]furan-8-yl)ethyl]
acetamide;

(17) the matrix according to the above-mentioned (1), which
comprises about 0.1 to about 50 % by weight of the drug
15 exerting its effect in the brain;

(18) a solid preparation comprising the matrix described in
the above-mentioned (1);

(19) the solid preparation according to the above-mentioned
(18), which is finely divided particles or powder;

20 (20) the solid preparation according to the above-mentioned
(19), which is spherical;

(21) the solid preparation according to the above-mentioned
(19), which has a particle diameter of about 0.1 to about
100 μm ;

25 (22) a method of improving transfer, into the brain, of a

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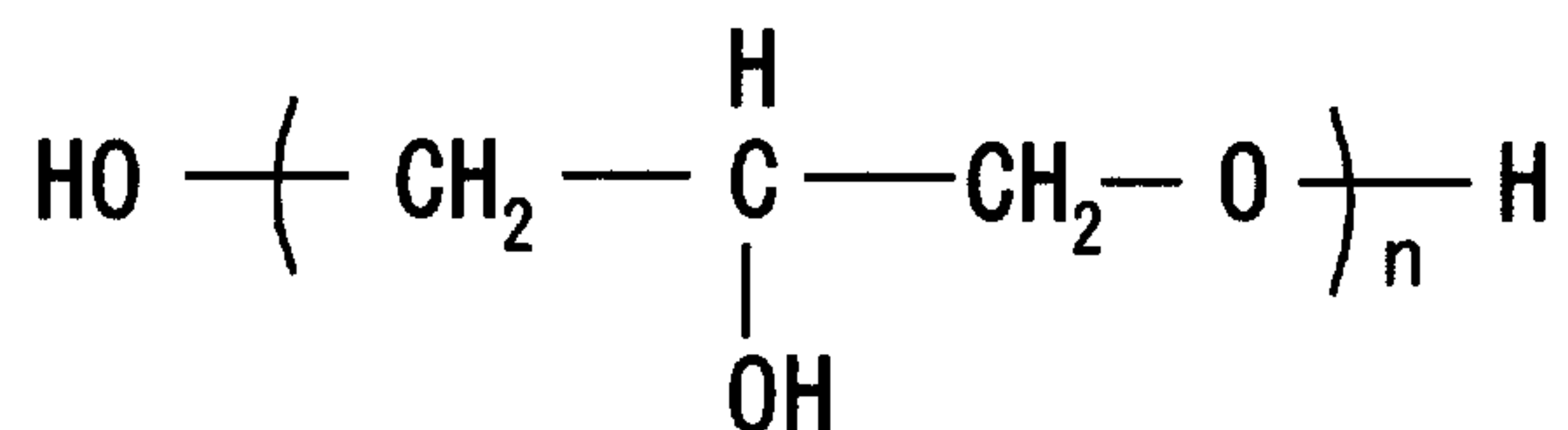
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drug exerting its effect in the brain, which comprises using a matrix comprising a polyglycerol fatty acid ester, the drug and a viscogenic substance; and

(23) use of a polyglycerol fatty acid ester, a drug
5 exerting its effect in the brain, and a viscogenic substance in producing a matrix adhering to the nasal mucosa which allows improved transfer of the drug into the brain.

In this invention, the polyglycerol fatty acid ester
10 may be any one of monoesters, diesters and polyesters insofar as they are esters of polyglycerols with fatty acids. The polyglycerol fatty acid ester is characterized in that it does not show crystalline polymorphism and hardly interacts with a drug so that even if the drug is
15 coexistent therewith, the drug is hardly inactivated and is thus stable for a prolonged period of time.

The polyglycerol is "a polyvalent alcohol having "n" (cyclic) to "n + 2" (linear or branched) hydroxyl groups and "n - 1" (linear or branched) to "n" (cyclic) ether
20 linkages in one molecule" ("Polyglycerol Ester" edited by Sakamoto Yakuhin Kogyo Co., Ltd. and published on October 4, 1994), and may be linear or branched. As the polyglycerol, use can be made of e.g. those compounds represented by:



wherein n, degree of polymerization, is an integer of 2 or more. n is usually 2 to 50, preferably 2 to 20 and more preferably 2 to 10. Examples of such polyglycerols include
 5 diglycerol, triglycerol, tetraglycerol, pentaglycerol, hexaglycerol, heptaglycerol, octaglycerol, nonaglycerol, decaglycerol, pentadecaglycerol, eicosaglycerol, triacontaglycerol etc. Among these polyglycerols, for example tetraglycerol, hexaglycerol, decaglycerol etc. are
 10 preferable.

As the fatty acid, for example fatty acids each containing 8 to 40 carbon atoms, preferably 12 to 22 carbon atoms, are exemplified. The fatty acid may be saturated or unsaturated, and includes e.g. palmitic acid, stearic acid,
 15 oleic acid, linolic acid, linolenic acid, myristic acid, lauric acid, ricinoleic acid, caprylic acid, capric acid, behenic acid etc. Among these, e.g. stearic acid, oleic acid, lauric acid, linolic acid, behenic acid etc. are preferable.

20 Examples of the polyglycerol fatty acid ester include e.g. behenic acid hexa(tetra)glyceride, behenic acid dodeca(deca)glyceride, behenic acid octa(hexa)glyceride, caprylic acid mono(deca)glyceride, caprylic acid

di(tri)glyceride, capric acid di(tri)glyceride, lauric acid
mono(tetra)glyceride, lauric acid mono(hexa)glyceride,
lauric acid mono(deca)glyceride, oleic acid
mono(tetra)glyceride, oleic acid mono(hexa)glyceride, oleic
5 acid mono(deca)glyceride, oleic acid di(tri)glyceride,
oleic acid di(tetra)glyceride, oleic acid
sesqui(deca)glyceride, oleic acid penta(tetra)glyceride,
oleic acid penta(hexa)glyceride, oleic acid
deca(deca)glyceride, linolic acid mono(hepta)glyceride,
10 linolic acid di(tri)glyceride, linolic acid
di(tetra)glyceride, linolic acid di(hexa)glyceride, stearic
acid mono(di)glyceride, stearic acid mono(tetra)glyceride,
stearic acid mono(hexa)glyceride, stearic acid
mono(deca)glyceride, stearic acid tri(tetra)glyceride,
15 stearic acid tri(hexa)glyceride, stearic acid
sesqui(hexa)glyceride, stearic acid penta(tetra)glyceride,
stearic acid penta(hexa)glyceride, stearic acid
deca(deca)glyceride, palmitic acid mono(tetra)glyceride,
palmitic acid mono(hexa)glyceride, palmitic acid
20 mono(deca)glyceride, palmitic acid tri(tetra)glyceride,
palmitic acid tri(hexa)glyceride, palmitic acid
sesqui(hexa)glyceride, palmitic acid penta(tetra)glyceride,
palmitic acid penta(hexa)glyceride, palmitic acid
deca(deca)glyceride etc. One or more, preferably two or
25 three of the above polyglycerol fatty acid esters may be

mixed and used in an arbitrary ratio.

The molecular weight of the polyglycerol fatty acid ester is usually about 200 to about 7000, preferably about 300 to about 3000 and more preferably about 500 to about 3000.

The HLB (hydrophile-lipophile balance) of the polyglycerol fatty acid ester is usually 1 to 22, preferably 1 to 15 and more preferably 1 to 9. The HLB may be adjusted as desired by suitably mixing two or more polyglycerol fatty acid esters which are different in HLB. By adjusting the HLB of the polyglycerol fatty acid ester, the releasability and dissolution of the drug can be controlled.

Although the melting point of the polyglycerol fatty acid ester is also varied depending on the type of the drug and the viscogenic substance, the melting point is e.g. about 15 to about 80°C, preferably about 30 to about 75°C and more preferably about 45 to about 75°C.

The polyglycerol fatty acid ester usually used in this invention is solid at ordinary temperature (15°C), but insofar as the matrix adhering to the nasal mucosa is solid at ordinary temperature, a polyglycerol fatty acid ester which is liquid at ordinary temperature may also be used.

The polyglycerol fatty acid ester is preferably an ester of a polyglycerol having a polymerization degree of 2

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to 20 with a fatty acid having 12 to 22 carbon atoms.

Preferable examples of the polyglycerol fatty acid ester include e.g. behenic acid hexa(tetra)glyceride (for example, Poem J-46B produced by Riken Vitamin Co., Ltd.; HB-310 produced by Sakamoto Yakuhin Kogyo, etc.), behenic acid dodeca(deca)glyceride (for example, OB-500 produced by Sakamoto Yakuhin Kogyo Co., Ltd., etc.), behenic acid octa(hexa)glyceride (for example, DB-750 produced by Sakamoto Yakuhin Kogyo Co., Ltd., etc.), stearic acid penta(tetra)glyceride (for example, PS-310 produced by Sakamoto Yakuhin Kogyo Co., Ltd., etc.), stearic acid mono(tetra)glyceride (for example, MS-310 produced by Sakamoto Yakuhin Kogyo Co., Ltd., etc.), stearic acid penta(hexa)glyceride (for example, PS-500 produced by Sakamoto Yakuhin Kogyo Co., Ltd., etc.), stearic acid sesqui(hexa)glyceride (for example, SS-500 produced by Sakamoto Yakuhin Kogyo Co., Ltd., etc.), stearic acid deca(deca)glyceride (for example, DAS-750 produced by Sakamoto Yakuhin Kogyo Co., Ltd., etc.), stearic acid mono(hexa)glyceride (for example, PO-500 produced by Sakamoto Yakuhin Kogyo Co., Ltd., etc.), oleic acid penta(tetra)glyceride (for example, PO-310 produced by Sakamoto Yakuhin Kogyo Co., Ltd., etc.), oleic acid deca(deca)glyceride (for example,

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DAO-750 produced by Sakamoto Yakuhin Kogyo Co., Ltd.,
etc.), stearic acid mono(deca)glyceride, polyglycerol-
condensed ricinoleic acid ester [polyglycerol
polyricinolate, for example, tetraglycerol polyricinolate
5 (for example, CRS-75 produced by Sakamoto
Yakuhin Kogyo Co., Ltd., etc.)] or the like. Two or more,
preferably two or three of the above polyglycerol fatty
acid esters may be mixed and used in an arbitrary ratio.

10 The content of the polyglycerol fatty acid ester in
the matrix adhering to the nasal mucosa is for example
about 5 to about 98 % by weight, preferably about 20 to
about 95 % by weight and more preferably about 40 to about
95 % by weight.

15 The polyglycerol fatty acid ester is used in an amount
of about 0.01 to about 10000 parts by weight, preferably
about 0.1 to about 1000 parts by weight, relative to 1 part
by weight of the drug exerting its effect in the brain.

20 The matrix adhering to the nasal mucosa according to
this invention may further contain lipid. Use is made of
lipid having a melting point of about 40 to about 120°C,
preferably about 40 to about 90°C. The lipid include e.g.
C₁₄₋₂₂ saturated fatty acids (for example, myristic acid,
palmitic acid, stearic acid, behenic acid etc.) or salts
thereof (for example, sodium salts, potassium salts); C₁₆₋₂₂
25 higher alcohols (for example, cetyl alcohol, stearyl

alcohol etc.); fatty acid glycerol esters, that is, monoglycerides, diglycerides and triglycerides with the above fatty acids (for example, 1-monostearin, 1-monopalmitin etc.); fats and oils (for example, soybean oil, olive oil, rapeseed oil, peppermint oil, sesame oil, castor oil, camellia oil, wheat malt oil, fennel oil, corn oil, sunflower oil, cottonseed oil, coconut oil, peanut oil and hardened oils thereof, tallow, lard etc.); wax (for example, beeswax, carnauba wax, spermaceti, white wax etc.); hydrocarbons (for example, paraffin, microcrystalline wax etc.); phospholipid (for example, hydrogenated lecithin etc.), etc. Among these lipids, for example fats and oils, wax, C₁₄₋₂₂ saturated fatty acids, C₁₆₋₂₂ higher alcohols, hydrocarbons etc. are preferable, and hardened cottonseed oil, hardened castor oil, hardened soybean oil, carnauba wax, stearic acid, stearyl alcohol, microcrystalline wax etc. are more preferable. In particular, hardened castor oil, carnauba wax etc. are preferable.

When the polyglycerol fatty acid ester is used in combination with lipid, the lipid is preferably fats and oils (preferably hardened oils) and wax.

Specific combination of the polyglycerol fatty acid ester and the lipid includes e.g. combinations of at least one member selected from behenic acid hexa(tetra)glyceride, behenic acid dodeca(deca)glyceride, behenic acid

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octa(hexa)glyceride, stearic acid penta(tetra)glyceride and stearic acid penta(hexa)glyceride and at least one member selected from hardened castor oil, carnauba wax and microcrystalline wax.

5 When the polyglycerol fatty acid ester is used in combination with the lipid, the content of the two components in the matrix adhering to the nasal mucosa, or the ratio thereof to the drug exerting its effect in the brain, shall be identical with the content or the ratio of
10 the polyglycerol fatty acid ester when used singly.

 In this invention, the viscogenic substance means a pharmaceutically acceptable substance which is rendered viscous with water to show adhesion to the nasal mucosa. In particular, a substance swelling with water and imparted
15 with significantly increased viscosity with water is preferable. The viscogenic substance includes e.g. a polymer, a naturally occurring viscogenic substance, etc.

 2 % aqueous solution of the polymer at 20°C has a viscosity of about 3 to about 50000 cps, preferably about
20 10 to about 30000 cps and more preferably about 15 to about 30000 cps. In the case of a polymer thickening upon neutralization, 0.2 % neutralized solution thereof at 20°C has a viscosity of about 100 to about 500000 cps, preferably about 100 to about 200000 cps and more
25 preferably about 1500 to about 100000 cps.

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The viscosity of the viscogenic substance shall be determined at 20°C with a Brookfield viscometer.

The polymer is preferably an acidic polymer, and the acidic polymer includes polymers having carboxyl groups, sulfo groups or salts thereof. In particular, the polymer having carboxyl groups or salts thereof is preferable.

The polymer having carboxyl groups or salts thereof includes e.g. acrylate type polymers (including copolymers) comprising acrylic acid as a constituent monomer, or salts thereof. The salts include monovalent metal salts such as sodium and potassium salts; and divalent metal salts such as magnesium and calcium salts. The acrylate type polymer or salts thereof include polymers containing about 58 to about 63 % by weight of carboxyl groups and having molecular weights of about 200,000 to 6,000,000, preferably 1,000,000 to 6,000,000, more preferably 1,000,000 to 5,000,000. Preferable acrylate type polymers and salts thereof include acrylate homopolymers and salts thereof. The acrylate polymer containing about 58 to about 63 % by weight of carboxyl groups is described as carboxy vinyl polymer in Non-Pharmaceutical Ingredient Standards in Japanese Pharmacopoeia (October, 1986). Examples of said polymer include e.g. Carbomer (trade mark: Carbopol produced by The B. F. Goodrich Company) 940, 934, 934P, 941, 1342, 974P (NF XVIII) etc.; HIVISWAKO 103, 104, 105 (trade

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mark, produced by Wako Pure Chemical Industries, Ltd.), NOVEON AA1 (trade mark, produced by The B. F. Goodrich Company), calcium polycarbofil (USP XXIII) etc.

5 The naturally occurring viscogenic substance includes e.g. mucin, agar, gelatin, pectin, carrageenan, sodium alginate, locust bean gum, xanthane gum, tragacanth gum, gum arabic, chitosan, pullulan, waxy starch, sucralfate, cellulose and derivatives thereof (for example, hydroxypropyl cellulose, hydroxypropylmethyl cellulose, 10 cellulose sulfate etc.). In particular, hydroxypropyl cellulose, hydroxypropylmethyl cellulose etc. are preferable.

Two or more naturally occurring viscogenic substances described above may be mixed and used in an arbitrary ratio.

15 The viscogenic substance is preferably an acrylate type polymer or a salt thereof.

The content of the viscogenic substance in the matrix adhering to the nasal mucosa is for example about 0.005 to about 99 % by weight, preferably about 0.5 to about 45 % by 20 weight and more preferably about 4 to about 30 % by weight.

The matrix adhering to the nasal mucosa according to this invention may further contain a swelling agent for the viscogenic substance. The swelling agent for the viscogenic substance refers to a pharmaceutically 25 acceptable substance swelling the viscogenic substance or

promoting swelling of the viscogenic substance with water.
The swelling agent can be used to provide the matrix
adhering to the nasal mucosa which is excellent in adhesion
to the nasal mucosa and can be retained in the nasal mucosa
5 for a prolonged period of time.

The swelling agent for the viscogenic substance
includes e.g. curdlan and low-substituted
hydroxypropylmethyl cellulose.

Curdlan is a linear water-insoluble polysaccharide (β -
10 1,3-glucan) produced by a microorganism (*Alcaligenes*
faecalis var. *myxogenes*), and particularly curdlan N (food
additive) can be used preferably.

The low-substituted hydroxypropyl cellulose (Japanese
Pharmacopoeia, 12th revised edition) is prescribed as
15 follows: alcohol groups on the cellulose have been replaced
by hydroxypropoxy groups, and the content of the
hydroxypropyl groups (% by weight) is 5.0 to 16.0 %. It is
possible to use a wide variety of such cellulose having a
content of substituent groups in this range and a varying
20 particle size, for example, LH-11 (hydroxypropoxyl group
content: 10.0 to 13.0 % by weight; particle size: 98 % by
weight or more particles pass through a screen of 150 μ m in
mesh size, and 0.5 % by weight or less particles are on a
screen of 180 μ m in mesh size), LH-20 (hydroxypropoxyl
25 group content: 13.0 to 16.0 % by weight; particle size:

90 % by weight or more pass through a screen of 75 μm , and 1.0 % by weight or less are on a screen of 106 μm), LH-21 (hydroxypropoxyl group content: 10.0 to 13.0 % by weight; particle size: 90 % by weight or more pass through a screen of 75 μm , and 1.0 % by weight or less are on a screen of 106 μm), LH-22 (hydroxypropoxyl group content: 7.0 to 10.0 % by weight; particle size: 90 % by weight or more pass through a screen of 75 μm , and 1.0 % by weight or less are on a screen of 106 μm) and LH-31 (hydroxypropoxyl group content: 10.0 to 13.0 % by weight; average particle diameter 30 μm or less; particle size: 50 % by weight or more pass through a screen of 45 μm , and 5.0 % by weight or less are on a screen of 75 μm). In particular, LH-22 and LH-31 are preferable.

The content of the swelling agent for the viscogenic substance in the matrix adhering to the nasal mucosa is for example about 0.5 to about 50 % by weight, preferably about 1 to about 50 % by weight and more preferably about 1 to about 30 % by weight.

In this invention, the drug exerting its effect in the brain (also referred simply to hereinafter as the drug) includes e.g. the following compounds, hormones, peptides, proteins etc. acting via the nerve center: antiinflammatory agents such naproxen sodium, isopropyl antipyrine, ibuprofen, ketoprofen and diclofenac; sympathetic nervous

agonists such as ephedrine hydrochloride, salbutamol sulfate, and phenylpropanolamine hydrochloride; antihistamines such as chlorpheniramine maleate, diphenhydramine hydrochloride, and clemastine fumarate; 5 antibiotics such as amoxicillin, cephalixin, clarisromycin and chloxasilin sodium [hereinafter, those underlined are phonetically transcribed]; antitumor agents such as fluorouracil, cisplatin and methotrexate; anti-epileptic agents such as phenytoin sodium, ethosuximide, and sodium 10 valproate; choline agonists such as bethanechol hydrochloride, neostigmine bromide, and carbachol; opioid compounds such as morphine hydrochloride, morphine sulfate, oxycodone, codeine, buprenorphine, and fentanyl; sedative-hypnotic agents or antianxiety agents such as melatonin, 15 diazepam, and chlordiazepoxide; antidepressant agents such as fluoxetine, sertraline, paroxetine, Venlafaxine, nefazodone, reboxetine, imipramine hydrochloride and duloxetine; anesthetics such as droperidol and halothane; anti-Parkinson drugs such as dopamine, L-dopa, and 20 apomorphine; drugs for mind and nerves, such as haloperidol, prochlorperazin; cerebral circulation-ameliorating drugs such as vinpocetine; drugs for treating schizophrenia, such as olanzapine, risperidone, quetiapine and iloperidone; intelligence improvers; drugs for treating migraines, such 25 as dihydroergotamine, sumatriptan, butrophanol, and

capsaicin; skeletal muscle-relaxing drugs; agents for treating Alzheimer's disease, such as tacrine and donepezil; agents for treating alcoholism; auxiliary agents for quitting smoking; agents for treating drug abuse; 5 vomiting-controlling drugs; drugs for the central nervous system, such as idebenone, indeloxazine hydrochloride, bifemelane hydrochloride, protirelin tartrate, and baclofen; neurotransmitters and related substances, such as acetyl choline, γ -aminobutyric acid, serotonin, β -endorphin, 10 methionine-enkephalin, Substance P, glycine, glutamic acid, aspartic acid, vasoactive intestinal polypeptide (VIP), epinephrine, norepinephrine and neurotensin; peptides released from the hypothalamus and involved in hormone synthesis and secretion, such as thyrotropin-releasing 15 hormone (TRH), corticotropin-releasing hormone (CRH), luteinizing hormone-releasing hormone (LHRH), follicle-stimulating hormone-releasing hormone (FSHRH), prolactin-releasing hormone (PrRH), growth hormone-releasing hormone (GRH), somatostatin, galanin, galanin-like peptide (GALP), 20 neuromedin U, ghrelin, apelin, urotensin II, orexin, and their related compounds such as agonists and antagonists, for example leuprorelin; pituitary hormones such as thyroid-stimulating hormone (TSH), adrenocorticotrophic hormone (ACTH), luteinizing hormone (LH), follicle-stimulating hormone (FSH), prolactin (PRL), growth hormone 25

(GH), vasopressin, oxytocin and neuropeptide Y; thyroid hormone; parathyroid hormone (PTH); saccharide metabolism-related hormones such as insulin and glucagon; adrenocorticotrophic medulla-related peptides such as
5 angiotensin, dehydroepiandrosterone; alimentary canal hormones such as gastrin, secretin, cholecystokinin and motilin; neuropeptides involved in appetite regulation, such as leptin, melanin concentrating hormone (MCH), opioid, cholecystokinin, bombesin, and their related compounds such
10 as agonists and antagonists; and compounds related to instinctive behaviors and body temperature.

Out of these drugs, those drugs which upon administration into blood vessels, digestive tracts, lungs, skin etc., undergo significant restriction of transfer
15 thereof to the brain because of their degradation with gastric acid or enzyme, metabolism by the initial passage effect, or the blood-brain barrier (that is, drugs hardly transferring into the brain), or exhibit side-effects because of an increase in their blood levels can be
20 effectively used in the matrix adhering to the nasal mucosa according to this invention.

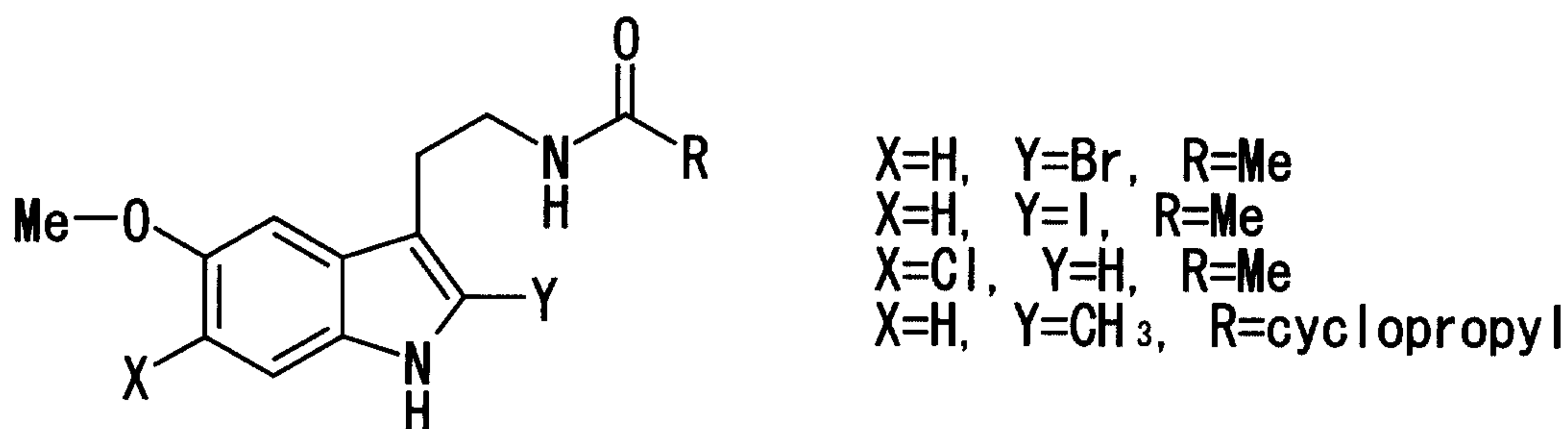
In the matrix adhering to the nasal mucosa, the content of the drug exerting its effect in the brain is for example about 0.005 to about 95 % by weight, preferably
25 about 0.1 to about 90 % by weight, more preferably about

0.1 to about 50 % by weight.

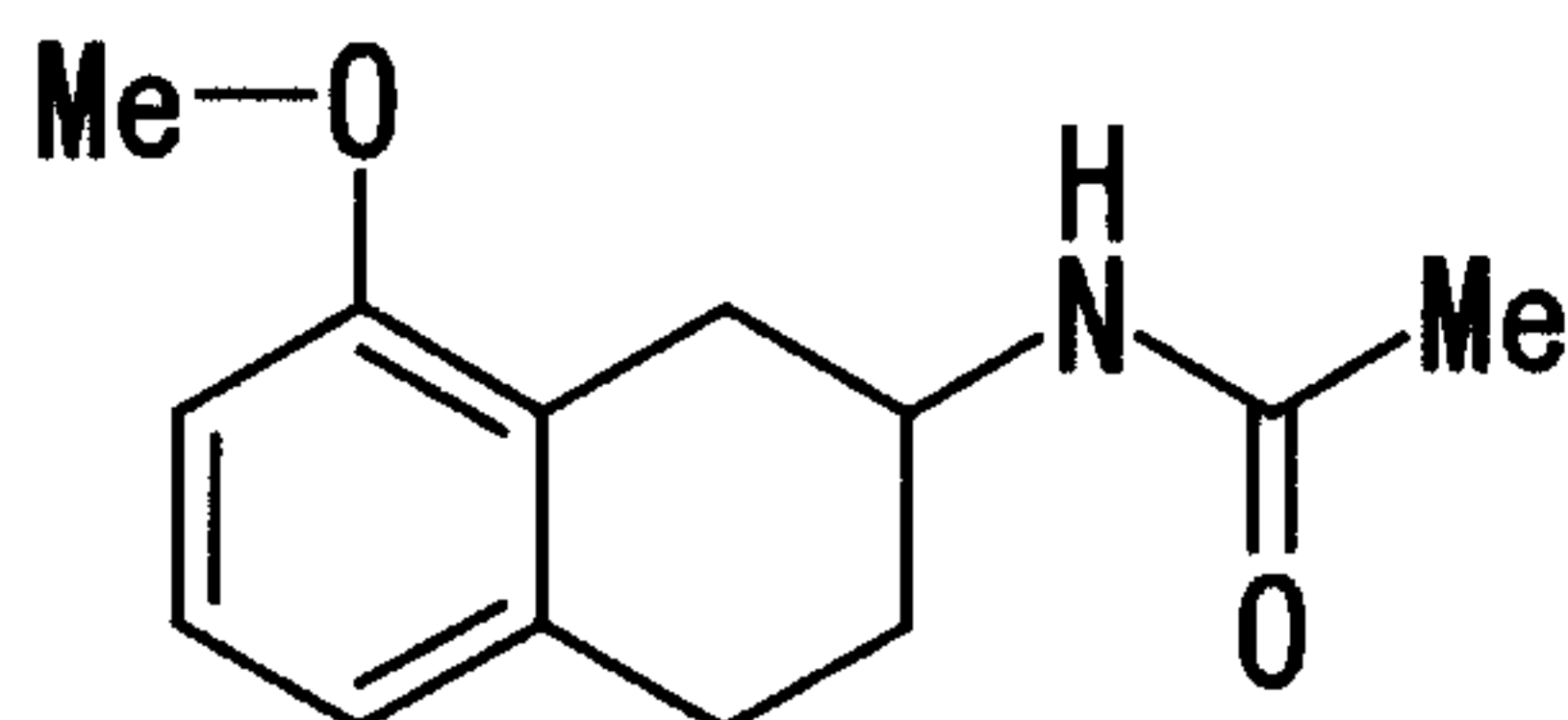
The drug exerting its effect in the brain is preferably is a sedative-hypnotic agent, an anti-anxiety agent, an antidepressant agent or an agent for treating
5 Alzheimer's disease.

For example, such drugs are preferably compounds having a melatonin receptor agonist action. The compounds having a melatonin receptor agonist action are not particularly limited insofar as they have such action, and
10 for example, such melatonin agonists or antagonists thereof include:

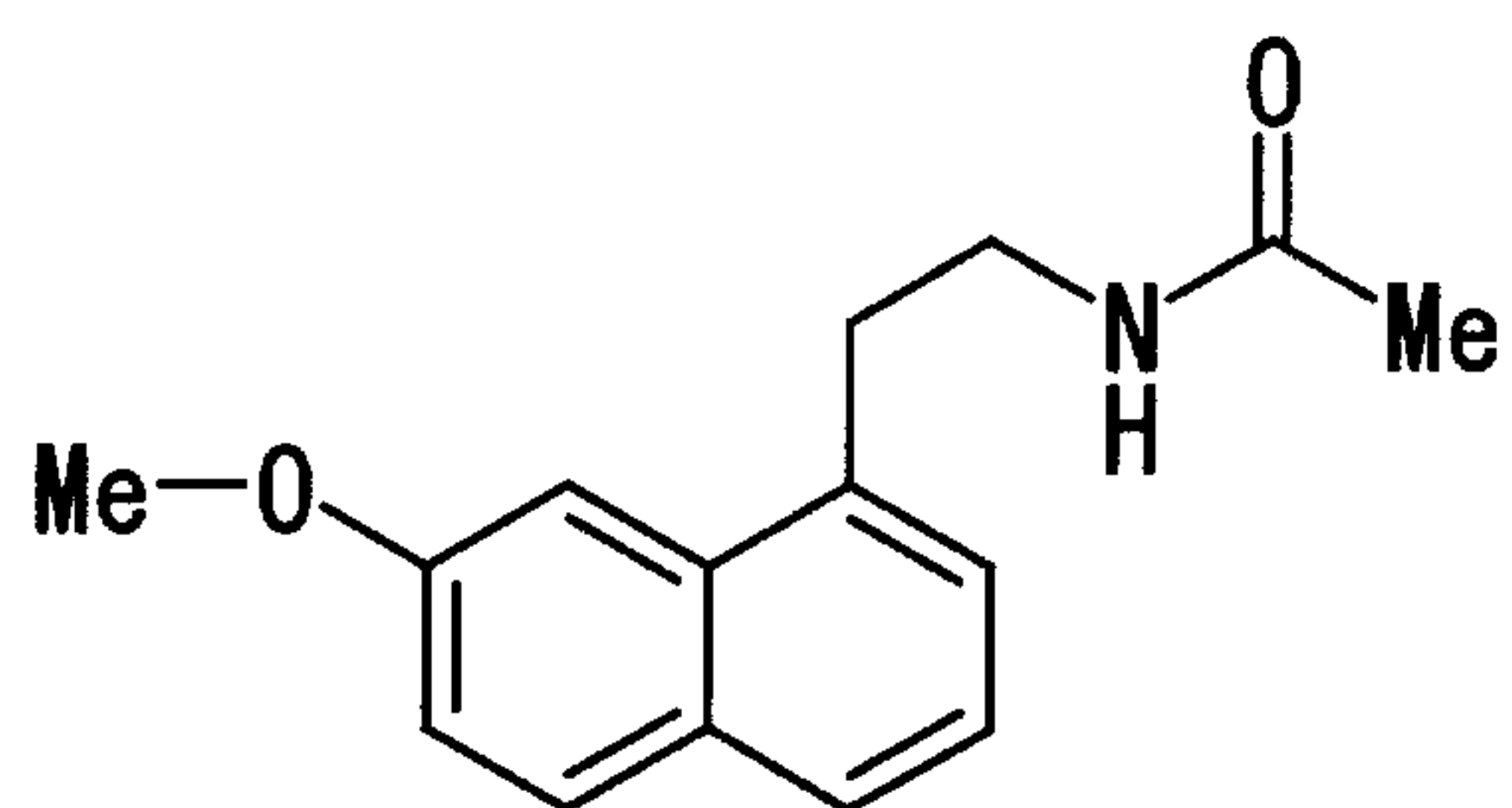
(1) compounds described in EP-A-578620, represented by the formula:



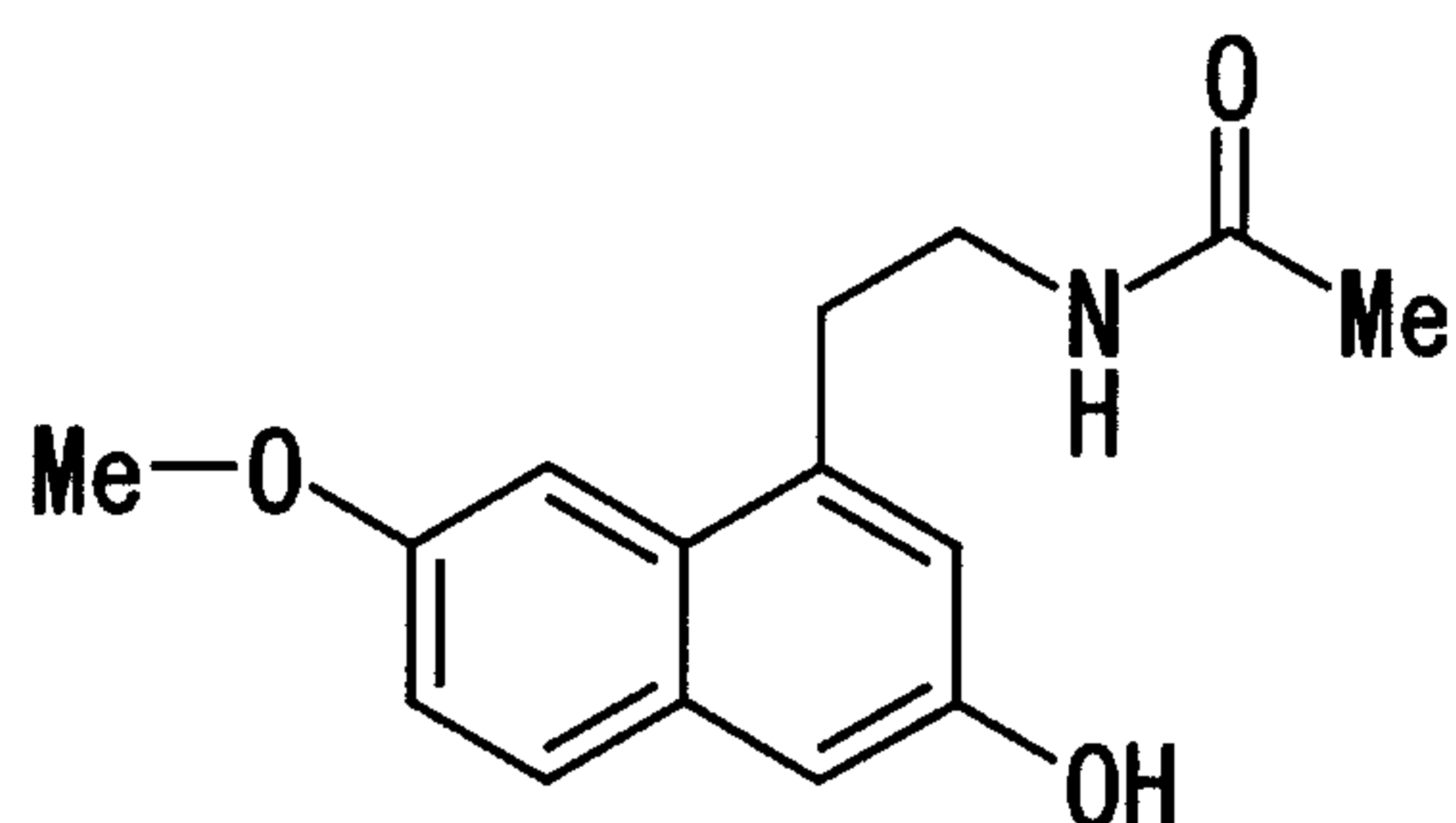
15 (2) a compound described in USP 411675, represented by the formula:



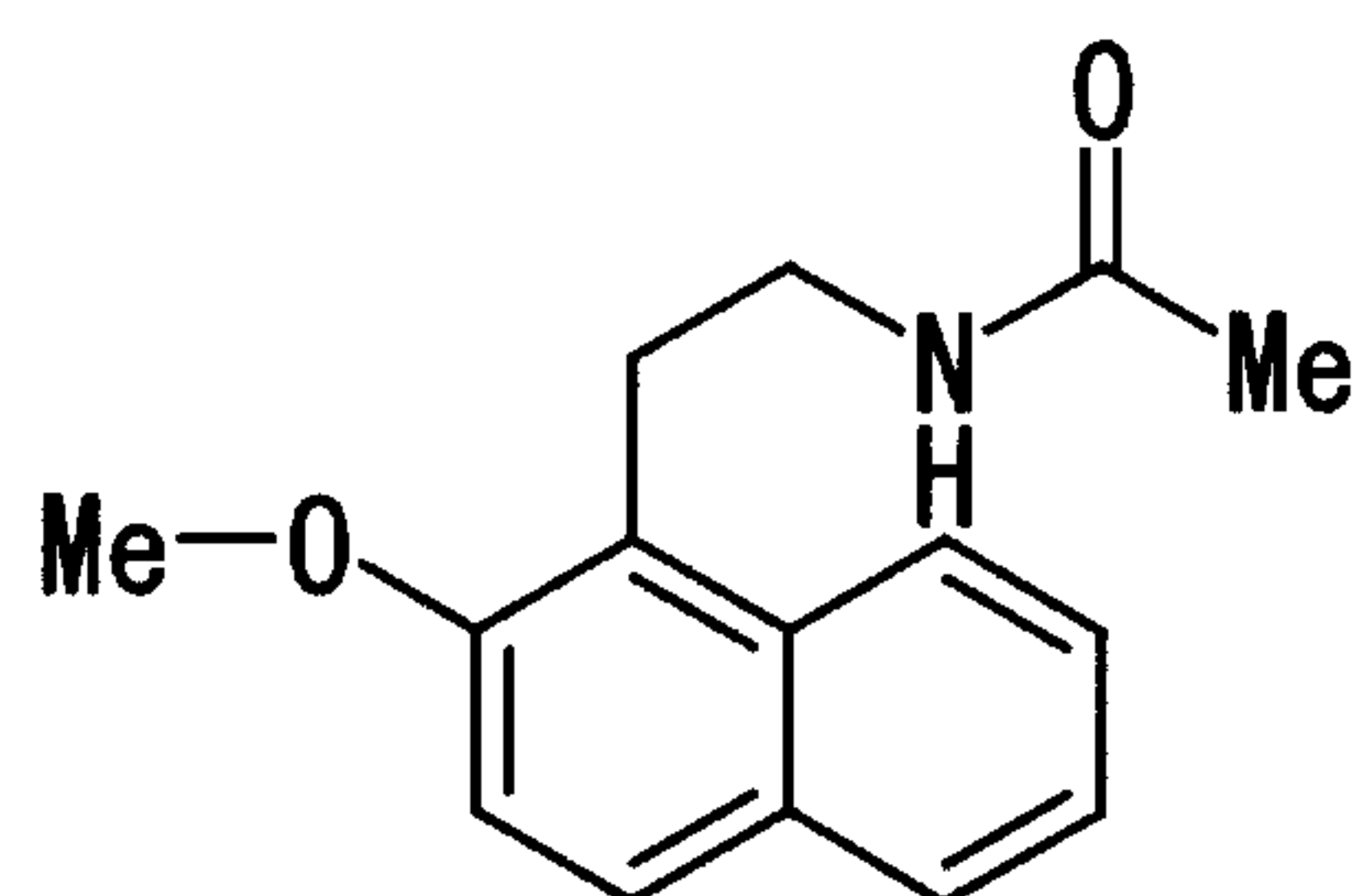
(3) a compound described in JP-A 7-048331 (EP-A-447285), represented by the formula:



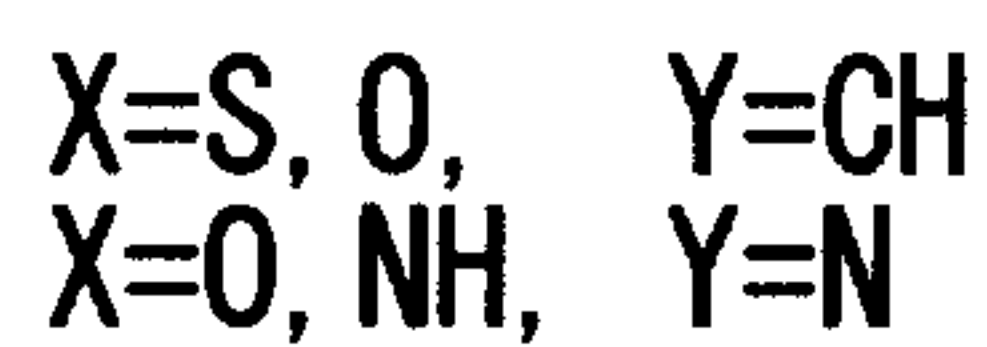
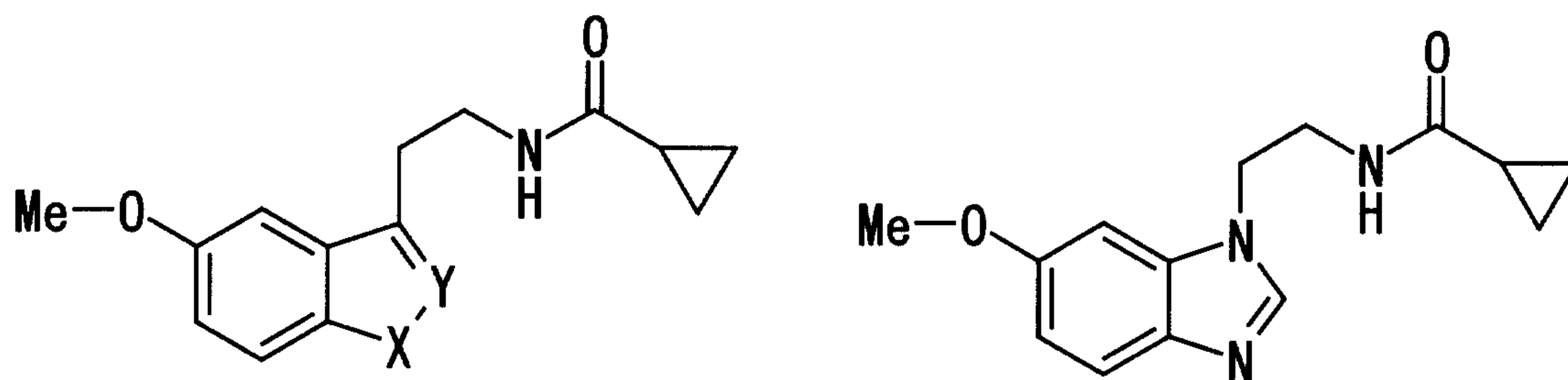
(4) a compound described in FR-014630, represented by the formula:



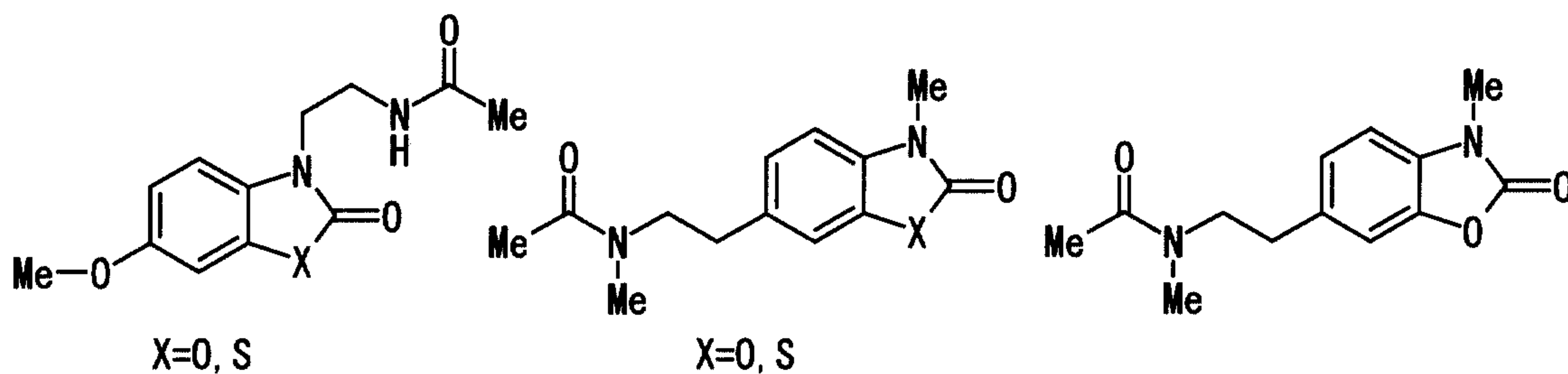
5 (5) a compound described in EP-A-591057, represented by the formula:



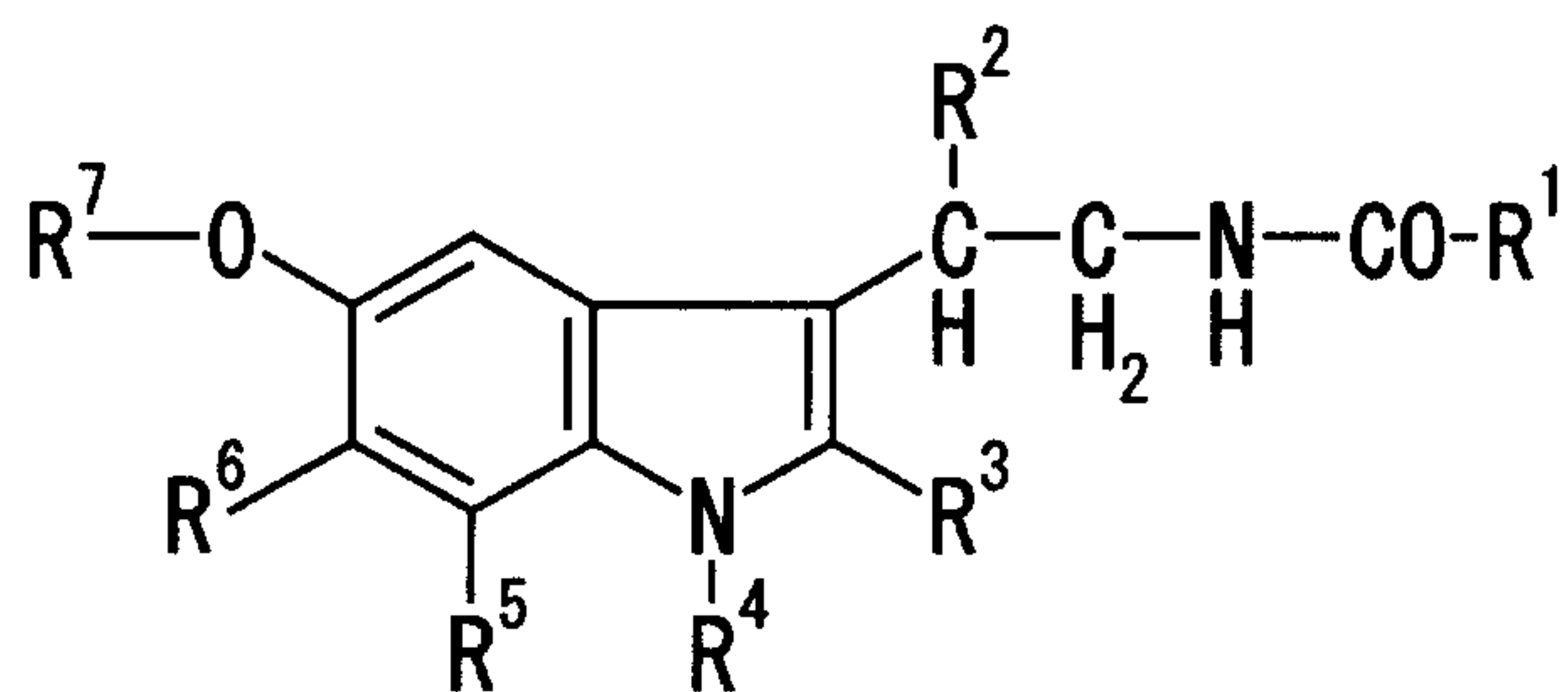
(6) compounds described in EP-A-527687, represented by the formulae:



(7) compounds described in EP-A-506539, represented by the formulae:



5 (8) compounds described in JP-A 7-196493 or JP-A 63-196563, represented by the formula:

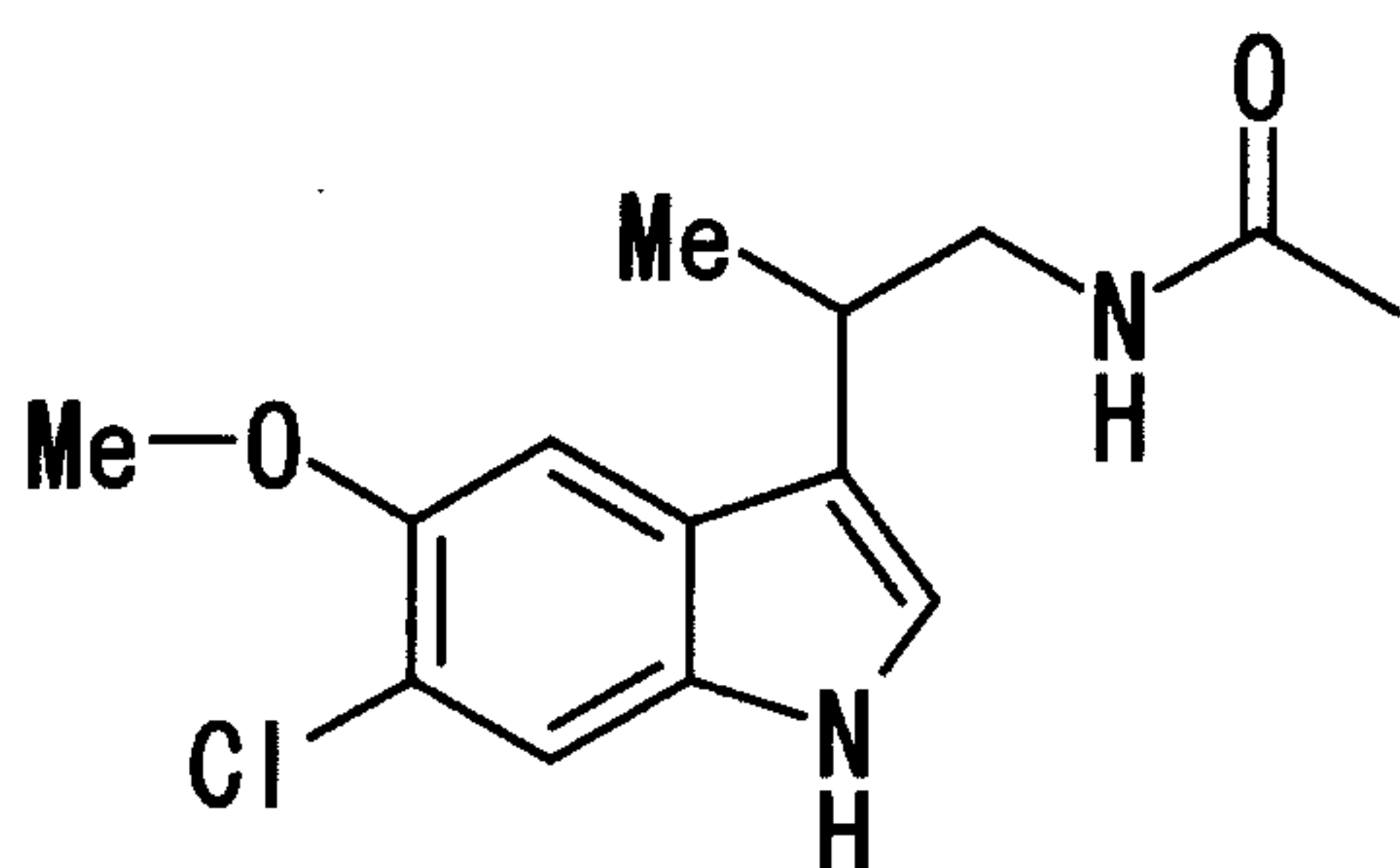


10 wherein R^1 is hydrogen, C_{1-4} alkyl or C_{1-4} alkoxy; R^2 is hydrogen or C_{1-4} alkyl; R^3 is hydrogen, C_{1-4} alkyl, phenyl or substituted phenyl; R^4 is hydrogen, haloacetyl, C_{1-5} alkanoyl, benzoyl, or halo- or methyl-substituted benzoyl;

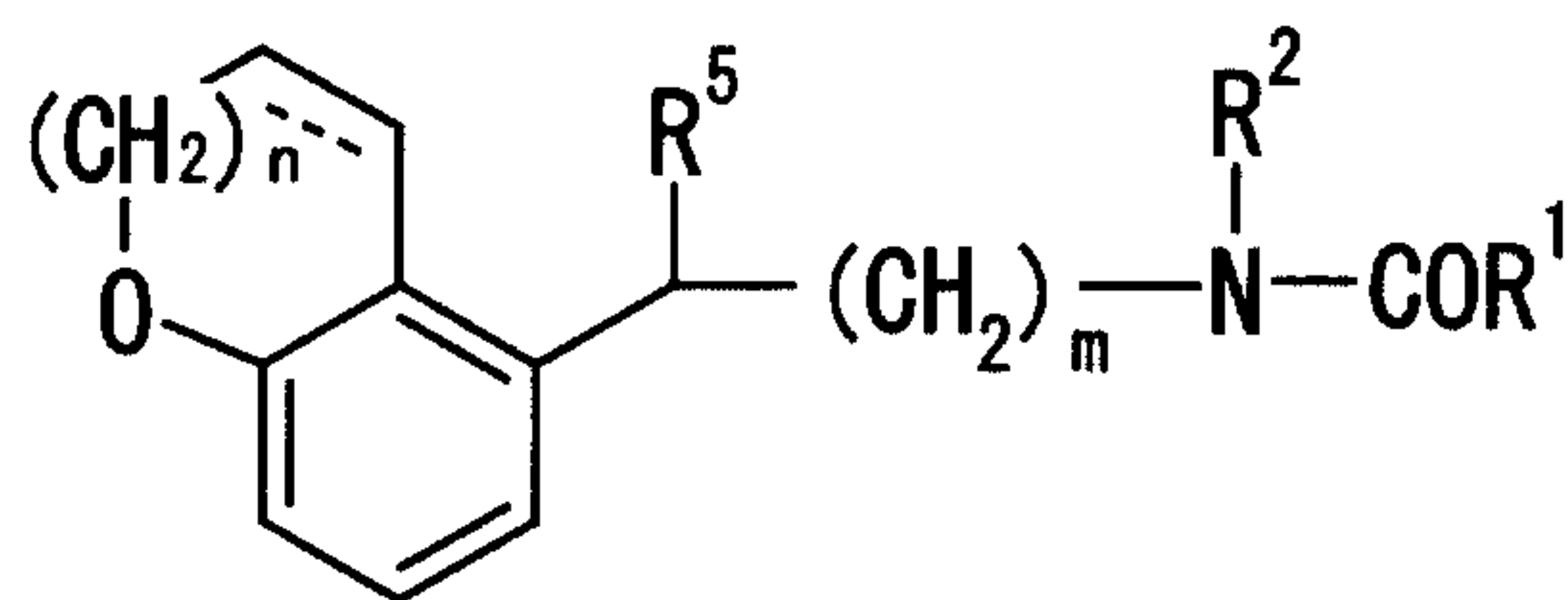
each of R^5 and R^6 is hydrogen or halo; and R^7 is hydrogen or C_{1-4} alkyl, provided that when R^3 , R^4 and R^5 each are hydrogen, R^2 is C_{1-4} alkyl;

or salts thereof, and

5 particularly a compound (LY156735) represented by the formula:



(9) compounds described in WO 97/43272, represented by the formula:



10

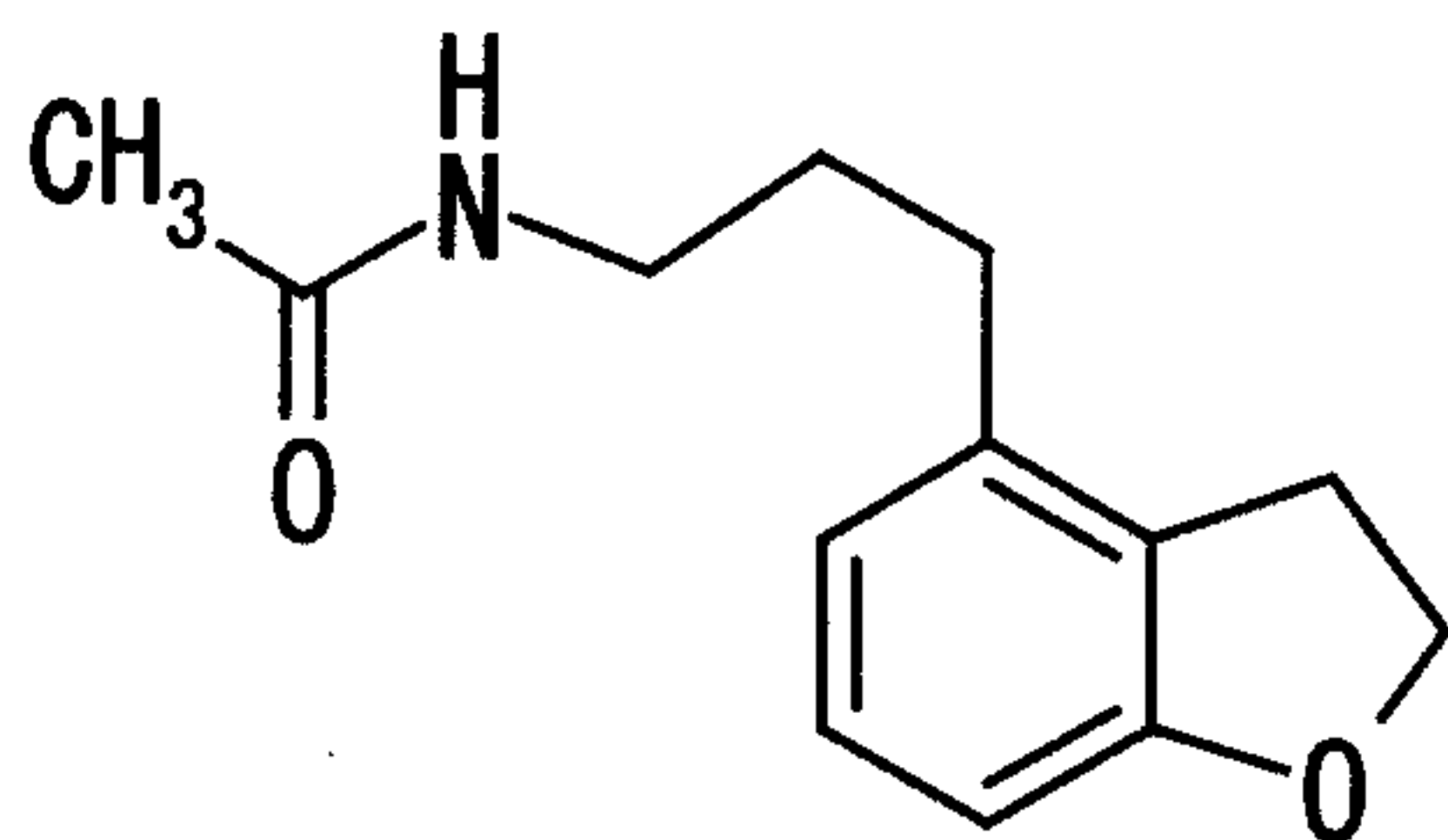
wherein R^1 and R^2 are the same or different and represent hydrogen, C_{1-6} alkyl, C_{3-7} cycloalkyl or aryl; R^3 and R^4 are the same or different and represent hydrogen, halogen, C_{1-6} alkyl or substituted aryl; R^5 is hydrogen or C_{1-6} alkyl; n is 0, 1 or 2; and m is 1, 2, 3 or 4;

15

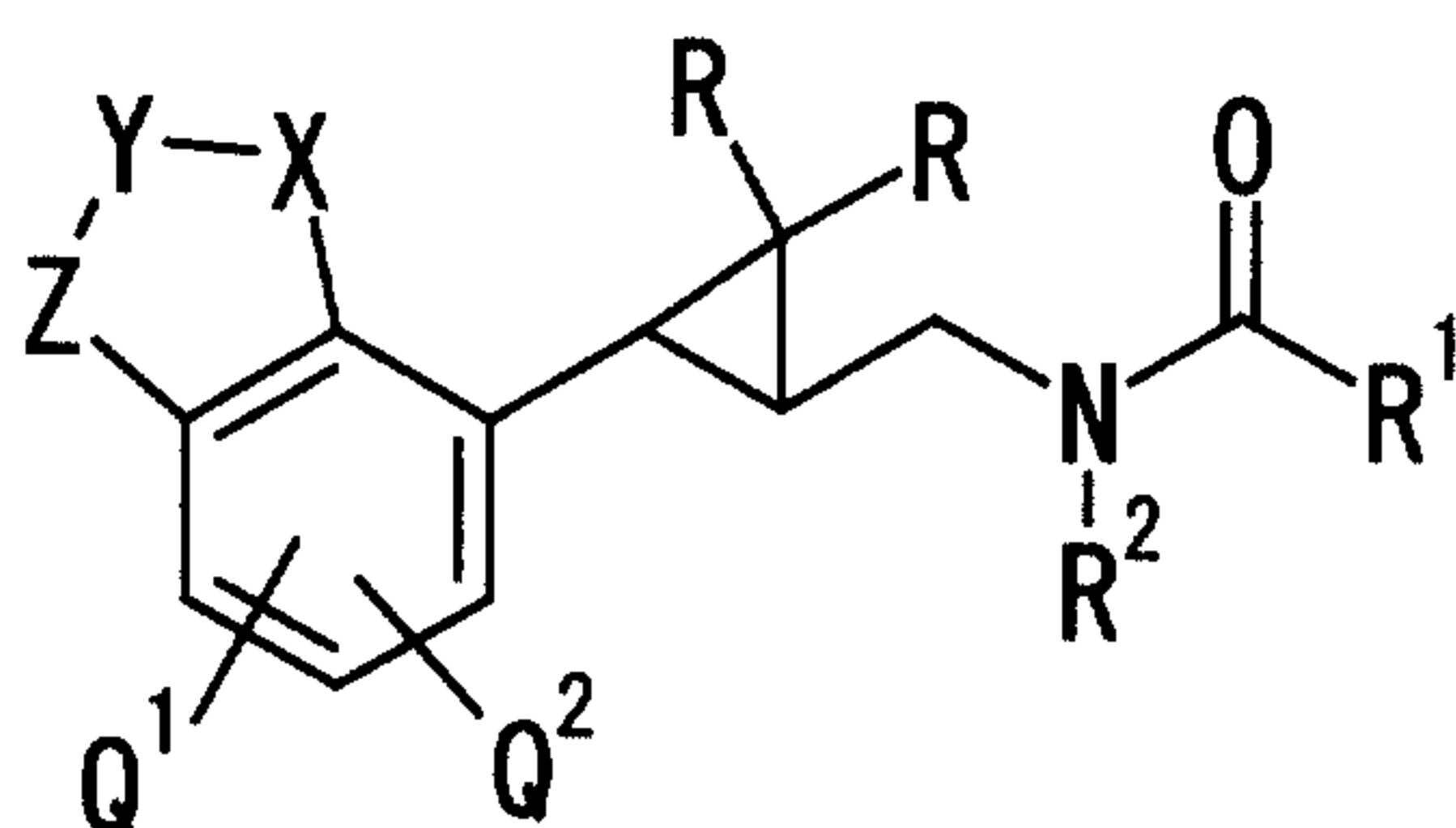
— is a single or double bond,

or salts thereof, and

particularly a compound represented by the formula:



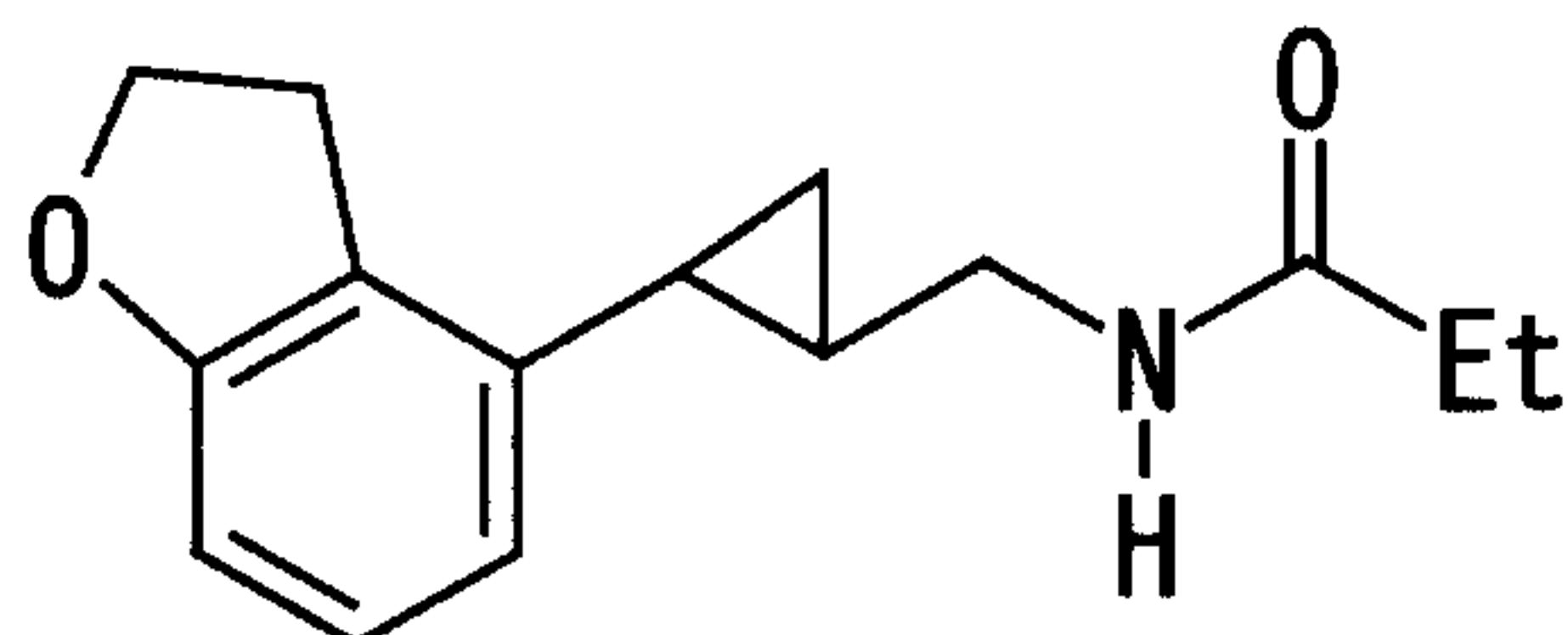
(10) compounds described in WO 98/25606, represented by the formula:



- 5 wherein each of Q^1 and Q^2 is hydrogen or halogen; X is CH_2 , CH or oxygen; Y is CR^3 , CR^3R^4 or $(CH_2)_n$ ($n = 1-4$); Z is CH_2 , CH or oxygen; R is hydrogen, halogen or C_{1-4} alkyl; m is 1 or 2; R^1 is C_{1-6} alkyl, C_{3-6} cycloalkyl, C_{1-3} haloalkyl, C_{1-6} alkylamino, C_{2-6} alkenyl, C_{1-4} alkoxy (C_{1-4}) alkyl, C_{1-4} alkylthio (C_{1-4}) alkyl or trifluoromethyl alkyl; R^2 is
- 10 hydrogen or C_{1-4} alkyl; and each of R^3 and R^4 is hydrogen or C_{1-4} alkyl,

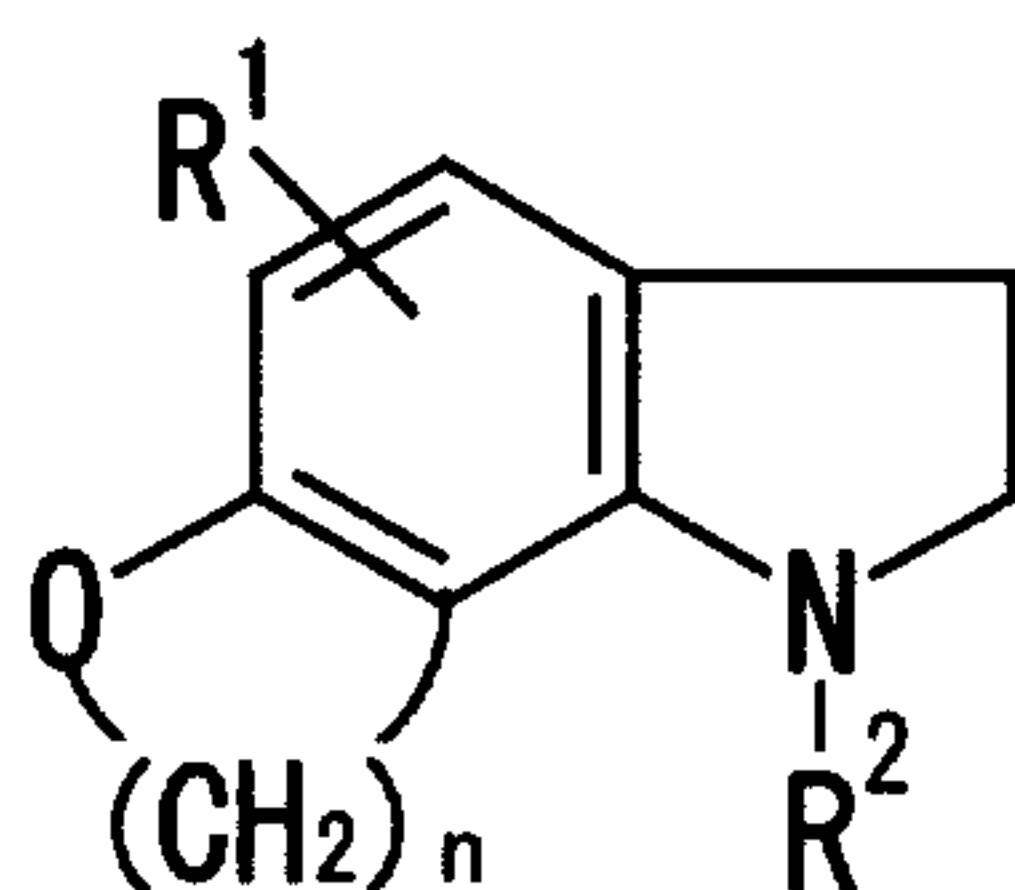
or salts thereof, and

particularly a compound represented by the formula:



15

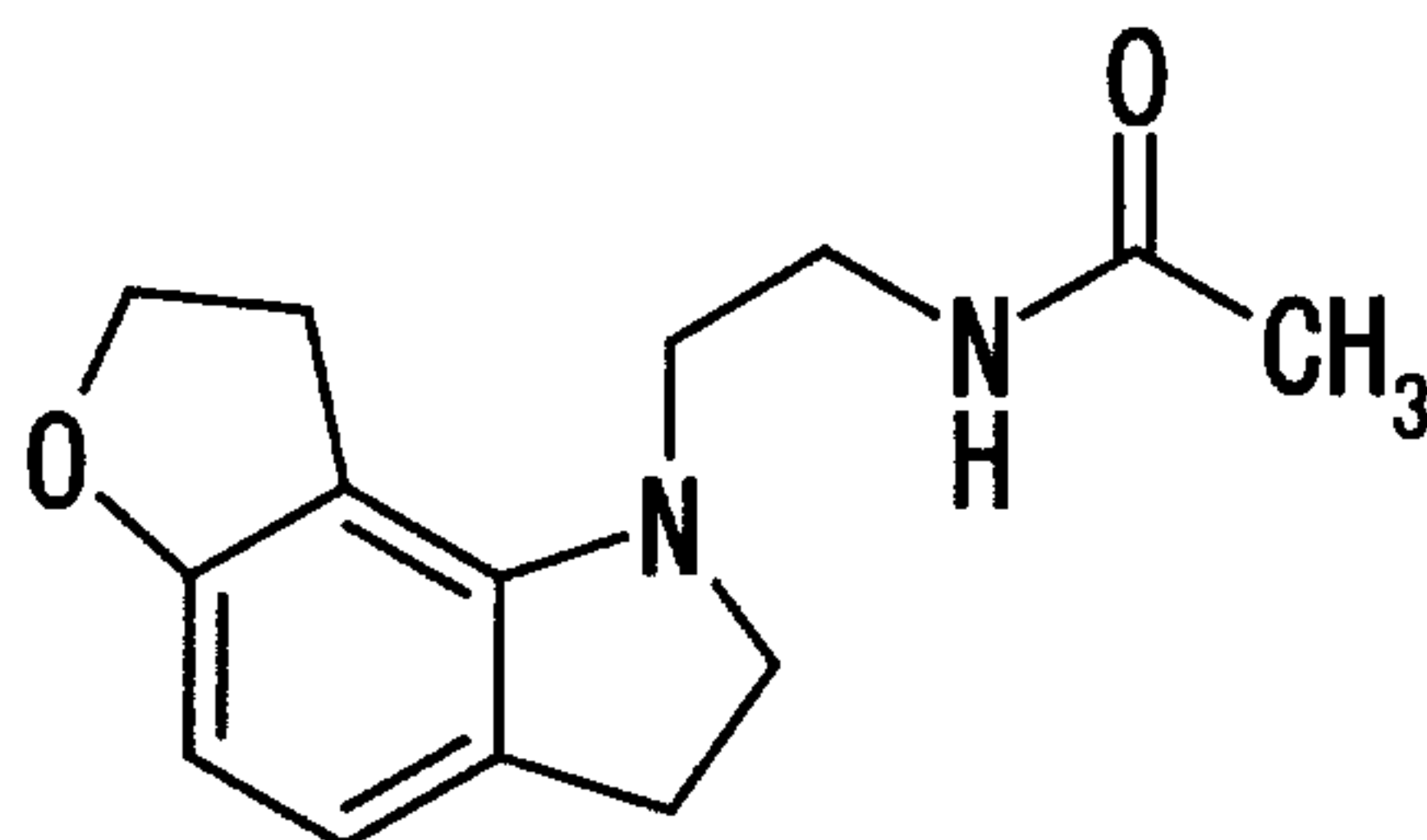
(11) compounds described in JP-A 9-507057, represented by the formula:



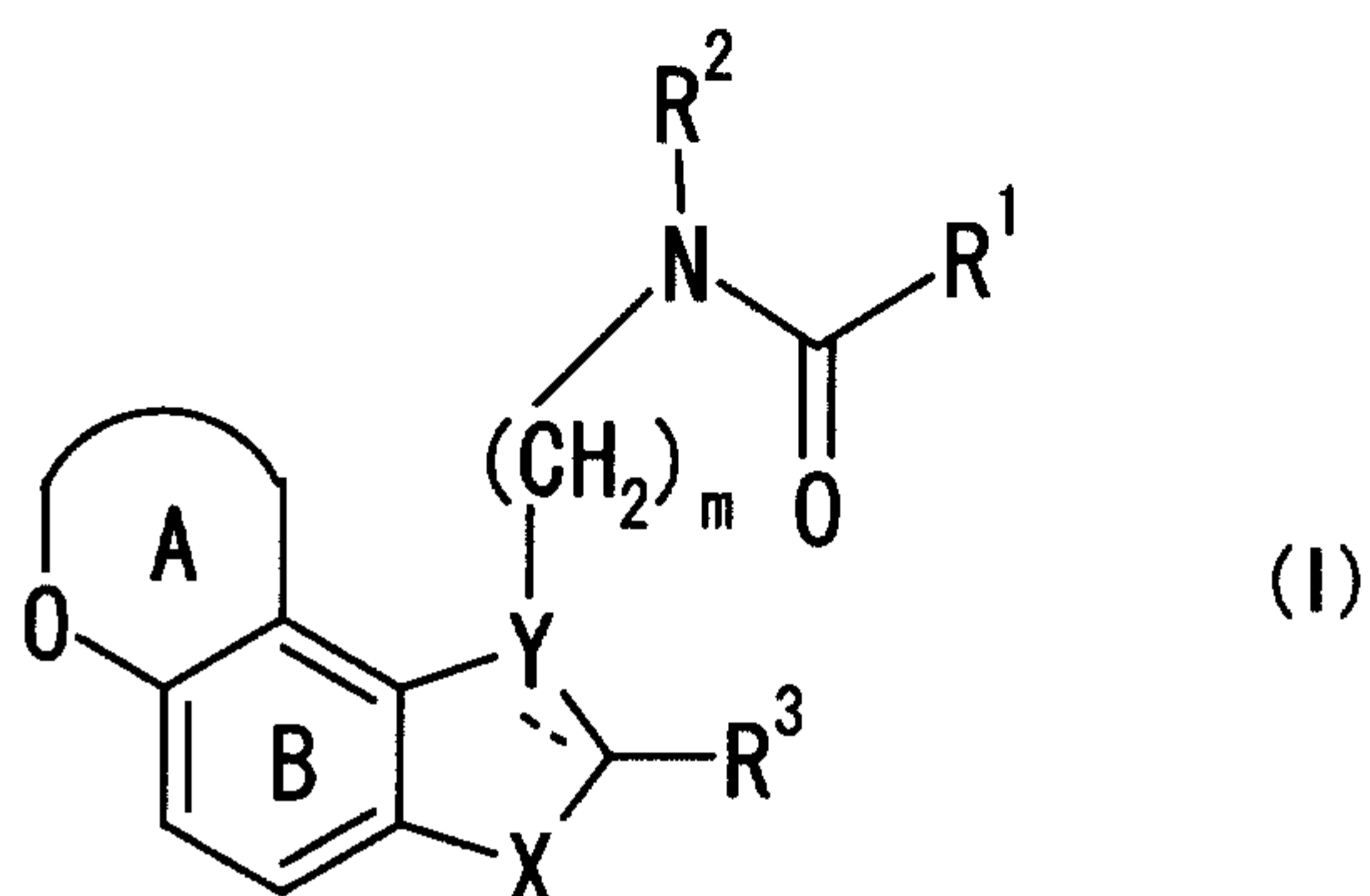
wherein R^1 is hydrogen, halogen or C_{1-6} alkyl; R^2 is a group of the formula $-CR^3R^4(CH_2)_pNR^5COR^6$; R^3 , R^4 and R^5 may be the same or different and represent hydrogen or C_{1-6} alkyl; R^6 is C_{1-6} alkyl or C_{3-7} cycloalkyl; n is an integer of 2, 3 or 4; and p is an integer of 1, 2, 3 or 4;

or salts thereof, and

particularly a compound represented by the formula:



(12) compounds described in WO 97/32871, represented by the formula:



wherein R^1 is a hydrocarbon group which may have a substituent group, an amino group which may have a

substituent group or a heterocyclic group which may have a substituent group,

R^2 is a hydrogen atom or a hydrocarbon group which may have a substituent group,

5 R^3 is a hydrogen atom, a hydrocarbon group which may have a substituent group or a heterocyclic group which may have a substituent group,

X is CHR^4 , NR^4 , O or S whereupon R^4 represents a hydrogen atom or a hydrocarbon group which may have a substituent group,

10 Y is C, CH or N provided that when X represents CH_2 , Y is C or CH,

— is a single or double bond,

.....
15 ring A is a 5- to 7-membered, oxygen atom-containing heterocyclic ring which may have a substituent group,

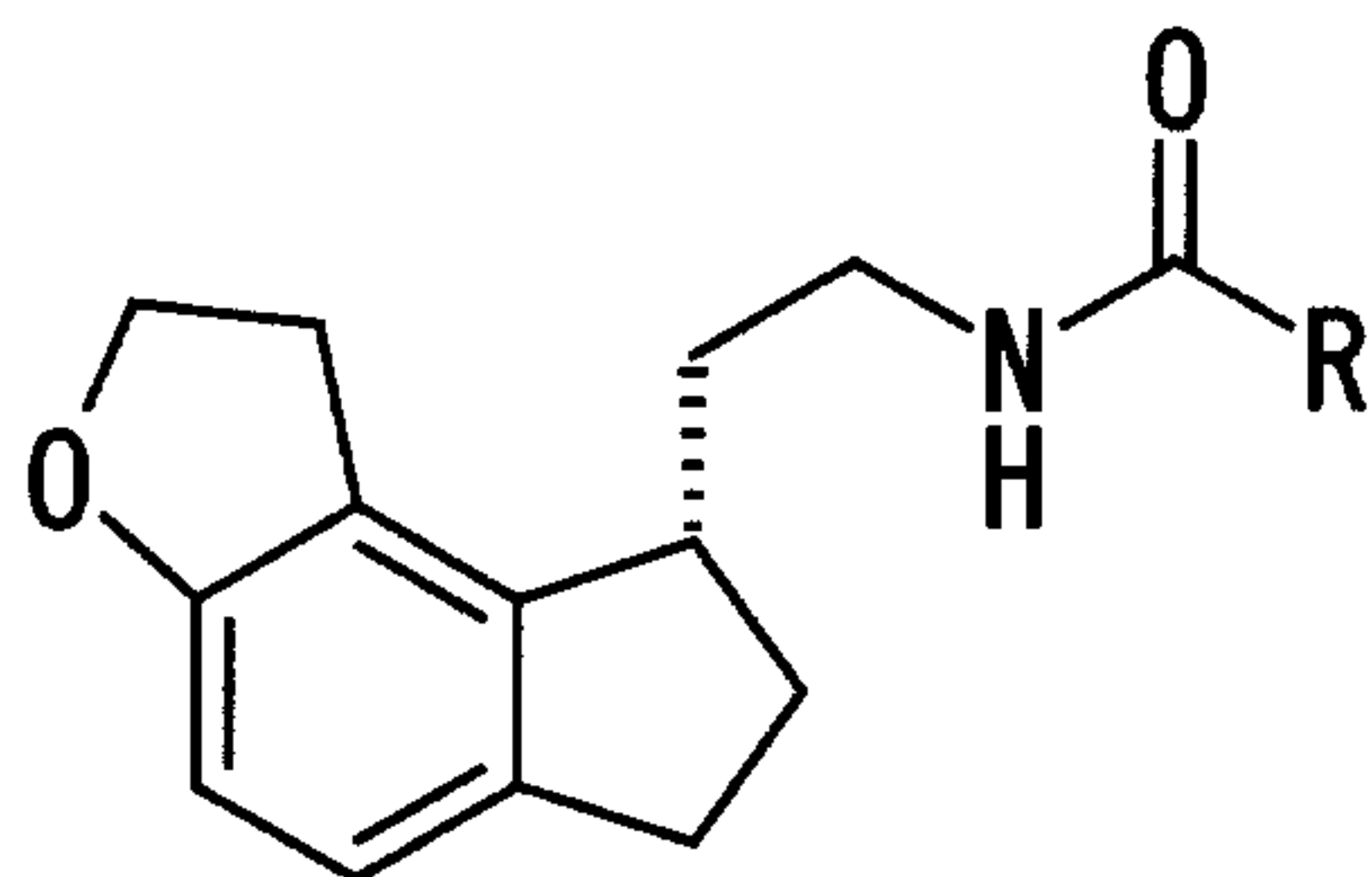
ring B is a benzene ring which may have a substituent group, and

m is an integer of 1 to 4;

or salts thereof.

20 In particular, Compound (I) having high affinity for melatonin receptors and high selectivity particularly for ML_1 receptor is preferable.

Compound (I) is preferably a compound represented by the formula:



wherein R represents a C₁₋₆ alkyl group (methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, hexyl etc.), and specifically Compound (I) is
5 preferably (S)-N-[2-(1,6,7,8-tetrahydro-2H-indeno [5,4-b]furan-8-yl)ethyl] propionamide or (S)-N-[2-(1,6,7,8-tetrahydro-2H-indeno [5,4-b]furan-8-yl)ethyl] acetamide.

In this specification, the matrix means a system where the ingredients constituting the matrix have been uniformly
10 dispersed, and is clearly distinguished from a system where the ingredients have been topically or unevenly distributed or have formed a layer, or from an emulsion or a simple mixture of the ingredients.

That is, in the matrix adhering to the nasal mucosa
15 according to this invention, the ingredients, that is, "the polyglycerol fatty acid ester", "the drug exerting its effect in the brain" and "the viscogenic substance" have been uniformly dispersed. Further, when the matrix further contains "the lipid" and "the swelling agent for the
20 viscogenic substance", the lipid and the swelling agent have also been uniformly dispersed.

The matrix adhering to the nasal mucosa according to

this invention is excellent in adhesion to the nasal mucosa and capable of releasing "the drug exerting its effect in the brain" continuously at a predetermined rate.

The particle diameter of the matrix is preferably
5 about 0.1 to about 1500 μm , more preferably about 0.1 to about 100 μm and most preferably about 5 to about 50 μm .

The matrix adhering to the nasal mucosa according to this invention is produced by uniformly dispersing e.g. the constituent ingredients, that is, "the polyglycerol fatty
10 acid ester", "the drug exerting its effect in the brain" and "the viscogenic substance". When the matrix further contains "the lipid" and "the swelling agent for the viscogenic substance", the lipid and the swelling agent are also dispersed uniformly.

15 For example, said matrix is produced by melting the polyglycerol fatty acid ester by heating it at the melting point or more, then adding the drug or the viscogenic substance thereto simultaneously or separately and cooling the resulting mixture. When the lipid is used, the lipid
20 is used in the same manner as for the polyglycerol fatty acid ester, and when the swelling agent for the viscogenic substance is used, the swelling agent is used in the same manner as for the viscogenic substance.

In this case, heating temperature is for example about
25 40 to about 150°C, preferably about 50 to about 110°C, and

more preferably about 50 to about 90°C.

The heating and dispersion step described above is conducted using e.g. a conventional granulator, and the cooling step is conducted by e.g. spray cooling. This
5 spray cooling is conducted for example by spray chilling, and in this case, a solid preparation (for example, finely divided particles) is obtained.

Spray chilling is conducted by dropping a mixture consisting of the polyglycerol fatty acid ester, the drug
10 and the viscogenic substance at a predetermined flow rate onto a high-speed rotating disk. The rotating disk used may be a smooth disk (e.g. an aluminum disk) having a diameter of 5 to 100 cm, preferably 10 to 20 cm. The rotational speed of the rotating disk is for example 10 to
15 25000 rpm, preferably 3000 to 20000 rpm, more preferably 6000 to 15000 rpm. The rate of dropping the mixture is selected depending on the desired particle diameter, but is usually about 2 to 200 g/min., preferably about 5 to about 100 g/min.

20 The matrix of this invention obtained by this spray chilling method is approximately spherical. Therefore, a stable rate of releasing the drug can be achieved, and thus spray chilling is preferable as a method of producing the matrix of this invention.

25 Alternatively, the matrix adhering to the nasal mucosa

according to this invention can also be produced by dispersing the constituent ingredients by kneading them in a conventional solvent (for example, methanol, acetonitrile, chloroform etc.), followed by granulation thereof.

5 The matrix adhering to the nasal mucosa according to this invention may be formed into a solid preparation by coating it with a coating agent containing the above viscogenic substance or pharmaceutical additives. The coating agent may further contain at least one additive
10 selected from the swelling agent for the viscogenic substance, the polyglycerol fatty acid ester and a water-insoluble polymer.

 The pharmaceutical additives may be those ordinarily used in the field of pharmaceutical manufacturing, and
15 include e.g. excipients such as lactose, corn starch, talc, crystalline cellulose, powdery sugar, magnesium stearate, mannitol, xylitol, sorbitol, erythritol, light silicic anhydride, magnesium carbonate, calcium carbonate and L-cysteine; binders such as starch, sucrose, gelatin, powder
20 of gum arabic, methyl cellulose, carboxymethyl cellulose, sodium carboxymethyl cellulose, hydroxypropyl cellulose, hydroxypropylmethyl cellulose, polyvinyl pyrrolidone, pullulan and dextrin; disintegrating agents such as calcium carboxymethyl cellulose, low-substituted hydroxypropyl
25 cellulose, sodium croscarmellose, sodium carboxymethyl

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starch, hydroxypropyl starch and partially pregelatinized starch; surfactants such as anionic surfactants such as sodium alkyl sulfate, and nonionic surfactants such as polyoxyethylene sorbitan fatty acid esters, polyoxyethylene fatty acid esters and polyoxyethylene castor oil derivatives; acid regulators and mucosa-protecting agents such as magnesium hydroxide, magnesium oxide, aluminum hydroxide, aluminum sulfate, magnesium metasilicate aluminate, magnesium silicate aluminate and sucralfate; coloring agents; taste correctives; adsorbents; preservatives; swelling agents; and antistatic additives. The amount of these pharmaceutical additives is suitably selected in the range where the adhesion of the solid preparation to the nasal mucosa is not deteriorated.

The "water-insoluble polymer" which may be added to the coating agent includes e.g. hydroxypropylmethyl cellulose phthalate, hydroxypropylmethyl cellulose acetate succinate, carboxymethylethyl cellulose, cellulose acetate trimellitate, cellulose acetate phthalate, ethyl cellulose, aminoalkyl methacrylate copolymers [trade mark: Eudragit RS-100, RL-100, RL-PO, RS-PO, RS-30D, RL-30D produced by Röhm Pharma Ltd.], methacrylic acid-ethyl acrylate copolymers [trade mark: Eudragit L100-55 produced by Röhm Pharma Ltd.], methacrylic acid-methyl methacrylate copolymers [trade mark: Eudragit L100, S100, L30D-55, NE-

30D, produced by Röhm Pharma Ltd.] and polyvinyl acetate. Two or more of these polymers can be mixed and used in an arbitrary ratio.

5 The content of the viscogenic substance in the coating agent is for example about 0.005 to about 100 % by weight, preferably about 0.05 to about 95 % by weight and more preferably about 1 to about 10 % by weight of the total solid content in the coating agent.

10 When the coating agent contains pharmaceutical additives, the content of the pharmaceutical additives is for example about 0.1 to about 70 % by weight, preferably about 1 to about 50 % by weight and more preferably about 20 to about 50 % by weight of the total solid content in the coating agent.

15 The amount of the coating agent applied is suitably selected depending on the shape of the solid preparation, the desired adhesion to mucosae, etc. For example, when the solid preparation is in the form of granules, the amount of the coating agent applied thereon is about 0.1 to
20 about 50 % by weight, preferably about 1 to about 20 % by weight, relative to the whole of the solid preparation. Further, when the solid preparation is in the form of finely divided particles, the amount of the coating agent applied thereon is about 0.1 to about 100 % by weight,
25 preferably about 1 to about 50 % by weight, relative to the

whole of the solid preparation.

As the coating method, it is possible to use any methods known in the art, for example pan coating, fluid coating, rolling coating etc. When the coating agent is a solution or dispersion containing water or an organic solvent, spray coating can also be used. The type of the organic solvent is not particularly limited, and use can be made e.g. alcohols such as methanol, ethanol and isopropyl alcohol; ketones such as acetone; halogenated hydrocarbons such as chloroform, dichloromethane and trichloroethane.

When the coating agent contains the polyglycerol fatty acid ester, the polyglycerol fatty acid ester and if necessary other additives may be coated by heating and melting them, then kneading and emulsifying the resultant mixture in water, spraying the resultant emulsion onto the matrix and drying it.

Further, when the coating agent contains the polyglycerol fatty acid ester, the matrix preheated with hot air in a device such as a coating pan may be coated therewith by introducing the coating agent into the device and then melting and extending it on the matrix.

The temperature for coating is usually about 25 to about 60°C, preferably about 25 to about 40°C.

The time necessary for coating is suitably selected in consideration of the coating method, the properties and

amount of the coating agent used, and the properties of the matrix.

The solid preparation may be in any form usable as a nasal agent, and the form of the preparation includes e.g.
5 finely divided particles, powder and granules. In particular, finely divided particles and powder are preferable.

The particle diameters of the finely divided particles are distributed such that for example, 75 to 500 μm
10 particles account for 85 weight % or more, 500 to 850 μm particles for 5 weight % or less, 850 μm or more particles for 0 weight %, and 74 μm or less particles for 10 weight % or less.

The particle diameters of the powder are distributed
15 such that for example, 500 to 850 μm particles account for 5 weight % or less, 500 μm or less particles for 95 weight % or more, and 850 μm or more particles for 0 weight %.

The particle diameters of the granules are distributed
20 such that for example, 500 to 1410 μm particles account for 90 weight % or more, and 177 μm or less particles for 5 weight % or less.

The solid preparation is preferably in a particle form, more preferably in a spherical form. The particle diameter
25 is selected from the range where the solid preparation can

be used as a nasal agent. The particle diameter of the solid preparation is preferably about 0.1 to about 1500 μm , more preferably about 0.1 to about 100 μm and most preferably about 5 to about 50 μm .

5 The most preferable form of using the matrix adhering to the nasal mucosa according to this invention is a preparation for nasal administration (preferably a spray) obtained by encapsulating the solid preparation (preferably finely divided particles or powder) obtained in the manner
10 described above, together with additives such as a stabilizer, a taste corrective, a suspending agent, an emulsifier, a perfume, a dispersant and a lubricant, into a suitable vessel and then sealing the vessel. Preferably, the jetted form of the spray is for example in the form of
15 spray, paste, foam or powder, and the powdery form is particularly preferable.

 The matrix adhering to the nasal mucosa according to this invention may be used after it is dissolved, suspended or emulsified in an aqueous solvent (for example, distilled
20 water, physiological saline, Ringer's solution) or an oil solvent (for example, vegetable oils such as olive oil, sesame oil, cottonseed oil and corn oil; propylene glycol etc.).

 The matrix adhering to the nasal mucosa according to
25 this invention is low-toxic and safely administered via the

nose into mammals (for example, humans, monkeys, dogs, cats, rabbits, cattle, horses, goats, rats, mice etc.).

The dose of the matrix adhering to the nasal mucosa according to this invention may be suitably determined in consideration of the type of the drug, the subject of administration, etc. For example, when the matrix adhering to the nasal mucosa according to this invention is administered as a spray into an adult (weighing about 50 kg) for the purpose of preventing and treating diseases such as encephalomyelitis etc., the daily dose of the matrix adhering to the nasal mucosa is usually about 1 to about 2000 mg and preferably about 20 to about 600 mg, more preferably about 20 to about 200 mg (or about 1 to about 1500 mg, preferably about 20 to about 500 mg and more preferably about 20 to 150 mg in terms of the drug). This dose may be administered in one to three portions.

The diseases to which the matrix adhering to the nasal mucosa according to this invention is applied are selected depending on the type of "the drug exerting its effect in the brain".

Best Mode for Carrying Out the Invention

Hereinafter, this invention is described in more detail by reference to the Examples, which however are not intended to limit this invention.

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Examples

Example 1

7.0 g behenic acid hexa(tetra)glyceride

5 (HB-310, produced by Sakamoto Yakuhin Kogyo Co., Ltd.) and
1.0 g hardened sesame oil [Lovely Wax 101 (LW-
101) produced by Freund Industrial Co., Ltd.] were weighed
and melted by heating at 84°C. To the resulting molten
mixture were added 1.0 g cephalixin and 1.0 g acrylate type
10 polymer (HIVISWAKO 104 produced by Wako Pure
Chemical Industries, Ltd.) in succession, and the mixture
was kept at 84 °C for 15 minutes under stirring. The
resulting molten mixture was dropped at a rate of 10 g/min.
onto an aluminum disk of 15 cm in diameter rotating at 9000
15 rpm, to give 6.8 g powder (spherical particles) having a
diameter of about 50 µm.

Example 2

8.0 g behenic acid hexa(tetra)glyceride.

20 (HB-310, produced by Sakamoto Yakuhin Co., Ltd.) was weighed
and melted by heating at 84°C. 1.0 g (S)-N-[2-(1,6,7,8-
tetrahydro-2H-indeno [5,4-b]furan-8-yl)ethyl] propionamide
(Compound A) and 1.0 g acrylate type polymer
(HIVISWAKO 104, Wako Pure Chemical Industries, Ltd.) were
25 added thereto in succession, and the mixture was dispersed

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by keeping it at 84°C for about 1 hour under stirring. The resulting molten mixture was dropped at a rate of 10 g/min. onto an aluminum disk of 15 cm in diameter rotating at 9000 rpm, to give about 50 µm spherical particles.

5

Experimental Example 1

10 mg of the particles (cephalexin content: 1 mg) obtained in Example 1 was charged into a polyethylene tube having an inner diameter of 0.58 mm and an outer diameter of 0.965 mm [PE50; produced by Nippon Becton Dickinson Ltd.], and the total amount of the powder in the tube was administered into the nasal cavity of each SD rat (9- to 10-week-old male) under anesthesia with ether.

15 Separately, 20 µl aqueous suspension of cephalexin (cephalexin content: 1 mg) was administered into the nasal cavity of each SD rat (9- to 10-week-old male) under anesthesia with ether, and this rat was used as the control.

20 One hour after administration, the concentrations of cephalexin in plasma and cerebrospinal fluid were measured by HPLC. The results are shown in Table 1.

Each concentration in the table shows an average concentration obtained using 4 rats.

Table 1

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	Concentration in plasma ($\mu\text{g/ml}$)	Concentration in cerebrospinal fluid ($\mu\text{g/ml}$)
Suspension	0.89	0.037
Powder in Example 1	0.77	0.326

As shown in Table 1, when the preparation of this invention was administered via the nose into the rat, the concentration of the drug in the cerebrospinal fluid was significantly higher than by the control suspension. That is, transfer of the drug into the brain was improved by the preparation of this invention.

Experimental Example 2

The particles obtained in Example 2 was charged into a polyethylene tube having an inner diameter of 0.58 mm and an outer diameter of 0.965 mm [PE50, produced by Nippon Becton Dickinson Ltd.], and then administered in a dose of 3 mg/rat into the nasal cavity of each SD male rat under anesthesia with ether. As the control, 25 μl suspension of Compound A was administered into the nasal cavity of each rat. The concentration of the drug in plasma for 2 hours after administration was measured, and its AUC was calculated. Further, the concentration of the drug in cerebrospinal fluid at 2 hours after administration was measured as an indicator of transfer of the drug into

the brain. The results are shown in Table 2.

Table 2

	AUC _{0-2h} (μg/ml)	Concentration in cerebrospinal fluid (ng/ml)
Suspension	1.57	9
Particles in Example 2	1.78	54

5 As shown in Table 2, when the preparation of this
invention was administered via the nose into the rat, the
concentration of the drug in the cerebrospinal fluid was
significantly higher than by the control suspension. That
is, transfer of the drug into the brain was improved by the
10 preparation of this invention.

Industrial Applicability

When "the drug exerting its effect in the brain" is
orally administered, transfer of said drug into the brain
15 is significantly restricted due to degradation with gastric
acid or enzyme, metabolism by the first pass effect, etc.
Further, when "the drug exerting its effect in the brain"
is subcutaneously or intravenously administered, transfer
of said drug into the brain is significantly restricted by
20 the blood-brain barrier.

By using the matrix adhering to the nasal mucosa
according to this invention, "the drug exerting its effect

in the brain" in said matrix can, without undergoing the above restriction, be transferred directly from the nasal cavity via the cerebrospinal fluid to brain tissues, thus achieving extremely high transfer of said drug into the
5 brain.

Furthermore, the matrix adhering to the nasal mucosa according to this invention is excellent in adhesion to the nasal mucosa and can be retained on the nasal mucosa for a prolonged period of time, thus allowing "the drug exerting
10 its effect in the brain" to be supplied continuously into the brain for a prolonged period of time.

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CLAIMS:

1. A matrix for adhering to nasal mucosa and for allowing improved transfer into the brain of a drug exerting its effect in the brain, the matrix comprising:

5 a polyglycerol fatty acid ester;

the drug exerting its effect in the brain; and

a pharmaceutically acceptable polymeric viscogenic substance which is rendered viscous when contacted with water to show adhesion to the nasal mucosa.

10 2. The matrix according to claim 1, wherein the polyglycerol fatty acid ester is an ester of a polyglycerol having a polymerization degree of 2 to 20 and a fatty acid having 12 to 22 carbon atoms.

3. The matrix according to claim 1 or 2, wherein the
15 polyglycerol fatty acid ester has a hydrophile-lipophile balance (HLB) of 1 to 9.

4. The matrix according to any one of claims 1 to 3, which comprises about 40 to about 95 % by weight of the polyglycerol fatty acid ester.

20 5. The matrix according to any one of claims 1 to 4, wherein the polyglycerol fatty acid ester has a molecular weight of 300 to 3000.

6. The matrix according to any one of claims 1 to 5, wherein the polyglycerol fatty acid ester has a melting
25 point of 30 to 75°C.

7. The matrix according to any one of claims 1 to 6, wherein the polymeric viscogenic substance is an acrylate polymer or a salt thereof.

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8. The matrix according to claim 7, wherein the acrylate polymer or the salt thereof has a molecular weight of 1,000,000 to 6,000,000.

9. The matrix according to any one of claims 1 to 8,
5 which comprises about 4 to about 30 % by weight of the viscogenic substance.

10. The matrix according to any one of claims 1 to 9, which further comprises a swelling agent for the viscogenic substance.

10 11. The matrix according to claim 10, wherein the swelling agent for the viscogenic substance is at least one member selected from the group consisting of curdlan and low-substituted hydroxypropylmethyl cellulose.

12. The matrix according to any one of claims 1 to 11,
15 which further comprises a lipid.

13. The matrix according to claim 12, wherein the lipid has a melting point of 40°C to 90°C.

14. The matrix according to any one of claims 1 to 13, wherein the drug exerting its effect in the brain is a drug
20 hardly transferring into the brain when not comprised in the matrix.

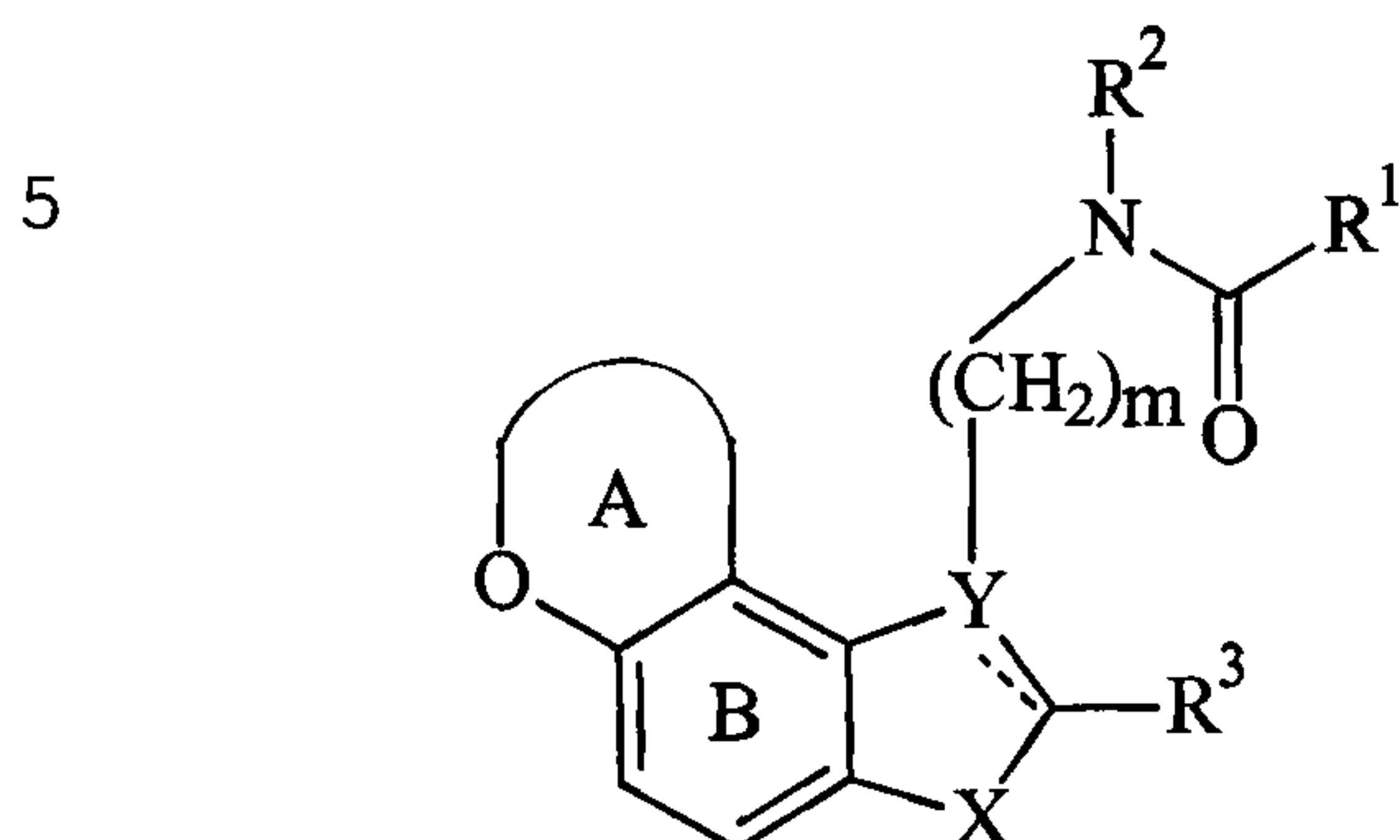
15. The matrix according to any one of claims 1 to 13, wherein the drug exerting its effect in the brain is a sedative-hypnotic agent, an anti-anxiety agent, an
25 antidepressant agent or an agent for treating Alzheimer's disease.

16. The matrix according to any one of claims 1 to 13, wherein the drug exerting its effect in the brain is a compound having a melatonin receptor antagonist action.

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17. The matrix according to any one of claims 1 to 13, wherein the drug exerting its effect in the brain is a compound represented by the formula:



or a pharmaceutically acceptable salt thereof,

10 wherein:

R^1 is a hydrocarbon group which may have a substituent group, an amino group which may have a substituent group or a heterocyclic group which may have a substituent group;

15 R^2 is a hydrogen atom or a hydrocarbon group which may have a substituent group;

R^3 is a hydrogen atom or a hydrocarbon group which may have a substituent group or a heterocyclic group which may have a substituent group;

20 X is CHR^4 , NR^4 , O or S where R^4 represents a hydrogen atom or a hydrocarbon group which may have a substituent group;

Y is C, CH or N provided that when X represents CH_2 , Y is C or CH;

25 --- is a single or double bond;

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ring A is a 5- to 7-membered, oxygen atom-containing heterocyclic ring which may have a substituent group;

ring B is a benzene ring which may have a substituent group; and

m is an integer of 1 to 4.

18. The matrix according to any one of claims 1 to 13, wherein the drug exerting its effect in the brain is (S)-N-[2-(1,6,7,8-tetrahydro-2H-indeno[5,4-b]furan-8-yl)ethyl]propionamide.

19. The matrix according to any one of claims 1 to 13, wherein the drug exerting its effect in the brain is (S)-N-[2-(1,6,7,8-tetrahydro-2H-indeno[5,4-b]furan-8-yl)ethyl]acetamide.

20. The matrix according to any one of claims 1 to 19, which comprises about 0.1 to about 50 % by weight of the drug exerting its effect in the brain.

21. A solid preparation comprising the matrix as defined in any one of claims 1 to 20.

22. The solid preparation according to claim 21, which is finely divided particles or powder.

23. The solid preparation according to claim 22, which is spherical.

24. The solid preparation according to claim 22 or 23, which has a particle diameter of about 0.1 to about 100 μm .

25. A method of producing a matrix containing a drug exerting its effect in the brain and having improved transfer of the drug through nasal mucosa and into the brain,

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which method comprises admixing the drug with a polyglycerol fatty acid ester and a pharmaceutically acceptable viscogenic substance which is rendered viscous when contacted with water to adhere to the nasal mucosa, to form
5 the matrix in which the polyglycerol fatty acid ester, the viscogenic substance and the drug are uniformly dispersed.

26. The method according to claim 25, wherein the polyglycerol fatty acid is melted; then the drug and the viscogenic substance are added simultaneously or separately;
10 and the resulting mixture is spray cooled to obtain the matrix as finely divided particles.

27. Use of a polyglycerol fatty acid ester, a drug exerting its effect in the brain, and a pharmaceutically acceptable polymeric viscogenic substance which is rendered
15 viscous when contacted with water to show adhesion to nasal mucosa, in producing a matrix adhering to the nasal mucosa which allows improved transfer of the drug into brain.

28. A matrix for adhering to nasal mucosa and for allowing improved transfer into brain of a drug exerting its
20 effect in the brain, which comprises the following ingredients, based on the matrix:

(A) 5 to 98 % by weight of a polyglycerol fatty acid ester, wherein the polyglycerol has a degree of polymerization of 2 to 50, the fatty acid contains 8 to 40
25 carbon atoms and the polyglycerol fatty acid ester has a hydrophilic-lipophilic balance (HLB) of 1 to 22 and a melting point of 15 to 80°C,

(B) the drug exerting its effect in the brain in such an amount that the polyglycerol fatty acid is 0.01
30 to 10,000 parts by weight relative to 1 part by weight of the drug, and

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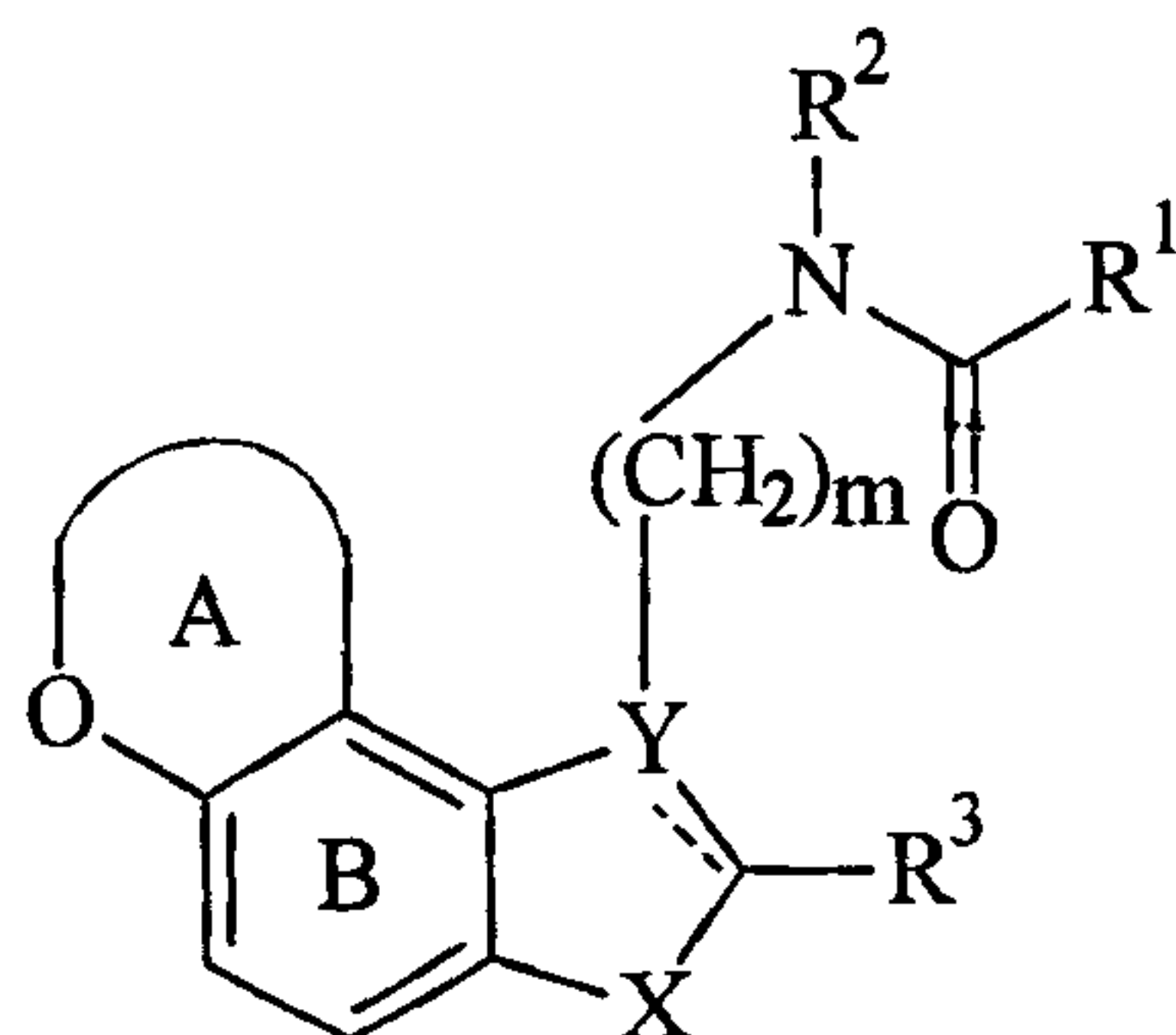
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(C) 0.5 to 45 % by weight of a pharmaceutically acceptable polymeric viscogenic substance which is rendered viscous when contacted with water to show adhesion to the nasal mucosa and which has a viscosity of 3 to 50,000 cps as measured in a 2 % aqueous solution at 20°C with a Brookfield viscometer,

wherein the ingredients (A), (B) and (C) are uniformly dispersed with each other in particles having a diameter of 0.1 to 1,500 μm .

29. The matrix according to claim 28, wherein the viscogenic substance is an acrylate polymer or a salt thereof.

30. The matrix according to claim 28 or 29, wherein the drug exerting its effect in the brain is a compound represented by the formula:



20

or a pharmaceutically acceptable salt thereof,

wherein R^1 , R^2 , R^3 , X, Y, ring A, ring B and m are as defined in claim 17.

31. The matrix according to claim 28 or 29, wherein the drug exerting its effect in the brain is (S)-N-[2-(1,6,7,8-tetrahydro-2H-indeno[5,4-b]furan-8-yl)ethyl]propionamide.

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32. The matrix according to claim 28 or 29, wherein the drug exerting its effect in the brain is (S)-N-[2-(1,6,7,8-tetrahydro-2H-indeno[5,4-b]furan-8-yl)ethyl]acetamide.

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