

**(12) PATENT**  
**(19) AUSTRALIAN PATENT OFFICE**

**(11) Application No. AU 199925478 B2**  
**(10) Patent No. 766088**

(54) Title  
**Indole derivatives and medicinal compositions containing the same**

(51)<sup>7</sup> International Patent Classification(s)  
**C07D 209/08 A61K 031/40**

(21) Application No: **199925478**

(22) Application Date: **1999.02.19**

(87) WIPO No: **WO99/43652**

(30) Priority Data

|                 |                   |              |
|-----------------|-------------------|--------------|
| (31) Number     | (32) Date         | (33) Country |
| <b>10-90572</b> | <b>1998.02.27</b> | <b>JP</b>    |

(43) Publication Date : **1999.09.15**

(43) Publication Journal Date : **1999.11.11**

(44) Accepted Journal Date : **2003.10.09**

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(56) Related Art  
**JP 7-330726**  
**US 5387603**

PCT

世界知的所有権機関  
国際事務局

特許協力条約に基づいて公開された国際出願

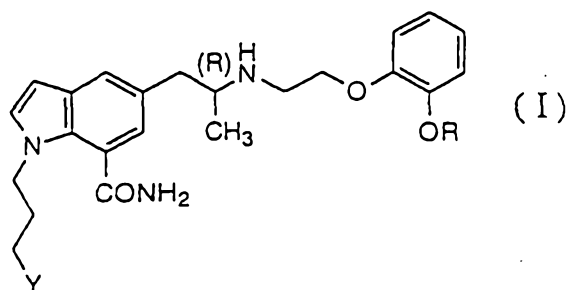
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| <p>(51) 国際特許分類6<br/>C07D 209/08, A61K 31/40</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | <p>A1</p> | <p>(11) 国際公開番号<br/>WO99/43652</p> <p>(43) 国際公開日<br/>1999年9月2日 (02.09.99)</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
| <p>(21) 国際出願番号<br/>PCT/JP99/00732</p> <p>(22) 国際出願日<br/>1999年2月19日 (19.02.99)</p> <p>(30) 優先権データ<br/>特願平10/90572      1998年2月27日 (27.02.98)      JP</p> <p>(71) 出願人 (米国を除くすべての指定国について)<br/>キッセイ薬品工業株式会社<br/>(KISSEI PHARMACEUTICAL CO., LTD.)[JP/JP]<br/>〒399-8710 長野県松本市芳野19番48号 Nagano, (JP)</p> <p>(72) 発明者 ; および</p> <p>(75) 発明者 / 出願人 (米国についてのみ)<br/>北澤牧雄(KITAZAWA, Makio)[JP/JP]<br/>〒399-0011 長野県松本市寿北2-2-6 Nagano, (JP)<br/>山口敏章(YAMAGUCHI, Toshiaki)[JP/JP]<br/>〒390-0851 長野県松本市大字島内3868-1<br/>フレグランスコンサートA102 Nagano, (JP)<br/>宮田廣志(MIYATA, Hiroshi)[JP/JP]<br/>〒390-0316 長野県松本市大字原453-1 Nagano, (JP)<br/>味澤幸義(AJISAWA, Yukiyoishi)[JP/JP]<br/>〒394-0044 長野県岡谷市湊4-17-1 Nagano, (JP)</p> |           | <p>(81) 指定国    AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, 欧州特許 (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI特許 (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG), ARIPO特許 (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), ユーラシア特許 (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM)</p> <p>添付公開書類<br/>国際調査報告書</p> <div data-bbox="1002 927 1390 1137" style="border: 1px solid black; padding: 10px; text-align: center;"> <p>IP AUSTRALIA</p> <p>15 SEP 1999</p> <p>R E C E I V E D</p> </div> |
| <p>(54)Title:    INDOLE DERIVATIVES AND MEDICINAL COMPOSITIONS CONTAINING THE SAME</p> <p>(54)発明の名称    インドール誘導体および当該誘導体を含有する医薬品組成物</p> <div data-bbox="491 1417 1050 1666" style="text-align: center;"> <p>(I)</p> </div> <p>(57) Abstract</p> <p>Indole derivatives represented by general formula (I) or pharmacologically acceptable salts thereof which have a remarkable and long-lasting effect of lowering ocular tension and thus are useful as drugs for lowering ocular tension. In said formula, R represents ethyl or 2,2,2-trifluoroethyl; Y represents hydroxy or pivaloyloxy; and the carbon atom marked with (R) means one having the R-configuration.</p>                        |           |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |

# ABSTRACT

The present invention relates to indole derivatives represented by the general formula:



5

(wherein R represents an ethyl group or a 2,2,2-trifluoroethyl group; Y represents a hydroxy group or a pivaloyloxy group; and the carbon atom marked with (R) represents a carbon atom in (R) configuration) and pharmaceutically acceptable salts thereof, which have potent and prolonged reducing effects on intraocular pressure and are useful as agents for lowering intraocular pressure.

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## DESCRIPTION

### INDOLE DERIVATIVES AND PHARMACEUTICAL COMPOSITIONS COMPRISING THE SAME

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#### **Technical Field**

The present invention relates to novel indole derivatives and pharmaceutically acceptable salts thereof which are useful as medicaments.

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#### **Background Art**

Up to this time, for example, Timolol maleate and Isopropyl unoprostone are known as compounds that have been used as agents for lowering intraocular pressure.

15

Recently, Bunazosin hydrochloride, which has  $\alpha_1$ -adrenoceptor blocking effect (hereinafter referred to as  $\alpha_1$ -blocking effect) quite different from the actions of these compounds, has been developed as an agent for the treatment of glaucoma and it is attracting public attention. However,

20

Bunazosin hydrochloride was primarily developed as an agent for the treatment of hypertension. Therefore, Bunazosin hydrochloride has potent action on the blood pressure and it is wondered that it might induce side effects such as hypotension and orthostatic hypotension.

25

Generally, most agents for lowering intraocular pressure are topically applied as eyedrops. Even in this case an active

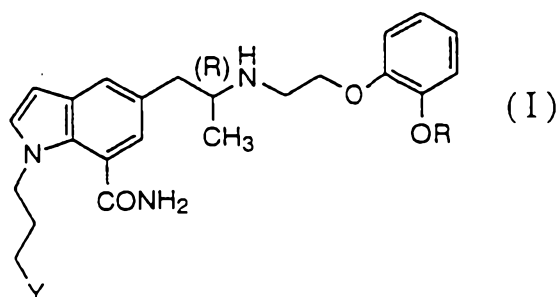
component distributes to all over the body via the blood flow and it is expected that it shows systemic action. Therefore, it is desired that expected systemic side effects are minimized even in topical administration.

5           Compounds which are absorbed into eyes immediately after the application and act for a long period are most preferable so as to act topically as much as possible.

          Consequently, compounds which have potent reducing effect on intraocular pressure with less incidence of side  
10 effects such as hypotension and orthostatic hypotension, are rapidly absorbed into eyes after the instillation and act for a long period are mostly recommended as agents for lowering intraocular pressure.

## 15   **Disclosure of the Invention**

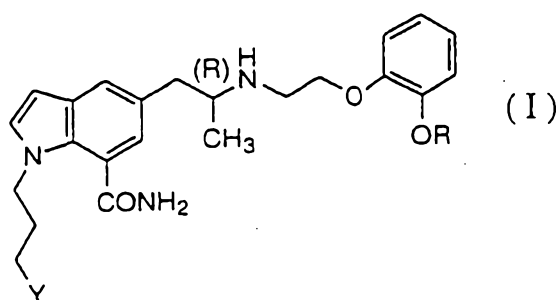
          The present invention relates to an indole derivative represented by the general formula:



(wherein R represents an ethyl group or a 2,2,2-trifluoroethyl  
20 group; Y represents a hydroxy group or a pivaloyloxy group with the proviso that Y represents a pivaloyloxy group when R represents a 2,2,2-trifluoroethyl group; and the carbon atom

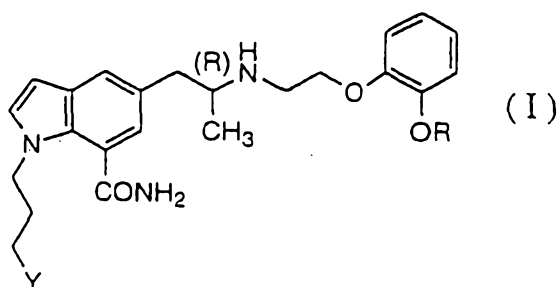
marked with (R) represents a carbon atom in (R) configuration) or a pharmaceutically acceptable salts thereof.

The present invention relates to a pharmaceutical composition comprising an indole derivative represented by the  
5 general formula:



(wherein R represents an ethyl group or a 2,2,2-trifluoroethyl group; Y represents a hydroxy group or a pivaloyloxy group with the proviso that Y represents a pivaloyloxy group when R  
10 represents a 2,2,2-trifluoroethyl group; and the carbon atom marked with (R) represents a carbon atom in (R) configuration) or a pharmaceutically acceptable salt thereof.

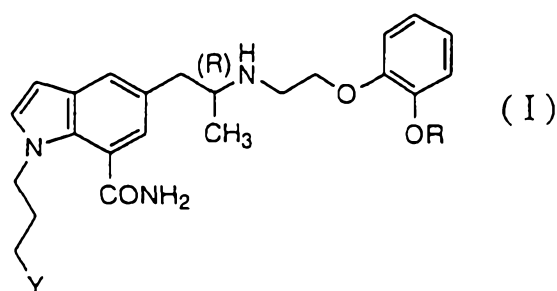
The present invention relates to an agent for lowering intraocular pressure which comprises as the active ingredient  
15 an indole derivative represented by the general formula:



(wherein R represents an ethyl group or a 2,2,2-trifluoroethyl group; Y represents a hydroxy group or a pivaloyloxy group; and

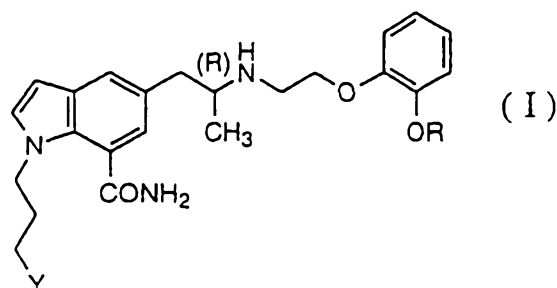
the carbon atom marked with (R) represents a carbon atom in (R) configuration) or a pharmaceutically acceptable salt thereof.

The present invention relates to an agent for the prevention or treatment of glaucoma or ocular hypertension  
5 which comprises as the active ingredient an indole derivative represented by the general formula:



(wherein R represents an ethyl group or a 2,2,2-trifluoroethyl group; Y represents a hydroxy group or a pivaloyloxy group; and  
10 the carbon atom marked with (R) represents a carbon atom in (R) configuration) or a pharmaceutically acceptable salt thereof.

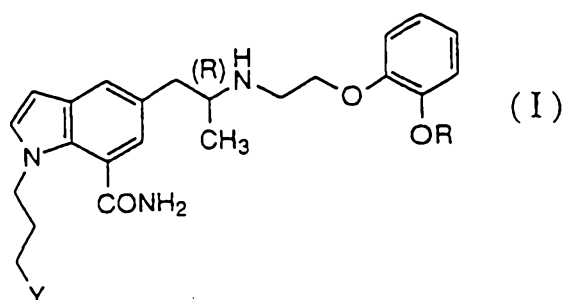
The present invention relates to a method for the prevention or treatment of glaucoma or ocular hypertension which comprises administering a therapeutically effective  
15 amount of an indole derivative represented by the general formula:



(wherein R represents an ethyl group or a 2,2,2-trifluoroethyl

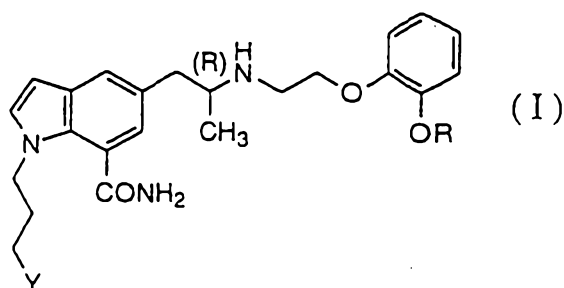
group; Y represents a hydroxy group or a pivaloyloxy group; and the carbon atom marked with (R) represents a carbon atom in (R) configuration) or a pharmaceutically acceptable salt thereof.

The present invention relates to a use of an indole  
5 derivative represented by the general formula:



(wherein R represents an ethyl group or a 2,2,2-trifluoroethyl group; Y represents a hydroxy group or a pivaloyloxy group; and the carbon atom marked with (R) represents a carbon atom in (R)  
10 configuration) or a pharmaceutically acceptable salt thereof for the manufacture of a pharmaceutical composition for the prevention or treatment of glaucoma or ocular hypertension.

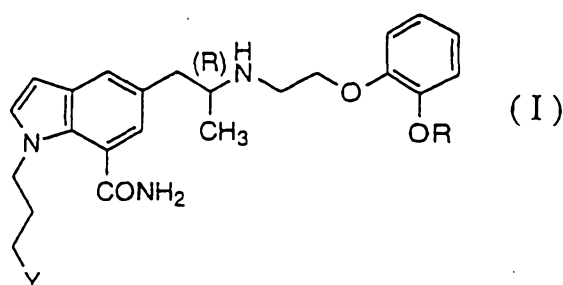
The present invention relates to a use of an indole derivative represented by the general formula:



15 (wherein R represents an ethyl group or a 2,2,2-trifluoroethyl group; Y represents a hydroxy group or a pivaloyloxy group; and the carbon atom marked with (R) represents a carbon atom in (R)

configuration) or a pharmaceutically acceptable salt thereof as an agent for the prevention or treatment of glaucoma or ocular hypertension.

Furthermore, the present invention relates a process for the manufacture of a pharmaceutical composition for the prevention or treatment of glaucoma or ocular hypertension, characterized in the use, as an essential constituent of said pharmaceutical composition, of an indole derivative represented by the general formula:



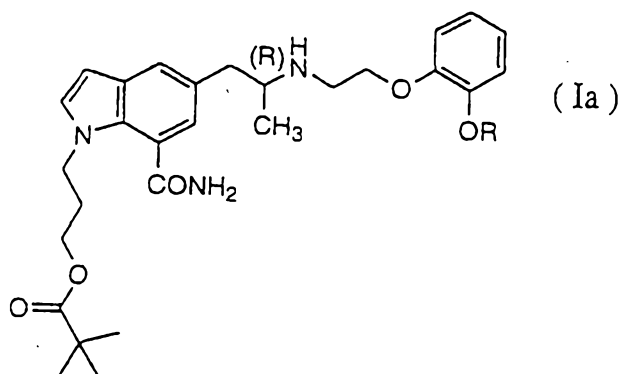
(wherein R represents an ethyl group or a 2,2,2-trifluoroethyl group; Y represents a hydroxy group or a pivaloyloxy group; and the carbon atom marked with (R) represents a carbon atom in (R) configuration) or a pharmaceutically acceptable salt thereof.

### Best Mode for Carrying Out the Invention

The present inventors have studied in order to find drugs which have potent and prolonged  $\alpha_1$ -blocking effect with less side effects such as hypotension and orthostatic hypotension and with high permeability into eyes. As a result, it has been found that (R)-1-(3-hydroxypropyl)-5-[2-[[2-[2-(2,2,2-trifluoroethoxy)phenoxy]ethyl]amino]propyl]-1H-indole-7-

carboxamide (hereinafter referred to as Compound A), one of indole derivatives which were previously developed as agents for the treatment of dysuria having selective suppressive effect on urethral contractions with less affecting the blood pressure (published Japanese patent application (*Kokai*) No. Hei 7-330726), and (R)-5-[2-[[2-(2-ethoxyphenoxy)ethyl]-amino]propyl]-1-(3-hydroxypropyl)-1*H*-indole-7-carboxamide (hereinafter referred to as Compound B) hydrochloride have extremely potent  $\alpha_1$ -blocking effect, more than 70-fold stronger than Bunazosin hydrochloride, with less incidence of side effects such as hypotension and orthostatic hypotension and that these compounds are expected to act for a long period because of low excretion rate after the permeation into eyes and are useful as preferred agents for lowering intraocular pressure.

Furthermore, because Compounds A and B have poor permeability of membranes such as cornea, the present inventors have studied in order to find derivatives which have high membrane permeability and rapidly convert into the poorly membrane permeable Compound A or B after the permeation. As a result, it has been found surprisingly that pivalic acid ester derivatives represented by the general formula:



(wherein R represents an ethyl group or a 2,2,2-trifluoroethyl group; and the carbon atom marked with (R) represents a carbon atom in (R) configuration) have extremely high membrane permeability, are rapidly converted into Compound A or B having poor membrane permeability by hydrolase after the permeation and are extremely stable in aqueous solution which is normal form of eyedrops, thereby forming the basis of the present invention.

Namely, the present inventors have found that Compounds A and B have potent  $\alpha_1$ -blocking effect and are preferred compounds as agents for lowering intraocular pressure. However, these compounds have poor corneal permeability and their concentration in aqueous humor is fairly low when these compounds are topically applied as eyedrops. Therefore, the present inventors have extensively studied in order to find the way to obtain fully drug concentration in aqueous humor even when applying as eyedrops.

In order to find derivatives of Compound A or B which are easily converted into Compound A or B respectively in the event of the permeation of cornea or in aqueous humor and are

able to show their effects rapidly, the present inventors have converted Compound A or B into various derivatives and assessed their facility of cleavage by endogenous hydrolase by measuring ratio of conversion into Compound A or B in the blood with the  
5 time course. As a result, for example, it has been found surprisingly that ratios of conversion of some ester derivatives of Compound A into Compound A after 30 minutes in the blood were extremely low, about 12 % in the case of the corresponding 2-ethylbutyrate derivative, about 4 % in the case  
10 of the corresponding 2,2-dimethylvalerate derivative, about 2 % in the case of the corresponding  $\alpha,\alpha$ -dimethylphenylacetate derivative and about 6 % in the case of the corresponding 2,2-dimethylbutyrate derivative, respectively. While the corresponding pivalate derivative was already converted into  
15 Compound A in the ratio of about 67 % after 30 minutes and almost Compound A after 2 hours. Thus, the present inventors have found that the pivalate derivatives represented by the above general formula (Ia) of the present invention are different from other carboxylate derivatives and are specific compounds  
20 which are very easily converted into Compound A or B by endogenous hydrolase in cornea or aqueous humor.

Then, the present inventors have measured drug concentration in aqueous humor after instillation on rabbit eyes with the time course in order to confirm corneal  
25 permeability of this pivalate derivative. For example, in the case of instillation on eyes of pivalate derivative

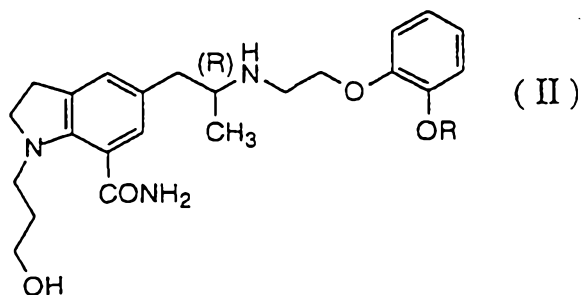
hydrochloride of Compound B, drug concentration of Compound B in aqueous humor was about 70 times higher after 20 minutes and about 27 times higher after 2 hours than that in the case of the instillation of Compound B hydrochloride. Thus, the  
5 pivalate derivatives represented by the above general formula (Ia) of the present invention are extremely excellent compounds in corneal permeability and long-acting compounds.

In addition, in the above experiment, pivalate derivative of Compound B was rapidly converted into Compound B in the event  
10 of the permeation of cornea or in aqueous humor and could not be detected in aqueous humor at all even after 20 minutes. Accordingly, the pivalate derivatives represented by the above general formula (Ia) of the present invention are permeable rapidly and favorably through corneal and have property to be  
15 converted into Compound A or B rapidly. Therefore, these are extremely preferred compounds to reveal the effect of Compound A or B surely and rapidly. In fact, in an experiment using rabbits, it was confirmed that the pivalate derivatives represented by the above general formula (Ia) show very potent  
20 and prolonged reducing effect on intraocular pressure. Accordingly, the pivalate derivatives represented by the above general formula (Ia) are extremely useful compounds as eyedrops for the prevention or treatment of glaucoma or ocular hypertension.

25 Furthermore, the pivalate derivatives represented by the above general formula (Ia) of the present invention are hardly

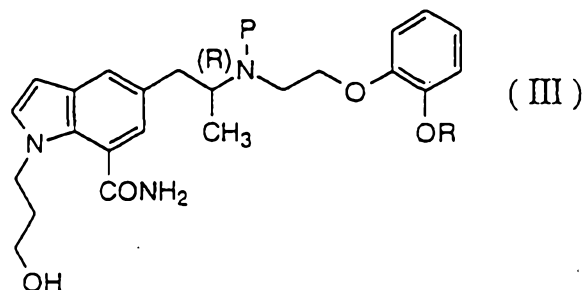
decomposed in the state of eyedrops under high temperature and are extremely stable compounds. For example, when pivalate derivative of Compound A was allowed to stand for about 1 month at 40°C in the state of aqueous solution, only about 0.1 % of this compound was decomposed into Compound A. Similarly, about 5 1.1 % of this compound was decomposed into Compound A even at 70°C. Thus, the pivalate derivatives represented by the above general formula (Ia) of the present invention are extremely stable compounds in the state of aqueous solution and eyedrops 10 containing the said compounds are excellent in long storage stability. Therefore, the pivalate derivatives represented by the above general formula (Ia) of the present invention are highly suitable compounds to topical application as eyedrops.

The compounds represented by the above general formula 15 (I) of the present invention, for example, can be prepared by protecting the secondary nitrogen atom of an indoline derivative represented by the general formula:

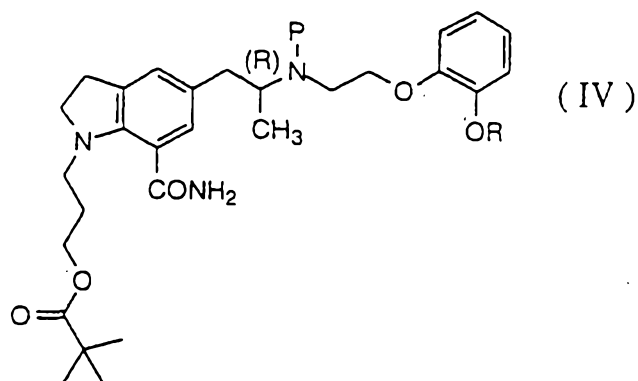


(wherein R and the carbon atom marked with (R) have the same 20 meanings as defined above) with a protecting group such as a tert-butoxycarbonyl group in the usual way, allowing to oxidize the indoline ring of the resulting compound in the presence

of a metal catalyst such as palladium carbon and ammonium formate to prepare an indole derivative represented by the general formula:



- 5 (wherein P represents an amino-protective group; and R and the carbon atom marked with (R) have the same meanings as defined above), allowing to react with a pivaloyl halide in the presence of a base as occasion demands and removing the protective group in the usual way.
- 10 Of the compounds represented by the above general formula (I) of the present invention, the pivalate derivatives represented by the above general formula (Ia) can be also prepared by protecting the secondary nitrogen atom of an indoline derivative represented by the above general formula
- 15 (II) with a protecting group such as a *tert*-butoxycarbonyl group in the usual way, allowing the resulting compound to react with a pivaloyl halide in the presence of a base to prepare an indoline derivative represented by the general formula:



(wherein P, R and the carbon atom marked with (R) have the same meanings as defined above), allowing to oxidize the indoline ring of the resulting compound in the presence of a metal catalyst such as palladium carbon and ammonium formate, and removing the protective group in the usual way.

The indole derivatives represented by the above general formula (I) of the present invention can be converted into their pharmaceutically acceptable salts in the usual way. Examples of such salts include acid addition salts with mineral acids (e.g., hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid, nitric acid, phosphoric acid and the like) and acid addition salts with organic acids (e.g., formic acid, acetic acid, methanesulfonic acid, benzenesulfonic acid, p-toluenesulfonic acid, propionic acid, citric acid, succinic acid, tartaric acid, fumaric acid, butyric acid, oxalic acid, malonic acid, maleic acid, lactic acid, malic acid, salicylic acid, benzoic acid, adipic acid, carbonic acid, glutamic acid, aspartic acid and the like).

When the indole derivatives represented by the above general formula (I) of the present invention and

pharmaceutically acceptable salts thereof are employed in the practical treatment, various administration forms are applicable. Among the forms, topical administration using eyedrops and the like is preferred. Eyedrops can be suitably formulated in accordance with conventional methods. For example, eyedrops can be prepared by adding the pivalate derivatives represented by the above general formula (Ia) of the present invention to sterile purified water, dissolving by adding suitably pharmaceutical additives such as antiseptics, isotonicities and buffers, if necessary, under warming and filtering to remove dusts and/or microbes.

The dosage is appropriately decided depending on the sex, age, body weight, degree of symptoms and the like of each patient to be treated. For example, instillation on eyes of solution ranging from 0.001 to 0.5 % 1 to 3 times per day is preferred in the case of eyedrops.

### Examples

The present invention is further illustrated in more detail by way of the following Reference Examples, Examples and Test Examples. The present invention is not limited thereto.

#### Reference Example 1

(R)-3-[7-Cyano-5-[2-[[2-(2-ethoxyphenoxy)ethyl]amino]-propyl]-2,3-dihydro-1H-indol-1-yl]propyl benzoate

To a solution of potassium carbonate (32.3g) in distilled water (120ml) was added ethyl acetate (120ml), and (R)-3-[5-(2-aminopropyl)-7-cyano-2,3-dihydro-1H-indol-1-yl]propyl benzoate L-tartrate (12.0g) was added portionwise to the mixture  
5 with stirring. After reaction for 1 hour, the reaction mixture was extracted with ethyl acetate, and the ethyl acetate layer was washed with 10% aqueous potassium carbonate solution and brine subsequently, and dried over anhydrous sodium sulfate. The solvent was removed *in vacuo* to give (R)-3-[5-(2-aminopropyl)-7-cyano-2,3-dihydro-1H-indol-1-yl]propyl  
10 benzoate (8.98g) as a brown oil.

The resulting (R)-3-[5-(2-aminopropyl)-7-cyano-2,3-dihydro-1H-indol-1-yl]propyl benzoate (8.98g) was dissolved in *tert*-butanol (43ml). 2-(2-Ethoxyphenoxy)ethyl methane-  
15 sulfonate (7.02g) and sodium carbonate (2.86g) were added to the solution, and the mixture was heated under reflux overnight. The reaction mixture was concentrated *in vacuo*, a saturated aqueous sodium bicarbonate solution was added to the residue and the mixture was extracted with ethyl acetate. The ethyl  
20 acetate layer was washed with a saturated aqueous sodium bicarbonate solution and brine subsequently and dried over anhydrous sodium sulfate. The solvent was removed *in vacuo*, the residue was purified by column chromatography on silica gel (eluent: ethyl acetate and ethyl acetate/methanol=100/6).  
25 Azeotropic concentration of the resulting oily material gave (R)-3-[7-cyano-5-[2-[[2-(2-ethoxyphenoxy)ethyl]amino]-

propyl]-2,3-dihydro-1H-indol-1-yl]propyl benzoate (7.46g) as a brown oil.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ ppm: 1.04 (d, J=6.0Hz, 3H), 1.41 (t, J=6.9Hz, 3H), 2.10-2.20 (m, 2H), 2.42 (dd, J=13.6, 6.9Hz, 1H), 2.63 (dd, J=13.6, 6.0Hz, 1H), 2.80-3.10 (m, 5H), 3.50-3.60 (m, 2H), 3.75 (t, J=7.3Hz, 2H), 4.00-4.15 (m, 4H), 4.40-4.50 (m, 2H), 6.85-7.00 (m, 6H), 7.40-7.50 (m, 2H), 7.50-7.60 (m, 1H), 8.00-8.10 (m, 2H)

Specific Rotation:  $[\alpha]_D^{27} = -14.8^\circ$  (c=1.04, Methanol)

10

Reference Example 2

(R)-5-[2-[[2-(2-Ethoxyphenoxy)ethyl]aminolpropyl]-1-(3-hydroxypropyl)-2,3-dihydro-1H-indole-7-carbonitrile

(R)-3-[7-Cyano-5-[2-[[2-(2-ethoxyphenoxy)ethyl]-aminolpropyl]-2,3-dihydro-1H-indol-1-yl]propyl benzoate (7.23g) was dissolved in methanol (46ml) and the solution was added to a solution of potassium hydroxide (1.54g) in distilled water (9.2ml). After being heated under reflux for 1 hour, the reaction mixture was concentrated *in vacuo*. Distilled water (100ml) was added to the residue and the resulting mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with a saturated aqueous sodium bicarbonate solution and brine, and dried over anhydrous sodium sulfate. The solvent was removed *in vacuo*, and the residue was dissolved in toluene (30ml) and the toluene was removed *in vacuo* to give (R)-5-[2-[[2-(2-ethoxyphenoxy)ethyl]aminolpropyl]-1-(3-

hydroxypropyl)-2,3-dihydro-1H-indole-7-carbonitrile (6.06g)  
as a pale brown oil.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ ppm: 1.05 (d, J=6.0Hz, 3H), 1.41 (t, J=6.9Hz, 3H), 1.50-1.90 (m, 1H), 1.85-2.00 (m, 2H), 2.43 (dd, J=13.6, 6.9Hz, 1H), 2.63 (dd, J=13.6, 6.3Hz, 1H), 2.80-3.10 (m, 5H), 3.50-3.60 (m, 2H), 3.67 (t, J=7.3Hz, 2H), 3.75-3.85 (m, 2H), 4.00-4.15 (m, 4H), 6.85-7.30 (m, 6H)

Specific Rotation:  $[\alpha]_D^{27} = -19.4^\circ$  (c=1.06, Methanol)

#### 10 Reference Example 3

(R)-5-[2-[[2-(2-Ethoxyphenoxy)ethyl]amino]propyl]-1-(3-hydroxypropyl)-2,3-dihydro-1H-indole-7-carboxamide

(R)-5-[2-[[2-(2-Ethoxyphenoxy)ethyl]amino]propyl]-1-(3-hydroxypropyl)-2,3-dihydro-1H-indole-7-carbonitrile

15 (5.95g) was dissolved in dimethylsulfoxide (16.4ml), and 5N sodium hydroxide solution (0.25ml) was added to the solution. To the mixture was added 30% hydrogen peroxide (1.55ml) keeping inner temperature below 25°C, and the mixture was stirred overnight at an inner temperature of 25-30°C. A solution of 20 sodium sulfite (2.39g) in distilled water (82ml) was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with a saturated aqueous sodium bicarbonate solution, distilled water and brine subsequently, and dried over anhydrous sodium sulfate. The 25 solvent was removed *in vacuo*, the residue was recrystallized from ethyl acetate to give (R)-5-[2-[[2-(2-ethoxyphenoxy)-

ethyl]amino]propyl]-1-(3-hydroxypropyl)-2,3-dihydro-1H-indole-7-carboxamide (4.72g).

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ ppm: 1.07 (d, J=6.2Hz, 3H), 1.37 (t, J=7.0Hz, 3H), 1.60-1.85 (m, 3H), 2.54 (dd, J=13.6, 6.5Hz, 1H), 2.68 (dd, J=13.6, 6.4Hz, 1H), 2.85-3.10 (m, 6H), 3.19 (t, J=6.6Hz, 2H), 3.35-3.45 (m, 2H), 3.75 (t, J=5.4Hz, 2H), 3.95-4.20 (m, 4H), 5.70 (br s, 1H), 6.66 (br s, 1H), 6.80-6.95 (m, 4H), 7.02 (s, 1H), 7.16 (s, 1H)

Specific Rotation:  $[\alpha]_D^{27} = -15.3^\circ$  (c=0.98, Methanol)

10

Reference Example 4

tert-Butyl (R)-N-[2-[7-carbamoyl-1-(3-hydroxypropyl)-2,3-dihydro-1H-indol-5-yl]-1-methylethyl]-N-[2-(2-ethoxyphenoxy)ethyl]carbamate

15

(R)-5-[2-[[2-(2-Ethoxyphenoxy)ethyl]amino]propyl]-1-(3-hydroxypropyl)-2,3-dihydro-1H-indole-7-carboxamide (10.9g) was dissolved in methylene chloride (100ml), and a solution of di-tert-butyl dicarbonate (5.87g) in methylene chloride (25ml) was added dropwise to the solution with stirring under ice-cooling. After being stirred for 30 minutes under the same condition, the reaction mixture was stirred for 10 hours at room temperature. The reaction mixture was concentrated *in vacuo*, and the residue was dissolved in ethyl acetate (150ml). The solution was washed with 10% aqueous citric acid solution, a saturated aqueous sodium bicarbonate solution and brine subsequently, and dried over anhydrous

20

25

sodium sulfate. The solvent was removed *in vacuo* to give pale brown amorphous *tert*-butyl (*R*)-*N*-[2-[7-carbamoyl-1-(3-hydroxypropyl)-2,3-dihydro-1*H*-indol-5-yl]-1-methylethyl]-*N*-[2-(2-ethoxyphenoxy)ethyl]carbamate (10.2g).

5 <sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ ppm: 1.20-1.50 (m, 15H), 1.70-1.85 (m, 2H), 2.50-4.40 (m, 18H), 5.75 (br h, 1H), 6.63 (br s, 1H), 6.80-7.20 (m, 6H)

Specific Rotation:  $[\alpha]_D^{27} = -50.4^\circ$  (c=1.27, Methanol)

#### 10 Example 1

(*R*)-5-[2-[[2-(2-Ethoxyphenoxy)ethyl]aminolpropyl]-1-(3-hydroxypropyl)-1*H*-indole-7-carboxamide (Compound B)

*tert*-Butyl (*R*)-*N*-[2-[7-carbamoyl-1-(3-hydroxypropyl)-2,3-dihydro-1*H*-indol-5-yl]-1-methylethyl]-*N*-[2-(2-ethoxyphenoxy)ethyl]carbamate (4.93g) was dissolved in 15 methanol (150ml), and 10% palladium on carbon (490mg) and ammonium formate (2.96g) were added to the solution. After the mixture was heated under reflux for 36 hours and cooled, the insoluble material was filtered off. The solvent was removed 20 *in vacuo*, and the residue was dissolved in methanol (150ml). 10% Palladium on carbon (490mg) and ammonium formate (2.96g) were added to the solution. After the mixture was heated under reflux for 24 hours and cooled, the insoluble material was filtered off. The filtrate was concentrated *in vacuo*, and the 25 residue was dissolved in ethyl acetate. The solution was washed with water and brine, and dried over anhydrous sodium sulfate.

The solvent was removed *in vacuo* to give white amorphous *tert*-butyl (R)-N-[2-[7-carbamoyl-1-(3-hydroxypropyl)-1*H*-indol-5-yl]-1-methylethyl]-N-[2-(2-ethoxyphenoxy)ethyl]-carbamate (4.55g).

- 5 <sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ ppm: 1.05-1.50 (m, 15H), 1.90-2.10 (m, 2H), 2.70-3.00 (m, 3H), 3.30-3.75 (m, 4H), 3.80-4.65 (m, 7H), 5.75-5.95 (m, 1H), 6.40-6.65 (m, 2H), 6.75-7.55 (m, 7H)  
Specific Rotation: [α]<sub>D</sub><sup>30</sup> = -47.8° (c=1.05, Methanol)

- 10 *tert*-Butyl (R)-N-[2-[7-carbamoyl-1-(3-hydroxypropyl)-1*H*-indol-5-yl]-1-methylethyl]-N-[2-(2-ethoxyphenoxy)ethyl]carbamate (4.45g) was dissolved in isopropanol (50ml), and concentrated hydrochloric acid (25ml) was added portionwise to the solution under ice-cooling with
- 15 stirring. After the mixture was stirred for 3 hours at room temperature, a saturated aqueous sodium bicarbonate solution was added to the reaction mixture under ice-cooling and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with brine, and dried over anhydrous sodium
- 20 sulfate. The solvent was removed *in vacuo*, and the residue was purified by column chromatography on aminopropyl silica gel (eluent: methylene chloride/methanol=20/1) to give white amorphous (R)-5-[2-[[2-(2-ethoxyphenoxy)ethyl]amino]-propyl]-1-(3-hydroxypropyl)-1*H*-indole-7-carboxamide (1.27g).
- 25 Unpurified mixture was further purified by column chromatography on aminopropyl silica gel (eluent: ethyl

acetate/ethanol=7/1) and the purified product was combined with the previously purified product to give white amorphous (R)-5-[2-[[2-(2-ethoxyphenoxy)ethyl]amino]propyl]-1-(3-hydroxypropyl)-1H-indole-7-carboxamide (2.39g).

5 <sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ ppm: 1.11 (d, J=6.3Hz, 3H), 1.25 (t, J=7.0Hz, 3H), 1.95-2.10 (m, 2H), 2.70-3.20 (m, 6H), 3.52 (t, J=5.6Hz, 2H), 3.93 (q, J=7.0Hz, 2H), 4.00-4.20 (m, 2H), 4.38 (t, J=7.0Hz, 2H), 5.90 (br s, 1H), 6.38 (br s, 1H), 6.49 (d, J=3.2Hz, 1H), 6.75-6.95 (m, 4H), 7.11 (d, J=3.2Hz, 1H), 7.19 (d, J=1.5Hz, 1H), 7.53 (d, J=1.4Hz, 1H)

Specific Rotation: [α]<sub>D</sub><sup>30</sup>=-15.5° (c=1.02, Methanol)

#### Example 2

15 (R)-5-[2-[[2-(2-Ethoxyphenoxy)ethyl]amino]propyl]-1-(3-hydroxypropyl)-1H-indole-7-carboxamide hydrochloride  
(Compound B hydrochloride)

(R)-5-[2-[[2-(2-Ethoxyphenoxy)ethyl]amino]propyl]-1-(3-hydroxypropyl)-1H-indole-7-carboxamide (862mg) was dissolved in ethanol (5ml), and 2N hydrochloric acid (985μl) was added to the solution. The solvent was removed in vacuo, the residue was dissolved in ethanol (3ml), and ethyl acetate (12ml) was added to the solution. After the mixture was allowed to stand, the resulting crystals were collected by filtration to give (R)-5-[2-[[2-(2-ethoxyphenoxy)ethyl]amino]propyl]-1-(3-hydroxypropyl)-1H-indole-7-carboxamide hydrochloride (821mg).

<sup>1</sup>H-NMR (DMSO-*d*<sub>6</sub>) δ ppm: 1.19 (d, *J*=6.4Hz, 3H), 1.26 (t, *J*=7.0Hz, 3H), 1.70-1.85 (m, 2H), 2.65-2.80 (m, 1H), 3.20-3.55 (m, 5H), 3.64 (br s, 1H), 4.02 (q, *J*=7.0Hz, 2H), 4.20-4.40 (m, 4H), 4.55 (t, *J*=5.0Hz, 1H), 6.45 (d, *J*=3.1Hz, 1H), 6.85-7.15 (m, 5H),  
5 7.36 (d, *J*=3.1Hz, 1H), 7.49 (d, *J*=1.3Hz, 1H), 7.60 (br s, 1H), 7.99 (br s, 1H), 9.05-9.30 (m, 2H)

Specific Rotation:  $[\alpha]_D^{30} = -7.8^\circ$  (*c*=1.16, Methanol)

### Example 3

10 (R)-3-[7-Carbamoyl-5-[2-[[2-(2-ethoxyphenoxy)ethyl]amino]-propyl]-1H-indol-1-yl]propyl pivalate (Compound C)

tert-Butyl (R)-N-[2-[7-carbamoyl-1-(3-hydroxy-propyl)-2,3-dihydro-1H-indol-5-yl]-1-methylethyl]-N-[2-(2-ethoxyphenoxy)ethyl]carbamate (6.24g) was dissolved in dry  
15 pyridine (9.4ml), and pivaloyl chloride (1.54ml) was added to the solution. The mixture was stirred overnight at room temperature, and a saturated aqueous sodium bicarbonate solution was added to the reaction mixture. The mixture was extracted with ethyl acetate, and the ethyl acetate layer was  
20 washed with a saturated aqueous sodium bicarbonate solution and brine, and dried over anhydrous sodium sulfate. The solvent was removed *in vacuo*, and the residue was purified by column chromatography on aminopropyl silica gel (eluent: hexane/ethyl acetate=1/1) to give colorless amorphous (R)-3-[5-[2-[N-(tert-butoxycarbonyl)-N-[2-(2-ethoxyphenoxy)ethyl]amino]-propyl]-7-carbamoyl-2,3-dihydro-1H-indol-1-yl]propyl  
25

pivalate(4.30g) .

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ ppm: 1.15-1.50 (m, 24H), 1.85-2.00 (m, 2H), 2.55-3.20 (m, 6H), 3.30-3.60 (m, 4H), 3.85-4.40 (m, 7H), 5.52 (br s, 1H), 6.80-7.40 (m, 7H)

5 Specific Rotation:  $[\alpha]_D^{27} = -38.3^\circ$  (c=1.03, Methanol)

(R)-3-[5-[2-[N-(tert-Butoxycarbonyl)-N-[2-(2-ethoxyphenoxy)ethyl]amino]propyl]-7-carbamoyl-2,3-dihydro-1H-indol-1-yl]propyl pivalate(8.53g) was dissolved in methanol  
10 (280ml), and 10% palladium on carbon(853mg) and ammonium formate(3.97g) were added to the solution. The mixture was heated under reflux for 13 hours, and the catalysts were filtered off. The solvent was removed *in vacuo* to give pale green amorphous (R)-3-[5-[2-[N-(tert-butoxycarbonyl)-N-[2-(2-ethoxyphenoxy)ethyl]amino]propyl]-7-carbamoyl-1H-indol-  
15 1-yl]propyl pivalate(8.20g) .

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ ppm: 1.05-1.50 (m, 24H), 1.90-2.10 (m, 2H), 2.70-3.05 (m, 2H), 3.30-3.75 (m, 2H), 3.85-4.70 (m, 9H), 5.66 (br s, 1H), 6.35-6.50 (m, 2H), 6.75-7.55 (m, 7H)

20 Specific Rotation:  $[\alpha]_D^{27} = -44.5^\circ$  (c=1.06, Methanol)

(R)-3-[5-[2-[N-(tert-Butoxycarbonyl)-N-[2-(2-ethoxyphenoxy)ethyl]amino]propyl]-7-carbamoyl-1H-indol-1-yl]propyl pivalate(7.81g) was dissolved in isopropanol(78ml),  
25 and concentrated hydrochloric acid(39ml) was added dropwise over a period of 10 minutes to the solution under ice-cooling

with stirring. After the mixture was stirred for 4 hours at room temperature, the reaction mixture was adjusted to pH 8 by adding sodium bicarbonate powder under ice-cooling with stirring. The mixture was diluted with water (200ml) and  
5 extracted with ethyl acetate. The ethyl acetate layer was washed with a saturated aqueous sodium bicarbonate solution, water and brine subsequently, and dried over anhydrous sodium sulfate. The solvent was removed *in vacuo*, and the residue was purified by column chromatography on aminopropyl silica gel  
10 (eluent: ethyl acetate) and recrystallized from diethyl ether/hexane (2/1) to give (R)-3-[7-carbamoyl-5-[2-[[2-(2-ethoxyphenoxy)ethyl]amino]propyl]-1H-indol-1-yl]propyl pivalate (5.21g) as colorless crystals.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ ppm: 1.11 (d, J=6.2Hz, 3H), 1.21 (s, 9H), 1.27  
15 (t, J=7.0Hz, 3H), 1.95-2.10 (m, 2H), 2.75 (dd, J=13.6, 6.4Hz, 1H), 2.85 (dd, J=13.6, 6.6Hz, 1H), 2.95-3.10 (m, 3H), 3.85-4.00 (m, 4H), 4.00-4.20 (m, 2H), 4.35-4.45 (m, 2H), 5.55-5.65 (br s, 1H), 6.05-6.20 (br s, 1H), 6.47 (d, J=3.2Hz, 1H), 6.75-6.95 (m, 4H), 7.06 (d, J=3.2Hz, 1H), 7.21 (d, J=1.5Hz, 1H),  
20 7.54 (d, J=1.5Hz, 1H)

Specific Rotation:  $[\alpha]_D^{27} = -15.8^\circ$  (c=1.06, Methanol)

#### Example 4

The following compound was prepared according to a  
25 similar manner to that described in Example 3 using *tert*-butyl (R)-N-[2-[7-carbamoyl-1-(3-hydroxypropyl)-2,3-dihydro-1H-

indol-5-yl]-1-methylethyl]-N-[2-[2-(2,2,2-trifluoroethoxy)phenoxy]ethyl]carbamate instead of tert-butyl (R)-N-[2-[7-carbamoyl-1-(3-hydroxypropyl)-2,3-dihydro-1H-indol-5-yl]-1-methylethyl]-N-[2-(2-ethoxyphenoxy)ethyl]carbamate.

(R)-3-[7-Carbamoyl-5-[2-[[2-[2-(2,2,2-trifluoroethoxy)phenoxy]ethyl]amino]propyl]-1H-indol-1-yl]propyl pivalate  
(Compound D)

10  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$  ppm: 1.11 (d,  $J=6.2\text{Hz}$ , 3H), 1.21 (s, 9H), 2.00-2.10 (m, 2H), 2.73 (dd,  $J=13.5$ , 6.5Hz, 1H), 2.84 (dd,  $J=13.5$ , 6.8Hz, 1H), 2.95-3.15 (m, 3H), 3.90-4.00 (m, 2H), 4.00-4.30 (m, 4H), 4.35-4.45 (m, 2H), 5.73 (br s, 1H), 6.10 (br s, 1H), 6.47 (d,  $J=3.2\text{Hz}$ , 1H), 6.80-7.05 (m, 4H), 7.07 (d,  $J=3.2\text{Hz}$ , 1H), 7.19 (d,  $J=1.4\text{Hz}$ , 1H), 7.54 (d,  $J=1.4\text{Hz}$ , 1H)  
15 Specific Rotation:  $[\alpha]_D^{27} = -17.5^\circ$  ( $c=0.79$ , Methanol)

#### Example 5

(R)-3-[7-Carbamoyl-5-[2-[[2-(2-ethoxyphenoxy)ethyl]amino]propyl]-1H-indol-1-yl]propyl pivalate hydrochloride  
20 (Compound C hydrochloride)

To a solution of (R)-3-[7-carbamoyl-5-[2-[[2-(2-ethoxyphenoxy)ethyl]amino]propyl]-1H-indol-1-yl]propyl pivalate(6.07g) in ethanol(58ml) was added dropwise 1N  
25 hydrochloric acid(11.6ml) under ice-cooling with stirring, and the mixture was stirred for 15 minutes under the same condition.

The reaction mixture was concentrated *in vacuo*, and to the residue was added ethanol. After azeotropic removal of water, the residue was dissolved in ethanol (6ml) and ethyl acetate (60ml) was added to the solution. After the mixture was allowed  
5 to stand for 16 hours at room temperature, the resulting colorless crude crystals (5.14g) were obtained. After the crystals were combined with another crude crystals obtained similarly, recrystallization of the combined crystal (8.12g) from ethanol/ethyl acetate (15/1) gave (R)-3-[7-carbamoyl-  
10 5-[2-[[2-(2-ethoxyphenoxy)ethyl]amino]propyl]-1H-indol-1-yl]propyl pivalate hydrochloride (7.46g) as colorless crystals.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ ppm: 1.21 (s, 9H), 1.29 (t, J=7.0Hz, 3H), 1.45 (d, J=6.5Hz, 3H), 1.95-2.10 (m, 2H), 3.12 (dd, J=14.0, 7.2Hz, 1H), 3.30-3.60 (m, 3H), 3.85-4.05 (m, 5H), 4.30-4.50 (m, 4H),  
15 5.87 (s, 1H), 6.40 (d, J=3.2Hz, 1H), 6.80-7.00 (m, 4H), 7.05 (d, J=3.2Hz, 1H), 7.33 (d, J=1.5Hz, 1H), 7.36 (s, 1H), 7.50 (d, J=1.5Hz, 1H), 9.10-9.30 (br s, 1H), 9.50-9.65 (br s, 1H)  
Specific Rotation:  $[\alpha]_D^{28} = -7.0^\circ$  (c=1.22, Methanol)

20

#### Reference Example 5

(R)-3-[7-Carbamoyl-5-[2-[[2-[2-(2,2,2-trifluoroethoxy)-phenoxy]ethyl]amino]propyl]-1H-indol-1-yl]propyl 2-ethyl-butyrates (Compound a)

25 To a solution of (R)-5-[2-[[2-[2-(2,2,2-trifluoroethoxy)phenoxy]ethyl]amino]propyl]-1-(3-hydroxypropyl)-

2,3-dihydro-1H-indole-7-carboxamide(3.0g) in methylene chloride (50ml) was added di-*tert*-butyl dicarbonate(1.32g) under ice-cooling, and the mixture was stirred for 30 minutes under ice-cooling and overnight at room temperature. The  
5 reaction mixture was concentrated in *vacuo*, and the residue was dissolved in ethyl acetate(50ml). The solution was washed with 10% aqueous citric acid solution, a saturated aqueous sodium bicarbonate solution and brine subsequently, and dried over anhydrous sodium sulfate. The solvent was removed in *vacuo*  
10 to give pale brown amorphous *tert*-butyl (*R*)-*N*-[2-[7-carbamoyl-1-(3-hydroxypropyl)-2,3-dihydro-1H-indol-5-yl]-1-methylethyl]-*N*-[2-[2-(2,2,2-trifluoroethoxy)phenoxy]-ethyl]carbamate (2.99g).

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ ppm: 1.20-1.50 (m, 12H), 1.70-1.85 (m, 2H),  
15 2.50-4.50 (m, 18H), 5.89 (br s, 1H), 6.69 (br s, 1H), 6.80-7.20 (m, 6H)

Specific Rotation:  $[\alpha]_D^{25} = -41.6^\circ$  (c=1.12, Methanol)

*tert*-Butyl (*R*)-*N*-[2-[7-carbamoyl-1-(3-hydroxy-  
20 propyl)-2,3-dihydro-1H-indol-5-yl]-1-methylethyl]-*N*-[2-[2-(2,2,2-trifluoroethoxy)phenoxy]ethyl]carbamate(12.0g) and ammonium formate(12.7g) were dissolved in methanol(300ml), and 10% palladium on carbon(1.20g) was carefully added to the solution. The mixture was heated overnight under reflux, and  
25 the solvent was removed in *vacuo*. Water was added to the residue, and the mixture was extracted with ethyl acetate. The ethyl

acetate layer was washed with brine, and dried over anhydrous sodium sulfate. The solvent was removed *in vacuo* to give amorphous *tert*-butyl (*R*)-*N*-[2-[7-carbamoyl-1-(3-hydroxy-propyl)-1*H*-indol-5-yl]-1-methylethyl]-*N*-[2-[2-(2,2,2-trifluoroethoxy)phenoxy]ethyl]carbamate (12.2g).

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ ppm: 1.1-1.4 (m, 12H), 1.95-2.1 (m, 2H), 2.7-3.0 (m, 2H), 3.25-3.7 (m, 4H), 3.8-4.2 (m, 3H), 4.3-4.6 (m, 4H), 5.91 (br s, 1H), 6.45-6.6 (m, 2H), 6.75-7.6 (m, 7H)  
Specific Rotation:  $[\alpha]_D^{27} = -44.5^\circ$  (c=1.11, Methanol)

10

*tert*-Butyl (*R*)-*N*-[2-[7-carbamoyl-1-(3-hydroxy-propyl)-1*H*-indol-5-yl]-1-methylethyl]-*N*-[2-[2-(2,2,2-trifluoroethoxy)phenoxy]ethyl]carbamate (2.00g) was dissolved in dry pyridine (3ml), and 2-ethylbutyryl chloride (0.54g) prepared from 2-ethylbutyric acid and oxalyl chloride was added to the solution. After the mixture was stirred overnight at room temperature, a saturated aqueous sodium bicarbonate solution was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with a saturated aqueous sodium bicarbonate solution and brine subsequently, and dried over anhydrous magnesium sulfate. The solvent was removed *in vacuo*, and the residue was purified by column chromatography on silica gel (eluent: hexane/ethyl acetate=2/1) to give white amorphous (*R*)-3-[5-[2-[*N*-(*tert*-butoxycarbonyl)-*N*-[2-[2-(2,2,2-trifluoroethoxy)phenoxy]ethyl]amino]propyl]-7-carbamoyl-1*H*-indol-1-

25

yl]propyl 2-ethylbutyrate(1.66g) .

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ ppm: 0.90 (t, J=7.4Hz, 6H) , 1.10-1.40 (m, 12H) ,  
1.45-1.70 (m, 4H) , 1.90-2.10 (m, 2H) , 2.15-2.30 (m, 1H) ,  
2.70-3.00 (m, 2H) , 3.30-3.70 (m, 2H) , 3.80-4.70 (m, 7H) , 4.36  
5 (q, J=8.4Hz, 2H) , 5.62 (br s, 1H) , 6.40-6.50 (m, 2H) , 6.85-7.40  
(m, 6H) , 7.45-7.55 (m, 1H)

Specific Rotation:  $[\alpha]_D^{31} = -41.8^\circ$  (c=0.99, Methanol)

(R)-3-[5-[2-[N-(tert-Butoxycarbonyl)-N-[2-[2-(2,2,2-  
10 trifluoroethoxy)phenoxy]ethyl]amino]propyl]-7-carbamoyl-  
1H-indol-1-yl]propyl 2-ethylbutyrate(1.56g) was dissolved in  
isopropanol(10ml) , and concentrated hydrochloric acid(5.0ml)  
was added dropwise to the solution under ice-cooling with  
stirring. After the mixture was stirred for 4 hours at room  
15 temperature, a saturated aqueous sodium bicarbonate solution  
was added to the reaction mixture under ice-cooling, and the  
mixture was extracted with ethyl acetate. The ethyl acetate  
layer was washed with brine and dried over anhydrous magnesium  
sulfate. The solvent was removed *in vacuo* , and the residue was  
20 purified by column chromatography on silica gel (eluent:  
methylene chloride/methanol=20/1) and recrystallized from  
diethyl ether-hexane to give (R)-3-[7-carbamoyl-5-[2-[2-  
[2-(2,2,2-trifluoroethoxy)phenoxy]ethyl]amino]propyl]-1H-  
indol-1-yl]propyl 2-ethylbutyrate (1.10g) as white crystals.  
25 <sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ ppm: 0.90 (t, J=7.4Hz, 6H) , 1.11 (d, J=6.2Hz,  
3H) , 1.45-1.70 (m, 4H) , 2.00-2.10 (m, 2H) , 2.15-2.25 (m, 1H) ,

2.65-2.90 (m, 2H), 2.95-3.15 (m, 3H), 3.99 (t,  $J=6.3\text{Hz}$ , 2H),  
4.00-4.30 (m, 4H), 4.41 (t,  $J=6.9\text{Hz}$ , 2H), 5.64 (br s, 1H), 6.07  
(br s, 1H), 6.47 (d,  $J=3.2\text{Hz}$ , 1H), 6.80-7.05 (m, 4H), 7.08 (d,  
 $J=3.2\text{Hz}$ , 1H), 7.19 (d,  $J=1.6\text{Hz}$ , 1H), 7.54 (d,  $J=1.6\text{Hz}$ , 1H)

5 Specific Rotation:  $[\alpha]_D^{30} = -16.4^\circ$  ( $c=1.00$ , Methanol)

#### Reference Example 6

The following compounds were prepared according to a  
similar manner to that described in Reference Example 5 using  
10 the corresponding acid halide instead of 2-ethylbutyryl  
chloride.

(R)-3-[7-Carbamoyl-5-[2-[[2-[2-(2,2,2-trifluoroethoxy)-  
phenoxy]ethyl]aminolpropyl]-1H-indol-1-yl]propyl 2,2-  
15 dimethylvalerate (Compound b)

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$  ppm: 0.90 (t,  $J=7.3\text{Hz}$ , 3H), 1.11 (d,  $J=6.2\text{Hz}$ ,  
3H), 1.18 (s, 9H), 1.19-1.28 (m, 2H), 1.49-1.53 (m, 2H),  
2.03-2.06 (m, 2H), 2.73 (dd,  $J=13.5, 6.5\text{Hz}$ , 1H), 2.84 (dd,  
 $J=13.5, 6.8\text{Hz}$ , 1H), 3.00-3.10 (m, 3H), 3.96 (t,  $J=6.2\text{Hz}$ , 2H),  
20 4.07-4.23 (m, 4H), 4.40 (t,  $J=6.9\text{Hz}$ , 2H), 5.66 (br s, 1H), 6.09  
(br s, 1H), 6.47 (d,  $J=3.2\text{Hz}$ , 1H), 6.84-7.03 (m, 4H), 7.07 (d,  
 $J=3.2\text{Hz}$ , 1H), 7.19 (d,  $J=1.6\text{Hz}$ , 1H), 7.54 (d,  $J=1.6\text{Hz}$ , 1H)

Specific Rotation:  $[\alpha]_D^{30} = -16.2^\circ$  ( $c=0.82$ , Methanol)

25 (R)-3-[7-Carbamoyl-5-[2-[[2-[2-(2,2,2-trifluoroethoxy)-  
phenoxy]ethyl]aminolpropyl]-1H-indol-1-yl]propyl  $\alpha,\alpha$ -

dimethylphenylacetate (Compound c)

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ ppm: 1.10 (d, J=6.2Hz, 3H), 1.60 (s, 6H),  
1.80-1.96 (m, 2H), 2.71 (dd, J=13.7, 6.4Hz, 1H), 2.82 (dd,  
J=13.5, 6.7Hz, 1H), 2.96-3.10 (m, 3H), 3.90 (t, 2H), 4.03-  
5 4.28 (m, 6H), 5.58 (br s, 1H), 6.00 (br s, 1H), 6.37 (d, J=3.1Hz,  
1H), 6.84-7.03 (m, 4H), 6.68 (d, J=3.2Hz, 1H), 7.19 (d, J=1.6Hz,  
1H), 7.54 (d, J=1.6Hz, 1H)

Specific Rotation:  $[\alpha]_D^{29} = -13.7^\circ$  (c=1.15, Methanol)

10 (R)-3-[7-Carbamoyl-5-[2-[[2-[2-(2,2,2-trifluoroethoxy)-  
phenoxy]ethyl]aminolpropyl]-1H-indol-1-yl]propyl 2,2-  
dimethylbutyrate (Compound d)

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ ppm: 0.85 (t, J=7.5Hz, 3H), 1.12 (d, J=6.2Hz,  
3H), 1.17 (s, 6H), 1.57 (q, J=7.5Hz, 4H), 2.00-2.10 (m, 2H),  
15 2.70-2.90 (m, 2H), 2.95-3.15 (m, 3H), 3.97 (t, J=6.2Hz, 2H),  
4.00-4.40 (m, 4H), 4.40 (t, J=7.0Hz, 2H), 5.70 (br s, 1H), 6.12  
(br s, 1H), 6.47 (d, J=3.2Hz, 1H), 6.80-7.05 (m, 4H), 7.07 (d,  
J=3.2Hz, 1H), 7.19 (d, J=1.6Hz, 1H), 7.54 (d, J=1.5Hz, 1H)

Specific Rotation:  $[\alpha]_D^{31} = -15.4^\circ$  (c=1.00, Methanol)

20

Test Example 1

Test for measuring  $\alpha_1$ -adrenoceptor blocking effect

Ductus deferens (about 1.5cm from testis side) were  
isolated from male Wistar rats (about 300 to 350g in body weight).

25 After removal of the blood vessel and connective tissue, each  
preparation was vertically suspended in Magnus bath containing

10ml of Krebs-Henseleit solution maintained at 37°C and gassed a mixture of 95% oxygen and 5% carbon dioxide under a resting tension of 1g. A solution of a mixture containing propranolol and yohimbine (final concentration: propranolol 1μM and yohimbine 0.1μM) was added into the Magnus bath. After 30 minutes, norepinephrine at the final concentration of 10μM was added into the Magnus bath until the maximum contraction was obtained, and each preparation was washed. This procedure was repeated several times until the heights of contraction were stable. Each preparation was pre-treated with a solution containing the test compound before 30 minutes, and the contractile responses by treatment of 10μM norepinephrine were measured. Contraction of each preparation without pre-treatment of the test compound was expressed as 100%. The α<sub>1</sub>-adrenoceptor blocking effect of the test compound was evaluated as the molar concentration of the compound required producing 50% inhibition of the contraction before the addition of norepinephrine (i.e., IC<sub>50</sub> value). The results were shown in Table 1.

[Table 1]

| Test compound            | IC <sub>50</sub> (nM) |
|--------------------------|-----------------------|
| Compound A               | 2.7                   |
| Compound B hydrochloride | 4.3                   |
| Bunazosin hydrochloride  | 315                   |

## Test Example 2

Test for measuring drug concentration in aqueous humor (1)

### (1) Method

After 0.1% solution of (R)-5-[2-[[2-(2-ethoxy-  
5 phenoxy)ethyl]amino]propyl]-1-(3-hydroxypropyl)-1*H*-indole-  
7-carboxamide hydrochloride (Compound B hydrochloride) (50 $\mu$ l)  
was instilled on eye of Japanese White rabbits (about 3kg in  
body weight; Japan SLC), aqueous humor was collected with the  
time course. To the collected aqueous humor (0.1ml) was added  
10 (R)-3-chloro-1-(3-hydroxypropyl)-5-[2-[[2-(2,2,2-  
trifluoroethoxy)phenoxy]ethyl]amino]propyl]-1*H*-indole-7-  
carboxamide (10ng) as an internal standard, and 0.1M phosphate  
buffer (pH 7.6) and sodium chloride (about 1g) were added to the  
mixture. The resulting mixture was extracted with diethyl  
15 ether (5ml), and the diethyl ether layer was concentrated under  
a stream of nitrogen. After the residue was dissolved in mobile  
phase (200 $\mu$ l), 100 $\mu$ l of the solution was injected into high  
performance liquid chromatography and the Compound B was  
determined in the following conditions. The results were shown  
20 in Table 2.

### (2) HPLC conditions

Analytical column: Inertsil ODS-3 (4.6x250mm)

Mobile phase: acetonitrile/0.1% phosphoric acid+2mM sodium  
laurylsulfate=1/1

25 Column temperature: 50°C

Flow rate: 1.0ml/minute

Fluorometry: excitation wave length 270nm, emission wave length 435nm

[Table 2]

| Test compound | Drug concentrations (ng/ml) |                  |                  |
|---------------|-----------------------------|------------------|------------------|
|               | 20 minutes<br>after         | 2 hours<br>after | 6 hours<br>after |
| Compound B    | 2                           | 20               | 8                |

## 5 Test Example 3

Test for rate of hydrolysis by endogenous enzyme

### (3) Method

To whole blood (0.5ml) collected from male Wistar rats as heparinized blood were respectively added each ester derivative (1 $\mu$ g) of (R)-1-(3-hydroxypropyl)-5-[2-[[2-[2-(2,2,2-trifluoroethoxy)phenoxy]ethyl]amino]propyl]-1H-indole-7-carboxamide (Compound A) and internal standard [(R)-3-chloro-1-(3-hydroxypropyl)-5-[2-[[2-[2-(2,2,2-trifluoroethoxy)phenoxy]ethyl]amino]propyl]-1H-indole-7-carboxamide] (1 $\mu$ g), and the mixture was incubated at 37°C. After 15 minutes, 30 minutes, 1 hour and 2 hours, 0.7M aqueous sodium fluoride solution (0.5ml) as an esterase inhibitor was added to each sample to stop the reaction. 0.1M Phosphate buffer (pH 7.6) and sodium chloride (about 1g) were added to the mixture, the resulting mixture was extracted with diethyl ether (5 ml), and the diethyl ether layer was concentrated under a stream of nitrogen. After the residue was dissolved in mobile

phase(300μl), 10μl of the solution was injected into high performance liquid chromatography, and the test compound and Compound A were determined in the following conditions. The results were shown in Table 3.

5 (2)HPLC conditions

Analytical column: Inertsil ODS-3 (4.6x250mm)

Mobile phase: acetonitrile/20mM acetate buffer(pH 5.0)=40/60

Column temperature: 50°C

Flow rate: 1.0ml/minute

10 Fluorometry: excitation wave length 270nm, emission wave length 435nm

[Table 3]

| Test compound | Decomposition rate(%) |                     |                 |                  |
|---------------|-----------------------|---------------------|-----------------|------------------|
|               | 15 minutes<br>after   | 30 minutes<br>after | 1 hour<br>after | 2 hours<br>after |
| Compound D    | 54.8                  | 67.1                | 86.5            | 98.6             |
| Compound a    | 8.4                   | 12.0                | 12.6            | 25.2             |
| Compound b    | 2.2                   | 3.8                 | 7.5             | 10.2             |
| Compound c    | 0.6                   | 1.6                 | 3.2             | 3.7              |
| Compound d    | 2.1                   | 5.6                 | 8.4             | 21.7             |

Test Example 4

15 Test for measuring drug concentration in aqueous humor (2)

(1)Method

After 0.1% solution (50μl) of (R)-3-[7-carbamoyl-5-[2-[[2-(2-ethoxyphenoxy)ethyl]amino]propyl]-1H-indol-1-

yl]propyl pivalate hydrochloride (Compound C hydrochloride) was instilled on eye of Japanese White rabbits (about 3kg in body weight; Japan SLC), aqueous humor was collected with the time course. To the collected aqueous humor (0.1ml) was added  
5 internal standard [(R)-3-chloro-1-(3-hydroxypropyl)-5-[2-  
[[2-[2-(2,2,2-trifluoroethoxy)phenoxy]ethyl]amino]propyl]-  
1*H*-indole-7-carboxamide] (10ng), and 0.1M phosphate buffer (pH7.6) and sodium chloride (about 1g) were added to the mixture. The resulting mixture was extracted with diethyl ether (5ml),  
10 and the diethyl ether layer was concentrated under a stream of nitrogen. After the residue was dissolved in mobile phase (200μl), 100μl of the solution was injected into high performance liquid chromatography, and the Compound C and (R)-5-[2-[[2-(2-ethoxyphenoxy)ethyl]amino]propyl]-1-(3-  
15 hydroxypropyl)-1*H*-indole-7-carboxamide (Compound B) was determined in the following conditions. The results were shown in Table 4.

(2) HPLC conditions

Analytical column: Inertsil ODS-3 (4.6x250mm)

20 Mobile phase: acetonitrile/0.1% phosphoric acid+2mM sodium laurylsulfate=1/1

Column temperature: 50°C

Flow rate: 1.0ml/minute

Fluorometry: excitation wave length 270nm, emission wave length  
25 435nm

[Table 4]

| Test compound | Drug concentrations (ng/ml) |                  |                  |
|---------------|-----------------------------|------------------|------------------|
|               | 20 minutes<br>after         | 2 hours<br>after | 6 hours<br>after |
| Compound B    | 140                         | 546              | 136              |
| Compound C    | <1                          | <1               | <1               |

## Test Example 5

## Stability test

- 5 The test compounds were dissolved in 0.1M acetate buffer (pH 5.0) to prepare 0.1% solutions. Each 0.1% solution was allowed to stand in the dark for 28 days at 40°C, 50°C, 60°C and 70°C, respectively. The results were shown in Table 5.

[Table 5]

| Test compound | Residual rate (%) |      |      |      |
|---------------|-------------------|------|------|------|
|               | 40°C              | 50°C | 60°C | 70°C |
| Compound D    | 99.9              | 99.7 | 99.5 | 98.9 |
| Compound A    | 0.1               | 0.3  | 0.5  | 1.1  |

10

## Test Example 6

## Acute toxicity test

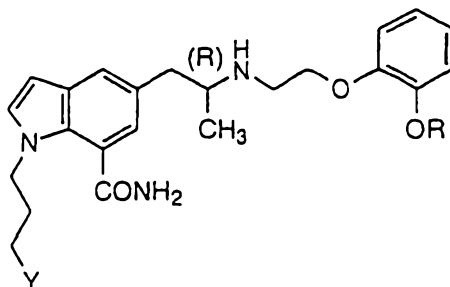
- Male SD rats of 7 weeks age (n=5; 190-210 g in body weight) were fasted for 18 hours. (R)-3-[7-Carbamoyl-5-[2-[[2-(2-ethoxyphenoxy)ethyl]amino]propyl]-1H-indol-1-yl]propyl pivalate hydrochloride which was suspended in 0.5% aqueous methylcellulose solution at a concentration of 100 mg/ml was
- 15

orally administered to the rats at a dose of 1000 mg/kg. Any fatal rats were not observed during 24 hours after the administration.

In the claims of this application and in the  
5 description of the invention, except where the context requires otherwise due to express language or necessary implication, the words "comprise" or variations such as "comprises" or "comprising" are used in an inclusive sense, i.e. to specify the presence of the stated features  
10 but not to preclude the presence or addition of further features in various embodiments of the invention.

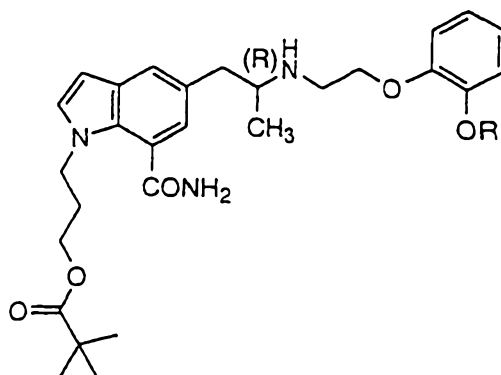
# CLAIMS

1. An indole derivative represented by the general formula:



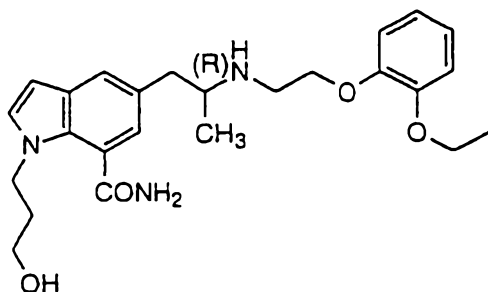
- 5 (wherein R represents an ethyl group or a 2,2,2-trifluoroethyl group; Y represents a hydroxy group or a pivaloyloxy group with the proviso that Y represents a pivaloyloxy group when R represents a 2,2,2-trifluoroethyl group; and the carbon atom marked with (R) represents a carbon atom in (R) configuration)
- 10 or a pharmaceutically acceptable salt thereof.

2. An indole derivative as claimed in claim 1, represented by the general formula:

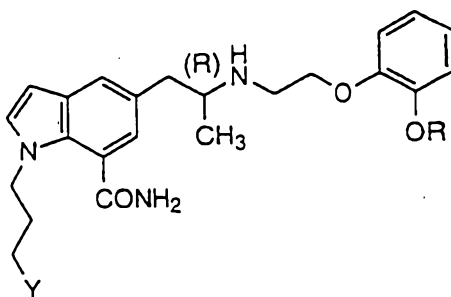


- 15 (wherein R represents an ethyl group or a 2,2,2-trifluoroethyl group; and the carbon atom marked with (R) represents a carbon atom in (R) configuration) or a pharmaceutically acceptable

3. The indole derivative as claimed in claim 1, represented by the formula:

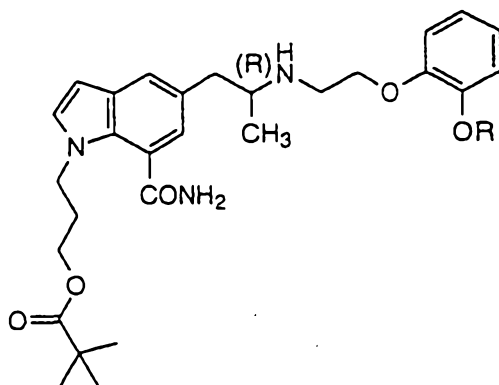


10 4. A pharmaceutical composition comprising an indole  
derivative represented by the general formula:



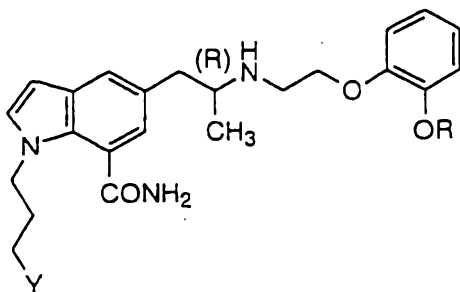
40

5. A pharmaceutical composition as claimed in claim 4, comprising an indole derivative represented by the general formula:



(wherein R represents an ethyl group or a 2,2,2-trifluoroethyl group; and the carbon atom marked with (R) represents a carbon atom in (R) configuration) or a pharmaceutically acceptable salt thereof.

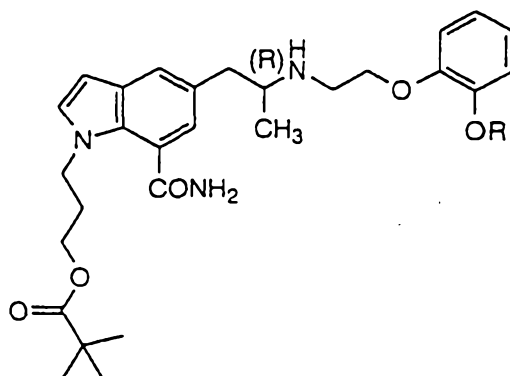
6. An agent for lowering intraocular pressure which comprises as the active ingredient an indole derivative represented by the general formula:



(wherein R represents an ethyl group or a 2,2,2-trifluoroethyl group; Y represents a hydroxy group or a pivaloyloxy group; and the carbon atom marked with (R) represents a carbon atom in (R)

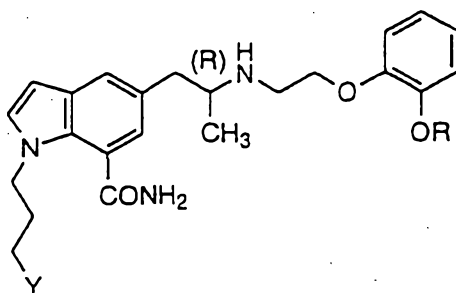
configuration) or a pharmaceutically acceptable salt thereof.

7. An agent for lowering intraocular pressure as claimed in claim 6, which comprises as the active ingredient an indole derivative represented by the general formula:



- (wherein R represents an ethyl group or a 2,2,2-trifluoroethyl group; and the carbon atom marked with (R) represents a carbon atom in (R) configuration) or a pharmaceutically acceptable salt thereof.

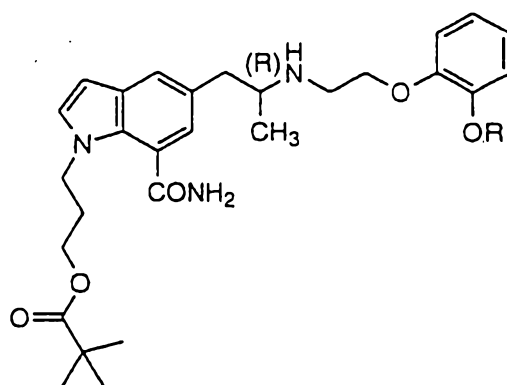
8. An agent for the prevention or treatment of glaucoma or ocular hypertension which comprises as the active ingredient an indole derivative represented by the general formula:



- (wherein R represents an ethyl group or a 2,2,2-trifluoroethyl group; Y represents a hydroxy group or a pivaloyloxymethyl group; and

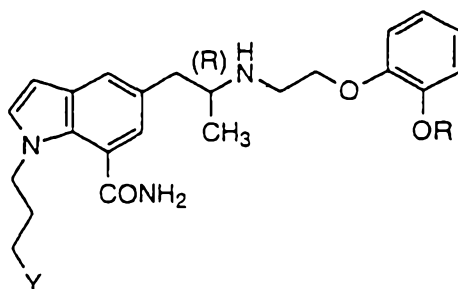
the carbon atom marked with (R) represents a carbon atom in (R) configuration) or a pharmaceutically acceptable salt thereof.

9. An agent for the prevention or treatment of glaucoma or ocular hypertension as claimed in claim 8, which comprises as the active ingredient an indole derivative represented by the general formula:



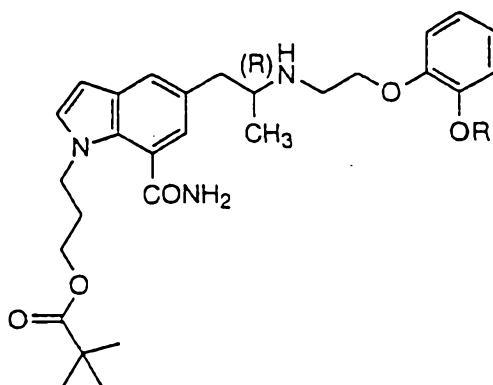
- (wherein R represents an ethyl group or a 2,2,2-trifluoroethyl group; and the carbon atom marked with (R) represents a carbon atom in (R) configuration) or a pharmaceutically acceptable salt thereof.

10. A method for the prevention or treatment of glaucoma or ocular hypertension which comprises administering a therapeutically effective amount of an indole derivative represented by the general formula:



(wherein R represents an ethyl group or a 2,2,2-trifluoroethyl group; Y represents a hydroxy group or a pivaloyloxy group; and the carbon atom marked with (R) represents a carbon atom in (R) configuration) or a pharmaceutically acceptable salt thereof.

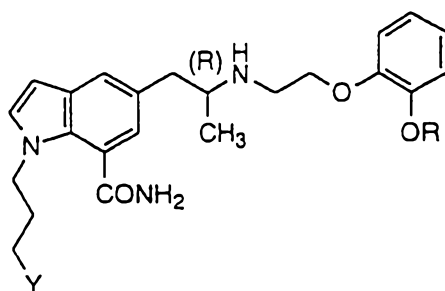
11. A method for the prevention or treatment of glaucoma or ocular hypertension as claimed in claim 10, which comprises administering a therapeutically effective amount of an indole derivative represented by the general formula:



(wherein R represents an ethyl group or a 2,2,2-trifluoroethyl group; and the carbon atom marked with (R) represents a carbon atom in (R) configuration) or a pharmaceutically acceptable salt thereof.

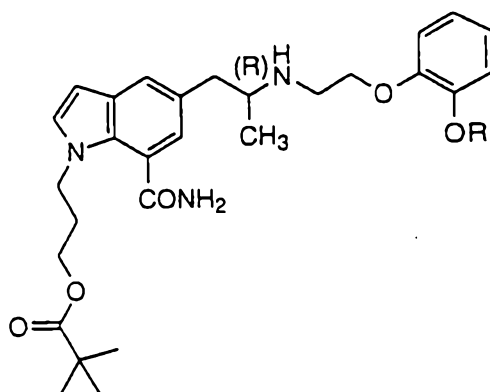
12. A use of an indole derivative represented by the general

formula:



(wherein R represents an ethyl group or a 2,2,2-trifluoroethyl group; Y represents a hydroxy group or a pivaloyloxy group; and  
5 the carbon atom marked with (R) represents a carbon atom in (R) configuration) or a pharmaceutically acceptable salt thereof for the manufacture of a pharmaceutical composition for the prevention or treatment of glaucoma or ocular hypertension.

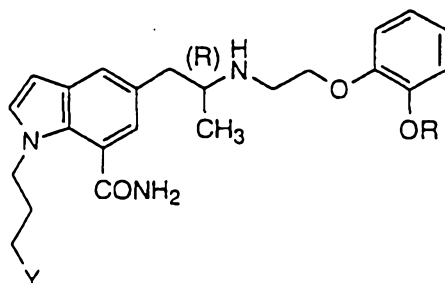
- 10 13. A use as claimed in claim 12, of an indole derivative represented by the general formula:



- (wherein R represents an ethyl group or a 2,2,2-trifluoroethyl group; and the carbon atom marked with (R) represents a carbon  
15 atom in (R) configuration) or a pharmaceutically acceptable salt thereof for the manufacture of a pharmaceutical composition for the prevention or treatment of glaucoma or

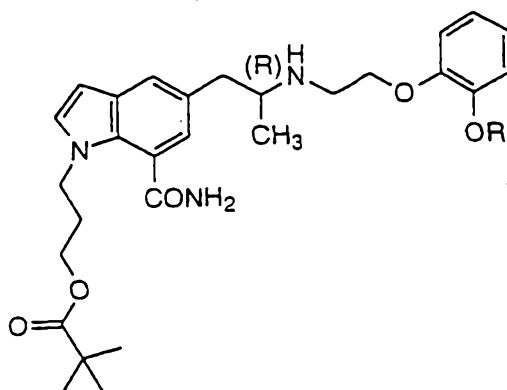
ocular hypertension.

14. A use of an indole derivative represented by the general formula:



5 (wherein R represents an ethyl group or a 2,2,2-trifluoroethyl group; Y represents a hydroxy group or a pivaloyloxy group; and the carbon atom marked with (R) represents a carbon atom in (R) configuration) or a pharmaceutically acceptable salt thereof  
10 as an agent for the prevention or treatment of glaucoma or ocular hypertension.

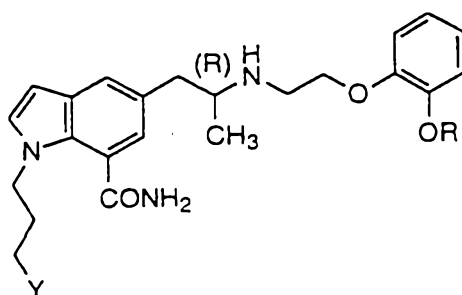
15. A use as claimed in claim 14, of an indole derivative represented by the general formula:



15 (wherein R represents an ethyl group or a 2,2,2-trifluoroethyl group; and the carbon atom marked with (R) represents a carbon

atom in (R) configuration) or a pharmaceutically acceptable salt thereof as an agent for the prevention or treatment of glaucoma or ocular hypertension.

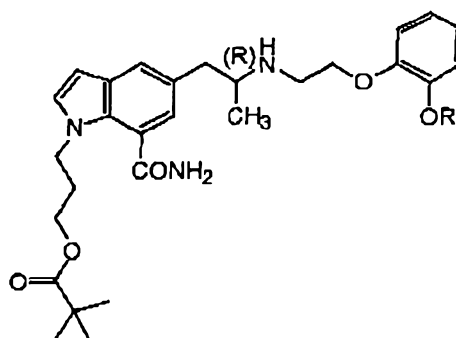
- 5 16. A process for the manufacture of a pharmaceutical composition for the prevention or treatment of glaucoma or ocular hypertension, characterized in the use, as an essential constituent of said pharmaceutical composition, of an indole derivative represented by the general formula:



(wherein R represents an ethyl group or a 2,2,2-trifluoroethyl group; Y represents a hydroxy group or a pivaloyloxy group; and the carbon atom marked with (R) represents a carbon atom in (R) configuration) or a pharmaceutically acceptable salt thereof.

15

17. A process for the manufacture of a pharmaceutical composition for the prevention or treatment of glaucoma or ocular hypertension as claimed in claim 16, characterized in the use, as an essential constituent of said pharmaceutical composition, of an indole derivative represented by the general formula:
- 20



(wherein R represents an ethyl group or a 2,2,2-trifluoroethyl group; and the carbon atom marked with (R) represents a carbon atom in (R) configuration) or a  
 5 pharmaceutically acceptable salt thereof.

18. Indole derivatives, pharmaceutical compositions or agents comprising them or methods or uses involving them, substantially as hereinbefore described with reference to  
 10 the accompanying examples (excluding the reference examples).

Dated this 28th day of July 2003  
 15 KISSEI PHARMACEUTICAL CO., LTD.  
 By their Patent Attorneys  
 GRIFFITH HACK  
 Fellows Institute of Patent and  
 Trade Mark Attorneys of Australia

20