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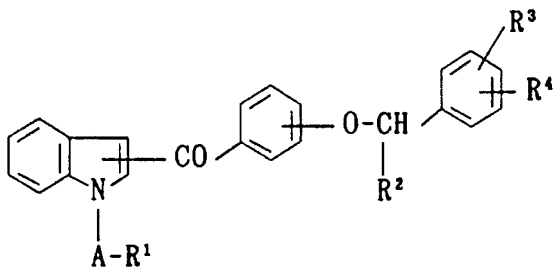
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(54) Title: INDOLE DERIVATIVES AS 5-ALPHA-REDUCTASE INHIBITORS



(I)

(57) Abstract

A compound of formula (I), wherein R^1 is a carboxy or protected carboxy, R^2 is a lower alkyl, halo(lower)alkyl or phenyl, R^3 is a lower alkyl, R^4 is a hydrogen or halogen, and A is a lower alkylene, with the proviso that when R^2 is a lower alkyl, R^4 is a halogen, and a pharmaceutically acceptable salt thereof. The compound of the present invention is useful as a testosterone 5α-reductase inhibitor and effective for testosterone 5α-reductase-mediated diseases such as prostatism, prostatic hypertrophy, prostatic cancer, alopecia, hirsutism (e.g. female hirsutism), androgenic alopecia (or male-pattern baldness), acne (e.g. acne vulgaris, pimple), other hyperandrogenisms, and the like.

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Indole derivatives as 5-alpha-reductase inhibitors

Technical Field

The present invention relates to novel indole derivatives and pharmaceutically acceptable salts thereof. More particularly, it relates to novel indole derivatives and pharmaceutically acceptable salts thereof, which have pharmacological activities such as inhibitory activity on testosterone 5α-reductase, to a process for the preparation thereof, to a pharmaceutical composition comprising the same, and to a use of the same as a medicament.

Background Art

It has hitherto been known that indole derivatives are effective for testosterone 5α-reductase mediated diseases. However, a testosterone 5α-reductase inhibitor with stronger effect has been demanded.

Disclosure of the Invention

Accordingly, one object of the present invention is to provide novel indole derivatives and pharmaceutically acceptable salts thereof, which are useful as a testosterone 5α-reductase inhibitor.

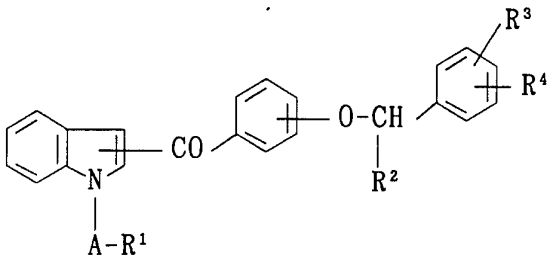
Another object of the present invention is to provide a process for the preparation of said indole derivatives or salts thereof.

A further object of the present invention is to provide a pharmaceutical composition comprising, as an active ingredient,

said indole derivative or a pharmaceutically acceptable salt thereof.

A still further object of the present invention is to provide use of said indole derivatives or pharmaceutically acceptable salts thereof as a medicament such as a testosterone 5α-reductase inhibitor useful for treating or preventing testosterone 5α-reductase mediated diseases such as alopecia, acnes and prostatism in human being or animals.

Indole derivatives of the present invention are novel and can be represented by the formula (I):



(I)

wherein R^1 is a carboxy or protected carboxy,

R^2 is a lower alkyl, halo(lower)alkyl or phenyl,

R^3 is a lower alkyl,

R^4 is a hydrogen or halogen, and

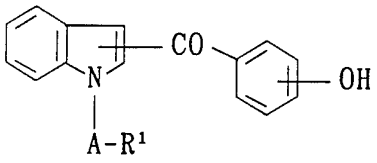
A is a lower alkylene,

with the proviso that

when R^2 is a lower alkyl, R^4 is a halogen.

According to the present invention, the object compound (I) and a salt thereof can be prepared by the following processes.

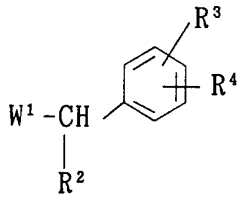
Process 1



(II)

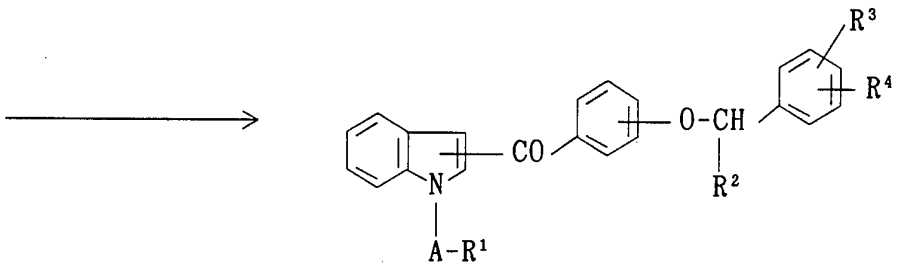
or a salt thereof

+



(III)

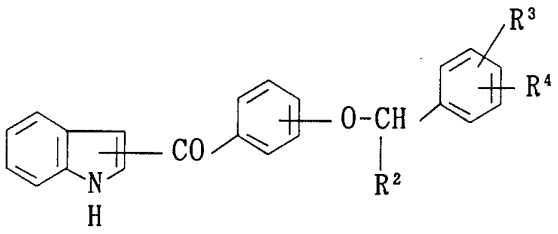
or a salt thereof



(I)

or a salt thereof

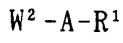
Process 2



(IV)

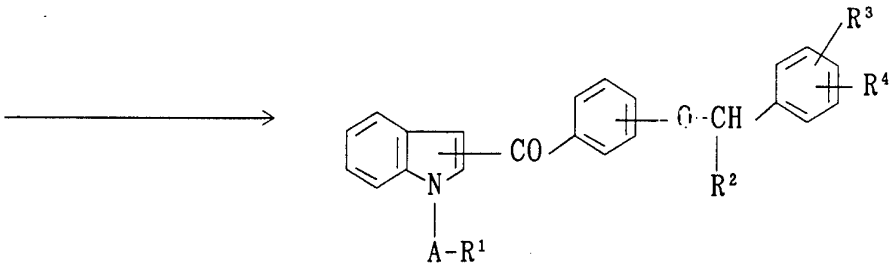
or a salt thereof

+



(V)

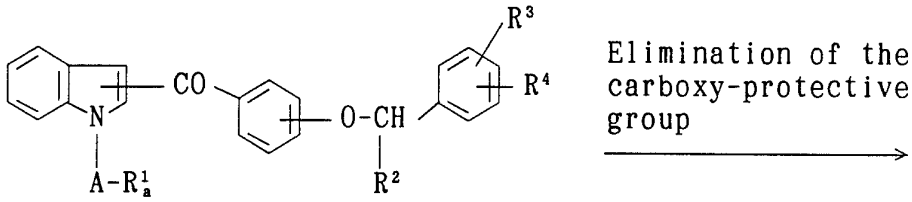
or a salt thereof



(I)

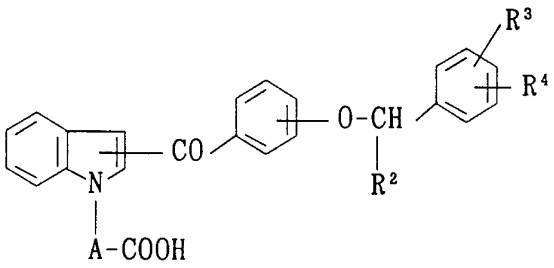
or a salt thereof

Process 3



(I-a)

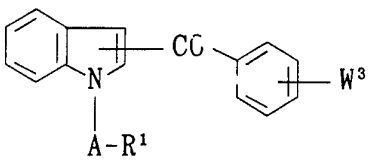
or a salt thereof



(I-b)

or a salt thereof

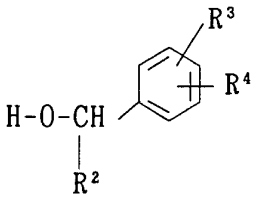
Process 4



(VI)

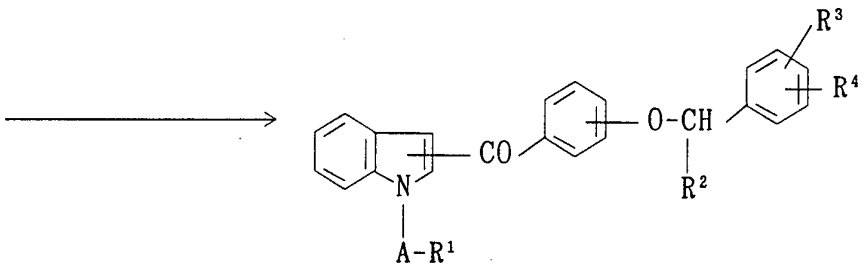
or a salt thereof

+



(VII)

or a salt thereof



(I)

or a salt thereof

wherein each of R^1, R^2, R^3, A, X and Y is as defined above,

R^1_a is a protected carboxy,

W^1 is a leaving group, and

W^2 and W^3 are each an acid residue.

Suitable salts of the compound (I) are conventional, non-toxic, pharmaceutically acceptable salts and include salts with base or acid addition salts. There are exemplified salts with inorganic base such as alkali metal salts (e.g. sodium salt, potassium salt, cesium salt), alkaline earth metal salts (e.g. calcium salt, magnesium salt) and ammonium salts; salts with organic base such as organic amine salts (e.g. triethylamine

salt, pyridine salt, picoline salt, ethanolamine salt, triethanolamine salt, dicyclohexylamine salt, N,N'-dibenzylethylenediamine salt); inorganic acid addition salts (e.g. hydrochloride, hydrobromide, sulfate, phosphate); organic carboxylic or sulfonic acid addition salts (e.g. formate, acetate, trifluoroacetate, maleate, tartrate, methanesulfonate, benzenesulfonate, p-toluenesulfonate); and salts with basic or acidic amino acid (e.g. arginine, aspartic acid, glutamic acid). The preferable examples thereof are acid addition salts.

Suitable examples of the salts of the compounds (I-a), (I-b), (II), (III), (IV), (V), (VI) and (VII) in Processes 1 to 4 are to be referred to those as exemplified for the object compound (I).

In the above and subsequent descriptions of the present specification, suitable examples and illustrations of the various definitions which the present invention includes within the scope thereof are detailedly as follows:

The term "lower" means that the number of carbon atom is from 1 to 6, preferably 1 to 4, unless otherwise indicated.

Suitable "lower alkyl" includes straight or branched ones having 1 to 6 carbon atoms, such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, t-butyl, pentyl and hexyl, preferable ones having 1 to 4 carbon atoms.

"Halo(lower)alkyl" has one, two or three halogen atoms. Suitable "mono- or di- or tri-halo(lower)alkyl" includes

chloromethyl, fluoromethyl, chloroethyl, dichloromethyl, difluoromethyl, trifluoromethyl, trifluoropropyl and trifluoromethylpropyl.

The term "halogen" means fluoro, chloro, bromo and iodo.

Suitable "lower alkylene" includes straight or branched bivalent lower alkanes such as methylene, ethylene, trimethylene, tetramethylene, pentamethylene, hexamethylene and propylene.

Suitable "leaving group" includes hydroxy, and reactive groups derived from hydroxy.

Suitable "reactive group derived from hydroxy" includes acid residues.

Suitable "acid residue" includes halogen (e.g. fluoro, chloro, bromo, iodo) and acyloxy (e.g. acetoxy, tosyloxy, mesyloxy).

Suitable "protected carboxy" includes esterified carboxyl groups.

Suitable examples of the ester moiety of "esterified carboxy" are, for instance, lower alkyl ester (e.g. methyl ester, ethyl ester, propyl ester, isopropyl ester, butyl ester, isobutyl ester, tert-butyl ester, pentyl ester, hexyl ester, 1-cyclopropylethyl ester) which may have one or more suitable substituents such as lower alkanoyloxy(lower)alkyl ester [e.g. acetoxymethyl ester, propionyloxymethyl ester, butyryloxymethyl ester, valeryloxymethyl ester, pivaloyloxymethyl ester, hexanoyl-oxymethyl ester, 1(or 2)-acetoxyethyl ester, 1(or 2 or 3)-

acetoxypropyl ester, 1(or 2 or 3 or 4)-acetoxybutyl ester, 1(or 2)-propionyloxyethyl ester, 1(or 2 or 3)-propionyloxypropyl ester, 1(or 2)-butyryloxyethyl ester, 1(or 2)-isobutyryloxyethyl ester, 1(or 2)-pivaloyloxyethyl ester, 1(or 2)-hexanoyloxyethyl 3,3-dimethylbutyryloxymethyl ester, 1(or 2)-pentanoyloxyethyl ester], lower alkanesulfonyl(lower)alkyl ester [e.g. 2-mesylethyl-ester], mono(or di or tri)-halo(lower)alkyl ester [e.g. 2-iodo-ethyl ester, 2,2,2-trichloroethyl ester], lower alkoxycarbonyl-oxy(lower)alkyl ester [e.g. methoxycarbonyloxymethyl ester, ethoxycarbonyloxymethyl ester, 2-methoxycarbonyloxyethyl ester, 1-ethoxycarbonyloxyethyl ester, 1-isopropoxycarbonyloxyethyl ester], phthalidylidene(lower)alkyl ester, or (5-lower alkyl-2-oxo-1,3-dioxol-4-yl)(lower)alkyl ester [e.g. (5-methyl-2-oxo-1,3-dioxol-4-yl)methyl ester, (5-ethyl-2-oxo-1,3-dioxol-4-yl)-methyl ester, (5-propyl-2-oxo-1,3-dioxol-4-yl)ethyl ester]; lower alkenyl ester [e.g. vinyl ester, allyl ester]; lower alkynyl ester [e.g. ethynyl ester, propynyl ester]; ar(lower)-alkyl ester which may have one or more suitable substituents [e.g. benzyl ester, 4-methoxybenzyl ester, 4-nitrobenzyl ester, phenethyl ester, trityl ester, benzhydryl ester, bis(methoxy-phenyl)methyl ester, 3,4-dimethoxybenzyl ester, 4-hydroxy-3,5-di-tert-butylbenzyl ester]; aryl ester which may have one or more suitable substituents [e.g. phenyl ester, 4-chlorophenyl ester, tolyl ester, tert-butylphenyl ester, xylyl ester, mesityl ester, cumenyl ester]; and phthalidyl ester.

Preferable examples of the esterified carboxy as mentioned

above include lower alkoxycarbonyl (e.g. methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, isopropoxycarbonyl, butoxycarbonyl, isobutoxycarbonyl, tert-butoxycarbonyl, pentyloxycarbonyl, tert-pentyloxycarbonyl, hexyloxycarbonyl, 1-cyclopropylethoxycarbonyl).

Particularly, the preferred embodiments of R^1, R^2, R^3, A, X and Y are as follows:

R^1 is carboxy and lower alkoxycarbonyl, more preferably, C_1-C_4 alkoxycarbonyl (e.g. ethoxycarbonyl),

R^2 is C_1-C_4 alkyl (e.g. propyl, butyl), mono- or tri-halo-(C_1-C_4)alkyl (e.g. chloroethyl, trifluoropropyl), and phenyl,

R^3 is C_1-C_4 alkyl (e.g. isobutyl),

R^4 is hydrogen and halogen (e.g. fluoro), and

A is C_1-C_4 alkylene (e.g. trimethylene).

The processes 1 to 4 for preparing the object compound (I) of the present invention are explained in detail in the following.

Process 1

The object compound (I) and a salt thereof can be prepared by reacting the compound (II) or a salt thereof with the compound (III) or a salt thereof.

Suitable salts of the compounds (II) and (III) can be referred to ones as exemplified for the compound (I).

This reaction is usually carried out in a solvent such as an alcohol [e.g. methanol, ethanol], dichloromethane, benzene,

N,N-dimethylformamide, tetrahydrofuran, diethyl ether, toluene or any other solvent which does not adversely affect the reaction. These solvents may be used alone or upon mixing with one another.

In this reaction, when W^1 in the compound (III) is an acid residue, the reaction may be carried out in the presence of an inorganic or organic base. Examples of the base are, for instance, alkali metal hydroxides [e.g. sodium hydroxide, potassium hydroxide], alkali metal carbonates [e.g. sodium carbonate, potassium carbonate], alkali metal bicarbonates [e.g. sodium bicarbonate, potassium bicarbonate], alkali metal hydrides [e.g. sodium hydride, potassium hydride], tri(lower)-alkylamines [e.g. trimethylamine, triethylamine, diisopropyl-ethylamine], and pyridine and its derivatives [e.g. picoline, lutidine, 4-dimethylaminopyridine]. In case where the base to be used is a liquid, it can also be used as a solvent.

When W^1 in the compound (III) is hydroxy, this reaction is usually carried out in the presence of a conventional condensing agent. Examples of the condensing agent are, for instance, N,N'-dicyclohexylcarbodiimide; N-cyclohexyl-N'-morpholinoethyl-carbodiimide; N-cyclohexyl-N'-(4-diethylaminocyclohexyl)carbo-diimide; N,N'-diethylcarbodiimide; N,N'-diisopropylcarbodiimide; N-ethyl-N'-(3-dimethylaminopropyl)carbodiimide; N,N'-carbonyl-bis(2-methylimidazole); pentamethyleneketene-N-cyclohexylimine; diphenylketene-N-cyclohexylimine; ethoxyacetylene; 1-alkoxy-1-chloroethylene; trialkyl phosphite; ethyl polyphosphate;

isopropyl polyphosphate; phosphorus oxychloride (phosphoryl chloride); phosphorus trichloride; thionyl chloride; oxalyl chloride; lower alkyl haloformate [e.g. ethyl chloroformate, isopropyl chloroformate]; a combination of triarylphosphine [e.g. triphenylphosphine] or tri(lower)alkylphosphine [e.g. triethylphosphine], and di(lower)alkyl azodicarboxylate [e.g. diethyl azodicarboxylate]; 2-ethyl-7-hydroxybenzisoxazolium salt; 2-ethyl-5-(m-sulfophenyl)isoxazolium hydroxide intramolecular salt; 1-(p-chlorobenzenesulfonyloxy)-6-chloro-1H-benzotriazole; so-called Vilsmeier reagent prepared by the reaction of N,N-dimethylformamide with thionyl chloride; phosgene; trichloromethyl chloroformate; and phosphorus oxychloride.

The reaction temperature is not critical, and the reaction can be carried out under cooling, at room temperature or under warming or heating.

Process 2

The object compound (I) or a salt thereof can be prepared by reacting the compound (IV) or a salt thereof with the compound (V) or a salt thereof.

This reaction can be carried out in substantially the same manner as Process 1, and therefore the reaction mode and reaction conditions [e.g. solvents, reaction temperature] of this reaction are to be referred to those as explained in Process 1.

Process 3

The object compound (I-b) and a salt thereof can be prepared by subjecting the compound (I-a) or a salt thereof to an elimination reaction of the carboxy-protective group.

In the present elimination reaction, all conventional methods used for the elimination of the carboxy-protective group, for example, hydrolysis, reduction, elimination using a Lewis acid, etc. are applicable. When the carboxy-protective group is an ester, it can be eliminated by hydrolysis or elimination using a Lewis acid. The hydrolysis is preferably carried out in the presence of a base or an acid.

Suitable base includes, for example, inorganic bases such as alkali metal hydroxides (e.g. sodium hydroxide, potassium hydroxide), alkaline earth metal hydroxides (e.g. magnesium hydroxide, calcium hydroxide), alkali metal carbonates (e.g. sodium carbonate, potassium carbonate), alkaline earth metal carbonates (e.g. magnesium carbonate, calcium carbonate), alkali metal bicarbonates (e.g. sodium bicarbonate, potassium bicarbonate), alkali metal acetates (e.g. sodium acetate, potassium acetate), alkaline earth metal phosphates (e.g. magnesium phosphate, calcium phosphate), and alkali metal hydrogen phosphates (e.g. disodium hydrogen phosphate, dipotassium hydrogen phosphate); and organic bases such as trialkylamines (e.g. trimethylamine, triethylamine), picoline, N-methylpyrrolidine, N-methylmorpholine, and 1,5-diazabicyclo-[4.3.0]non-5-one, 1,4-diazabicyclo[2.2.2]octane, and 1,5-diazabicyclo[5.4.0]undecene-5. The hydrolysis using a base is

often carried out in water or a hydrophilic organic solvent or a mixed solvent thereof.

Suitable acid includes organic acids (e.g. formic acid, acetic acid, propionic acid) and inorganic acids (e.g. hydrochloric acid, hydrobromic acid, sulfuric acid). The present hydrolysis is usually carried out in an organic solvent, water or a mixed solvent thereof.

The reaction temperature is not critical, and it may be selected suitably in accordance with the kind of carboxy protective group and elimination method.

The elimination using a Lewis acid is preferable for eliminating a substituted or unsubstituted ar(lower)alkyl ester, and carried out by reacting the compound (I-a) or a salt thereof with a Lewis acid. Examples of the Lewis acid are boron trihalides (e.g. boron trichloride, boron trifluoride), titanium tetrahalides (e.g. titanium tetrachloride, titanium tetrabromide), tin tetrahalides (e.g. tin tetrachloride, tin tetrabromide), aluminum halides (e.g. aluminum chloride, aluminum bromide), and trihaloacetic acids (e.g. trichloroacetic acid, trifluoroacetic acid). This elimination reaction is preferably carried out in the presence of cation trapping agents (e.g. anisole, phenol) and is usually carried out in a solvent such as nitroalkane (e.g. nitromethane, nitroethane), alkylene halide (e.g. methylene chloride, ethylene chloride), diethyl ether, carbon disulfide or any other solvent which does not adversely affect the reaction.

These solvents may be used alone or upon mixing with one another.

The reduction elimination can be preferably conducted for eliminating a protective group such as halo(lower)alkyl (e.g. 2-iodoethyl, 2,2,2-trichloroethyl) ester, and ar(lower)alkyl (e.g. benzyl) ester.

The reduction applicable for the elimination reaction includes the reduction using a combination of a metal (e.g. zinc, zinc amalgam) or salt of chromium compound (e.g. chromous chloride, chromous acetate) and an organic or inorganic acid (e.g. acetic acid, propionic acid, hydrochloric acid); and conventional catalytic reduction in the presence of a conventional metallic catalyst (e.g. palladium carbon, Raney nickel).

The reaction temperature is not critical, and the reaction is usually carried out under cooling, at ambient temperature or under warming.

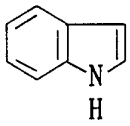
Process 4

The object compound (I) or a salt thereof can be prepared by reacting the compound (VI) or a salt thereof with the compound (VII) or a salt thereof.

This reaction can be carried out in substantially the same manner as Process 1, and therefore the reaction mode and reaction conditions [e.g. solvents, reaction temperature] of this reaction are to be referred to those as explained in Process 1.

The starting compounds (IV) and (VI) include novel compounds which can be prepared by the following methods or in a conventional manner. The details of the following methods and conventional ones are shown in Preparation Examples to be mentioned below.

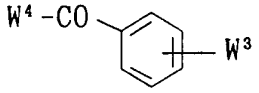
Method A-(1)



(VIII)

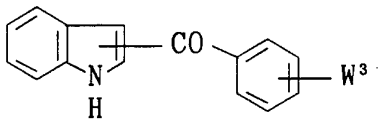
or a salt thereof

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(IX)

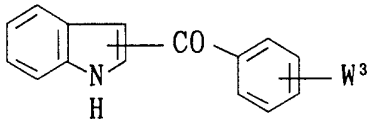
or a salt thereof



(X)

or a salt thereof

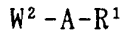
Method A-(2)



(X)

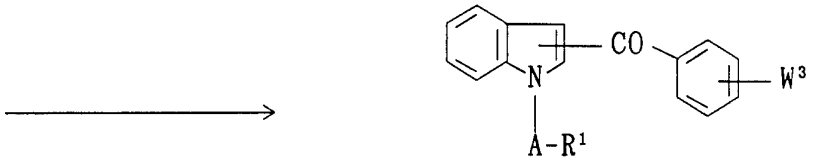
or a salt thereof

+



(V)

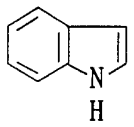
or a salt thereof



(VI)

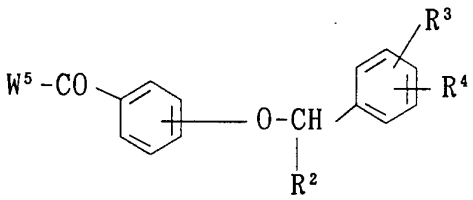
or a salt thereof

Method B

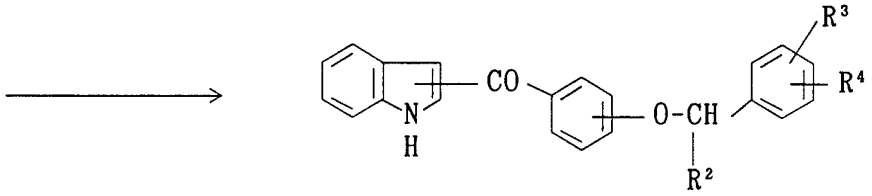


(VIII)
or a salt thereof

+



(XI)
or a salt thereof



(IV)

or a salt thereof

wherein R^1, R^2, R^3, A, X, Y, W^2 and W^3 are each as defined above,

and W^4 and W^5 are each an acid residue.

Methods A and B can be carried out in a conventional manner.

The object compound (I) of the present invention can be isolated and purified in a conventional manner such as extraction, precipitation, fractional crystallization, recrystallization, or chromatography.

The object compound (I) thus obtained can be converted to its salt by a conventional method.

The object compound (I) of the present invention is useful as a testosterone 5 α-reductase inhibitor and effective for testosterone 5α-reductase mediated diseases such as prostatism, prostatic hypertrophy, prostatic cancer, alopecia, hirsutism (e.g. female hirsutism), androgenic alopecia (or male-pattern baldness), acne (e.g. acne vulgaris, pimple), other hyperandrogenism, and the like.

For therapeutic or preventive administration, the object compound (I) of the present invention is used in the form of a conventional pharmaceutical preparation which contains said compound as an active ingredient, in admixture with pharmaceutically acceptable, substantially non-toxic carriers such as an organic or inorganic solid or liquid excipient which is suitable for oral, parenteral and external administration. The pharmaceutical preparation may be in a solid form such as tablet, granule, powder or capsule, or a liquid form such as solution, suspension, syrup, emulsion, lemonade or lotion.

If needed, there may be included in the above preparations auxiliary substances, stabilizing agents, wetting agents and other commonly used additives such as lactose, citric acid, tartaric acid, stearic acid, magnesium stearate, terra alba, sucrose, corn starch, talc, gelatin, agar, pectin, peanut oil, olive oil, cacao butter, and ethylene glycol.

While the dosage of the compound (I) may vary depending

upon age and conditions of patients, the kind of diseases or conditions, the kind of the compound (I) to be used, etc. In general, amounts between about 0.01 mg and about 500 mg or even more per day may be administered to a patient. An average single dose of about 0.05 mg, 0.1 mg, 0.25 mg, 0.5 mg, 1 mg, 20 mg, 50 mg, 100 mg of the object compound (I) of the present invention may be used for treating diseases.

The following Preparation Examples and Examples are given for the purpose of illustrating the present invention.

Preparation Example 1

To a solution of 4'-isobutyl-3-chloropropiophenone (1.12 g) in methanol was added sodium borohydride at 0℃ while stirring, and the mixture was reacted for 1 hour. Then, an aqueous potassium biphosphate solution was added thereto and concentrated in vacuo. The residue was extracted with diethyl ether. The organic layer was washed with water and brine, dried over sodium sulfate and concentrated in vacuo. The residue was chromatographed on silica gel (hexane : ethyl acetate = 4 : 1 by v/v) to give 1-(4-isobutylphenyl)-3-chloropropanol as an oil (1.10 g).

^{1}H-NMR ($CDCl_3$, δ) : 0.90 (d, 6H, J=7Hz), 1.75 - 2.4 (m, 4H), 2.48 (d, 2H, J=7Hz), 3.5 - 3.8 (m, 4H), 4.91 (dd, 1H, J=3Hz, 7Hz), 7.14 (d, 2H, J=8.5Hz), 7.28 (d, 2H, J=7Hz)

Preparation Example 2

To a solution of benzoyl chloride (7.03 g) in methylene chloride was added aluminum chloride, and the mixture was

reacted. After 10 minutes, isobutylbenzene (6.71 g) was added to the reaction mixture. After 3 hours, water was added to the reaction mixture and it was extracted with methylene chloride. The organic layer was washed with an aqueous sodium hydrogencarbonate solution and brine, dried over sodium sulfate and evaporated in vacuo. The residue was chromatographed on silica gel (hexane : methylene chloride = 1 : 1 by v/v) to give 4'-isobutylbenzophenone (11.8 g).

^{1}H-NMR ($CDCl_3$, δ) : 0.94 (d, 6H, J=7Hz), 1.75 - 2.05 (m, 1H), 2.57 (d, 2H, J=7Hz), 7.27 (d, 2H, J=9Hz), 7.35 - 7.85 (m, 7H)

Preparation Example 3

(4-Isobutylphenyl)phenyl methanol was obtained from 4'-isobutylbenzophenone (10.80 g) obtained in Pre. Ex. 2, in a manner similar to that of Pre. Ex. 1.

Yield : 10.70 g

^{1}H-NMR ($CDCl_3$, δ) : 0.89 (d, 6H, J=7Hz), 1.7 - 1.95 (m, 1H), 2.19 (d, 1H, J=4Hz), 2.45 (d, 2H, J=7Hz), 5.33 (d, 1H, J=4Hz), 7.11 (d, 2H, J=8Hz), 7.15 - 7.45 (m, 7H)

Preparation Example 4

A mixture of 3-fluoro-4-methylbenzoic acid (19.32 g), iodomethane (15.6 ml) and potassium carbonate (34.6 g) in N,N-dimethylformamide (150 ml) was stirred at room temperature for 14 hours. The reaction mixture was filtered and the filtrate was poured into a mixture of ethyl acetate and water. The organic layer was separated, washed with water and brine, dried

over magnesium sulfate and concentrated. The residue was chromatographed on silica gel column with a mixture of n-hexane and ethyl acetate (9 : 1 by v/v) as eluent to give methyl 3-fluoro-4-methylbenzoate as an oil (20.13 g).

^{1}H-NMR ($CDCl_3$, δ) : 2.33 (s, 3H), 3.91 (s, 3H), 7.26 (t, 1H, J=7.5Hz), 7.6 - 7.8 (m, 2H)

Preparation Example 5

A mixture of methyl 3-fluoro-4-methylbenzoate (20.1 g), N-bromosuccinimide (23.4 g) and benzoyl peroxide (29 mg) in carbon tetrachloride (200 ml) was heated under reflux for 4 hours. The reaction mixture was cooled and filtered. The filtrate was concentrated and the residue was chromatographed on silica gel colomn with a mixture of n-hexane and ethyl acetate (40 : 1 by v/v) as eluent to give methyl 4-(bromomethyl)-3-fluorobenzoate (14.7 g) as an oil.

^{1}H-NMR ($CDCl_3$, δ) : 3.94 (s, 3H), 4.52 (s, 2H), 7.48 (t, 1H, J=7.5Hz), 7.7 - 7.85 (m, 2H)

Preparation Example 6

A mixture of methyl 4-(bromomethyl)-3-fluorobenzoate (14.57 g) obtained in Pre. Ex. 5 and triethylphosphite (15.2 ml) was heated under nitrogen atmosphere at 50℃ for 30 minutes. The temperature was then raised to 200℃ and the temperature was kept for 2 hours. The obtained bright yellow liquid was then cooled and chromatographed on silica gel column with ethyl acetate as eluent to give diethyl (2-fluoro-4-methoxycarbonyl-benzyl)-phosphonate as an oil (15.66 g).

^{1}H-NMR ($CDCl_3$, δ) : 1.27 (t, 6H, J=7Hz), 3.26 (d, 2H, J=22Hz), 3.92 (s, 3H), 4.05 (q, 4H, J=7Hz), 7.4 - 7.5 (m, 1H), 7.65 - 7.85 (m, 2H)

Preparation Example 7

To a suspension of 60% sodium hydride-oil dispersion (1.16 g) in N,N-dimethylformamide (40 ml) was added dropwise diethyl (2-fluoro-4-methoxycarbonylbenzyl)phosphonate obtained in Pre. Ex. 6 (7.9 g) in N,N-dimethylformamide (40 ml). After stirring at room temperature for 2 hours, acetone (10.7 ml) was added thereto, and the stirring was continued at room temperature for 2 hours. The reaction mixture was then poured into diluted hydrochloric acid cooled with ice. The mixture was extracted with diethyl ether. The organic layer was washed with water and brine, dried over magnesium sulfate and concentrated. The residue was chromatographed on silica gel column with a mixture of n-hexane and ethyl acetate (9 : 1 by v/v) as eluent to give methyl 3-fluoro-4-(2-methyl-1-propenyl)-benzoate as an oil (4.45 g).

^{1}H-NMR ($CDCl_3$, δ) : 1.82 (s, 3H), 1.97 (s, 3H), 3.92 (s, 3H), 6.25 (s, 1H), 7.30 (t, 1H J=7.5Hz), 7.65 - 7.8 (m, 2H)

Preparation Example 8

A mixture of methyl 3-fluoro-4-(2-methyl-1-propenyl)-benzoate obtained in Pre. Ex. 7 (8.65 g) and 10% palladium carbon (0.4 g) in methanol (50 ml) and 1,4-dioxane (50 ml) was stirred at room temperature under hydrogen atmosphere for 1 hour. The catalyst was removed by filtration and the filtrate

was concentrated to give methyl 3-fluoro-4-isobutylbenzoate as an oil (8.72 g).

^{1}H-NMR ($CDCl_3$, δ) : 0.92 (d, 6H, J=7Hz), 1.8 - 2.05 (m, 1H), 2.57 (d, 2H, J=7Hz), 3.91 (s, 3H), 7.21 (t, 1H J=7.5Hz), 7.6 - 7.8 (m, 2H)

Preparation Example 9

To a solution of methyl 3-fluoro-4-isobutylbenzoate obtained in Pre. Ex. 8 (8.72 g) in tetrahydrofuran (100 ml) was added 1.0 M solution of lithium aluminum hydride in tetrahydrofuran (25 ml) at 0 ℃ and the mixture was stirred at 0℃ for 2 hours. To the reaction mixture was added dropwise an aqueous solution of tetrahydrofuran (THF : water = 1 : 1 by v/v) while cooling. The resulting mixture was poured into a mixture of ethyl acetate and 0.5N hydrochloric acid. The organic layer was separated, washed with water and brine, dried over magnesium sulfate and concentrated to give 3-fluoro-4-isobutylbenzyl alcohol as an oil (7.25 g).

^{1}H-NMR ($CDCl_3$, δ) : 0.91 (d, 6H, J=7Hz), 1.69 (t, 1H, J=6Hz), 1.75 - 2.05 (m, 1H), 2.50 (d, 2H, J=7Hz), 4.67 (d, 2H, J=6Hz), 7.0 - 7.3 (m, 3H)

Preparation Example 10

To a mixture of 3-fluoro-4-isobutylbenzyl alcohol obtained in Pre. Ex. 9 (7.04 g) and triethylamine (32.3 ml) in dimethyl sulfoxide (50 ml) was added a mixture of sulfur trioxide pyridine complex (24.6 g) in dimethyl sulfoxide (100 ml). The mixture was stirred at room temperature for 30 minutes and then

poured into a mixture of ethyl acetate and 0.5N hydrochloric acid. The organic layer was separated, washed with water and brine, dried over magnesium sulfate, and concentrated to give 3-fluoro-4-isobutylbenzaldehyde as an oil (6.90 g).

^{1}H-NMR ($CDCl_3$, δ) : 0.94 (d, 6H, J=7Hz), 1.85 - 2.05 (m, 1H), 2.59 (d, 2H, J=7Hz), 7.33 (t, 1H, J=7.5Hz), 7.5 - 7.65 (m, 2H), 9.95 (s, 1H)

Preparation Example 11

A solution of propylmagnesium bromide was prepared in a usual manner, using diethyl ether (10 ml), magnesium (194 mg) and 1-bromopropane (0.727 ml). A solution of 3-fluoro-4-isobutylbenzaldehyde (721 mg) in diethyl ether (5 ml) was added dropwise to a Grinard solution and the mixture was stirred at 0℃ for 30 minutes. Aqueous ammonium chloride was added to the mixture, the organic phase was separated, washed with water and brine, dried over magnesium sulfate, and concentrated. The residue was chromatographed on silica gel column with a mixture of hexane and ethyl acetate (85 : 15 by v/v) as eluent to give 1-(3-fluoro-4-isobutylphenyl)butanol as an oil (825 mg).

^{1}H-NMR ($CDCl_3$, δ) : 0.85 - 1.0 (m, 9H), 1.2 - 1.55 (m, 2H), 1.6 - 2.05(m, 4H), 2.49 (d, 2H, J=7Hz), 4.6 - 4.7 (m, 1H), 6.95-7.2 (m, 3H)

Preparation Example 12

Chromium(VI) oxide (1.46 g) was added portionwise to pyridine (20 ml). After stirring for 30 minutes at room temperature, 1-(3-fluoro-4-isobutylphenyl)butanol (0.82 g) was

added thereto, and the mixture was stirred at room temperature for 3 hours. Water was added to the mixture and extracted with diethyl ether. The organic solution was washed with 0.5N hydrochloric acid, water and brine, dried over magnesium sulfate, and consentrated. The residue was chromatographed on silica gel column with a mixture of hexane and ethyl acetate (25 : 1 by v/v) as eluent to give 3'-fluoro-4'-isobutylbutyrophenone as an oil (0.78 g).

^{1}H-NMR ($CDCl_3$, δ) : 0.85 - 1.05 (m, 9H), 1.65 - 2.05 (m, 3H), 2.57 (d, 2H, J=7Hz), 2.90 (t, 2H, J=7.5Hz), 7.23 (t, 1H, J=7.5Hz), 7.55 - 7.7 (m, 2H)

Preparation Example 13

3'-Fluoro-4'-isobutylbutyrophenone (0.78 g) obtained in Pre. Ex. 12 was added to a solution of (+)-B-chlorodiisopinocampheyl-borane (1.34 g) in tetrahydrofuran at -20℃. After 7 hours, the solvent was removed and the residue was dissolved in diethyl ether (20 ml), diethanolamine (0.80 ml) was added, and the mixture was stirred at room temperature for 1 hour. The resultant solid was filtered off and washed with diethyl ether, the combined filtrates were concentrated and the residue was chromatographed on silica gel column (hexane : ethyl acetate = 6 : 1 by v/v, as eluent) to give (R)-1-(3-fluoro-4-isobutylphenyl)butanol as an oil (0.48 g).

^{1}H-NMR ($CDCl_3$, δ) : 0.8 - 1.0 (m, 9H), 1.15 - 2.0 (m, 6H), 2.49 (d, 2H, J=7Hz), 4.64 (t, 1H, J=6.5Hz), 6.95 - 7.2 (m, 3H)

Preparation Example 14

1-(3-Fluoro-4-isobutylphenyl)pentanol was prepared from 3-fluoro-4-isobutylbenzaldehyde (5.70 g) and 1-bromobutane (6.8 ml) in a manner similar to that of Pre. Ex. 11.

Yield : 7.31 g

^{1}H-NMR ($CDCl_3$, δ) : 0.8 - 0.95 (m, 9H), 1.15 - 1.5 (m, 2H), 1.6 - 2.0 (m, 4H), 2.49 (d, 2H, J=7Hz), 4.55 - 4.7 (m, 1H), 6.95 - 7.2 (m, 3H)

Preparation Example 15

3'-Fluoro-4'-isobutylvalerophenone was prepared from 1-(3-fluoro-4-isobutylphenyl)pentanol (7.25 g) obtained in Pre. Ex. 14, in a manner similar to that of Pre. Ex. 12.

Yield : 6.76 g

^{1}H-NMR ($CDCl_3$, δ) : 0.85 - 1.0 (m, 9H), 1.3 - 1.5 (m, 2H), 1.6 - 1.8 (m, 2H), 1.8 - 2.05 (m, 1H), 2.57 (d, 2H, J=7Hz), 2.92 (t, 2H, J=7.5Hz), 7.23 (t, 1H, J=7.5Hz), 7.55 - 7.7 (m, 2H)

Preparation Example 16

(R)-1-(3-Fluoro-4-isobutylphenyl)pentanol was prepared from 3'-fluoro-4'-isobutylvalerophenone (6.70 g) obtained in Pre. Ex. 15, in a manner similar to that of Pre. Ex. 13.

Yield : 6.02 g

^{1}H-NMR ($CDCl_3$, δ) : 0.8 - 1.0 (m, 9H), 1.15 - 1.5 (m, 2H), 1.6 - 2.0 (m, 4H), 2.49 (d, 2H, J=7Hz), 4.6 - 4.7 (m, 1H), 6.95 - 7.2 (m, 3H)

Preparation Example 17

To a solution of 4,4,4-trifluorobutyric acid (4.15 g) in dichloromethane (50 ml) was added oxalyl chloride (2.55 ml) and several drops of N,N-dimethylformamide. After the mixture was stirred at room temperature for 1 hour, the solvent was evaporated. The residue was dissolved in dichloromethane (100 ml), and then aluminum chloride (3.89 g) was added to the solution at 0℃. After the mixture was stirred at 0℃ for 30 minutes, isobutylbenzene (3.92 g) was added. The mixture was stirred at 0℃ for 1 hour and poured into ice water. The organic phase was separated, washed with water, aqueous sodium bicarbonate and brine, and dried over magnesium sulfate. Evaporation of the solvent gave 4'-isobutyl-4,4,4-trifluoro-butyrophenone (6.80 g) as an oil.

^{1}H-NMR ($CDCl_3$, δ) : 0.91 (6H, d, J=7Hz), 1.75 - 2.05 (1H, m), 2.45 - 2.7 (4H, m), 3.25 (2H, t, J=8Hz), 7.26 (2H, d, J=8Hz), 7.39 (2H, d, J=8Hz)

Preparation Example 18

4,4,4-Trifluoro-1-(4-isobutylphenyl)butanol was obtained according to a method similar to that of Preparation Example 1.

^{1}H-NMR ($CDCl_3$, δ) : 0.90 (6H, d, J=7Hz), 1.75 - 2.4 (6H, m), 2.48 (2H, d, J=7Hz), 4.72 (1H, t, J=6.5Hz), 7.15 (2H, d, J=8Hz), 7.25 (2H, d, J=8Hz)

Example 1

Diethyl azodicarboxylate (0.121 ml) was added to a mixture of ethyl 4-[3-(4-hydroxybenzoyl)-1-indolyl]butyrate (246 mg), 1-(4-isobutylphenyl)-3-chloropropanol obtained in Pre. Ex. 1

(175 mg) and triphenylphosphine (202 mg) in a mixture (9 ml) of tetrahydrofuran and toluene at -20 ℃. After the mixture was reacted for 4 hours, the reaction mixture was evaporated in vacuo and chromatographed on silica gel (hexane : ethyl acetate = 3 : 1 by v/v as eluent) to give ethyl 4-[3-[4-[1-(4-isobutylphenyl)-3-chloropropoxy]benzoyl]-1-indolyl]butyrate as an oil (296 mg).

^{1}H-NMR ($CDCl_3$, δ) : 0.89 (d, 6H, J=7Hz), 1.20 (t, 3H, J=7Hz), 1.75 - 1.95 (m, 1H), 2.1 - 2.35 (m, 5H), 2.4 - 2.6 (m, 3H), 3.55 - 3.7 (m, 1H), 3.75 - 3.9 (m, 1H), 4.10 (q, 2H, J=7Hz), 4.23 (t, 2H, J=7Hz), 5.47 (dd, 1H, J=4Hz, 7Hz), 6.94 (d, 2H, J=9Hz), 7.13 (d, 2H, J=8.5Hz), 7.25 - 7.45 (m, 5H), 7.53 (s, 1H), 7.73 (d, 2H, J=9Hz), 8.3 - 8.4 (m, 1H)

Example 2

To a solution of ethyl 4-[3-[4-[1-(4-isobutylphenyl)-3-chloropropoxy]benzoyl]-1-indolyl]butyrate obtained in Ex. 1 (112 mg) in a mixture of ethanol (2 ml) and 1,4-dioxane (2 ml) was added 1N aqueous solution of sodium hydroxide (1 ml). The mixture was stirred at room temperature for 2 hours, and then poured into a mixture of ethyl acetate and 0.5N hydrochloric acid. The organic layer was separated, washed with water and brine, dried over magnesium sulfate and evaporated to give 4-[3-[4-[1-(4-isobutylphenyl)-3-chloropropoxy]benzoyl]-1-indolyl]butyric acid (98 mg).

^{1}H-NMR ($CDCl_3$, δ) : 0.88 (d, 6H, J=7Hz), 1.75 - 1.95 (m, 1H), 2.1 - 2.6 (m, 8H), 3.5 - 3.9 (m, 2H), 4.23 (t, 2H, J=7Hz),

5.45 (dd, 1H, J=4Hz, 7Hz), 6.94 (d, 2H, J=9Hz), 7.12 (d, 2H, J=8.5Hz), 7.2 - 7.45 (m, 5H), 7.54 (s, 1H), 7.73 (d, 2H, J=9Hz), 8.3 - 8.4 (m, 1H)

Example 3

Ethyl 4-[3-[4-[(4-isobutylphenyl)phenylmethoxy]benzoyl]-1-indolyl]butyrate was prepared from 4-(isobutylphenyl)phenyl-methanol (397 mg) obtained in Pre. Ex. 3 and ethyl 4-[3-(4-hydroxybenzoyl)-1-indolyl]butyrate (527 mg), in a manner similar to that of Ex. 1.

Yield : 285 mg

^{1}H-NMR ($CDCl_3$, δ) : 0.89 (d, 6H, J=7Hz), 1.20 (t, 3H, J=7Hz), 1.7 - 2.0 (m, 1H), 2.1 - 2.35 (m, 4H), 2.46 (d, 2H, J=7Hz), 4.10 (q, 2H, J=7Hz), 4.24 (t, 2H, J=7Hz), 6.29 (s, 1H), 7.04 (d, 2H, J=9Hz), 7.13 (d, 2H, J=8Hz), 7.2 - 7.5 (m, 10H), 7.54 (s, 1H), 7.77 (d, 2H, J=9Hz), 8.3 - 8.4 (m, 1H)

Example 4

4-[3-[4-[(4-Isobutylphenyl)phenylmethoxy]benzoyl]-1-indolyl]butyric acid was prepared from ethyl 4-[3-[4-[(4-isobutylphenyl)phenylmethoxy]benzoyl]-1-indolyl]butyrate (269 mg) obtained in Ex. 3, in a manner similar to that of Ex. 2.

Yield : 232 mg

^{1}H-NMR ($CDCl_3$, δ) : 0.88 (d, 6H, J=7Hz), 1.7 - 2.0 (m, 1H), 2.1 - 2.25 (m, 2H), 2.3 - 2.5 (m, 4H), 4.23 (t, 2H, J=7Hz), 6.28 (s, 1H), 7.03 (d, 2H, J=9Hz), 7.12 (d, 2H, J=8Hz), 7.2 - 7.5 (m, 10H), 7.54 (s, 1H), 7.77 (d, 2H, J=9Hz), 8.3 - 8.4 (m, 1H)

Example 5

(S)-Ethyl 4-[3-[4-[1-(3-fluoro-4-isobutylphenyl)butoxy]-benzoyl]-1-indolyl]butyrate was prepared from (R)-1-(3-fluoro-4-isobutylphenyl)butanol (197 mg) obtained in Pre. Ex. 13 and ethyl 4-[3-(4-hydroxybenzoyl)-1-indolyl]butyrate (281 mg), in a manner similar to that of Ex. 1.

Yield : 350 mg

^{1}H-NMR ($CDCl_3$, δ) : 0.85 - 1.05 (m, 9H), 1.21 (t, 3H, J=7Hz), 1.3 - 1.65 (m, 2H), 1.7 - 2.35 (m, 7H), 2.48 (d, 2H, J=7Hz), 4.10 (q, 2H, J=7Hz), 4.23 (t, 2H, J=7Hz), 5.15 (dd, 1H, J=5Hz, 8Hz), 7.92 (d, 2H, J=9Hz), 6.95 - 7.2 (m, 3H), 7.25 - 7.45 (m, 3H), 7.53 (s, 1H), 7.74 (d, 2H, J=9Hz), 8.3 - 8.4 (m, 1H)

Example 6

4-[3-[4-[1-(3-Fluoro-4-isobutylphenyl)butoxy]benzoyl]-1-indolyl]butyric acid was prepared from (S)-ethyl 4-[3-[4-[1-(3-fluoro-4-isobutylphenyl)butoxy]benzoyl]-1-indolyl]butyrate (265 mg) obtained in Ex. 5, in a manner similar to that of Ex. 2.

Yield : 219 mg

^{1}H-NMR ($CDCl_3$, δ) : 0.85 - 1.05 (m, 9H), 1.3 - 1.65 (m, 2H), 1.7 - 2.3 (m, 5H), 2.3 - 2.5 (m, 4H), 4.25 (t, 2H, J=7Hz), 5.13 (dd, 1H, J=5Hz, 8Hz), 6.91 (d, 2H, J=9Hz), 6.95 - 7.15 (m, 3H), 7.25 - 7.45 (m, 3H), 7.55 (s, 1H), 7.74 (d, 2H, J=9Hz), 8.3 - 8.4 (m, 1H)

Example 7

(S)-Ethyl 4-[3-[4-[1-(3-fluoro-4-isobutylphenyl)pentyloxy]-

benzoyl]-1-indolyl]butyrate was prepared from (R)-1-(3-fluoro-4-isobutylphenyl)pentanol (191 mg) obtained in Pre. Ex. 16 and ethyl 4-[3-(4-hydroxybenzoyl)-1-indolyl]butyrate (281 mg), in a manner similar to that of Ex. 1.

Yield : 273 mg

^{1}H-NMR ($CDCl_3$, δ) : 0.85 - 1.0 (m, 9H), 1.20 (t, 3H, J=7Hz), 1.25 - 1.6 (m, 4H), 1.75 - 2.35 (m, 7H), 2.48 (d, 2H, J=7Hz), 4.10 (q, 2H, J=7Hz), 4.24 (t, 2H, J=7Hz), 5.13 (dd, 1H, J=5Hz, 8Hz), 6.91 (d, 2H, J=7Hz), 6.95 - 7.2 (m, 3H), 7.25 - 7.45 (m, 3H), 7.53 (s, 1H), 7.74 (d, 2H, J=9Hz), 8.3 - 8.4 (m, 1H)

Example 8

(S)-4-[3-[4-[1-(3-Fluoro-4-isobutylphenyl)pentyloxy]-benzoyl]-1-indolyl]butyric acid was prepared from (S)-ethyl 4-[3-[4-[1-(3-fluoro-4-isobutylphenyl)pentyloxy]benzoyl]-1-indolyl]butyrate (232 mg) obtained in Ex. 7, in a manner similar to that of Ex. 2.

Yield : 197 mg

^{1}H-NMR ($CDCl_3$, δ) : 0.8 - 1.0 (m, 9H), 1.15 - 1.6 (m, 4H) 1.7 - 2.3 (m, 5H), 2.3 - 2.5 (m, 4H), 4.23 (t, 2H, J=7Hz), 5.12 (dd, 1H, J=5Hz, 8Hz), 6.91 (d, 2H, J=9Hz), 6.95 - 7.2 (m, 3H), 7.25 - 7.45 (m, 3H), 7.56 (s, 1H), 7.74 (d, 2H, J=9Hz), 8.3 - 8.4 (m, 1H)

Example 9

Ethyl 4-[3-[4-[carboxyl-(4-isobutylphenyl)methoxy]benzoyl]-1-indolyl]butyriate was hydrolyzed by using 1N sodium hydroxide

to give 4-[3-[4-[carboxyl-(4-isobutylphenyl)methoxy]benzoyl]-1-indolyl]butyric acid.

^{1}H-NMR ($CDCl_3$ + CD_3OD, δ) : 8.37 (m, 1H), 7.81 (d, 2H, J=8Hz), 7.58 (s, 1H), 7.53 (d, 2H, J=8Hz), 7.25 - 7.5 (m, 3H), 7.20 (d, 2H, J=8Hz), 7.05 (d, 2H, J=8Hz), 5.69 (s, 1H), 4.29 (t, 2H, J=7Hz), 2.2 - 2.4 (m, 4H), 1.87 (m, 1H), 0.90 (d, 6H, J=7Hz)

Example 10

Benzyl 4-[3-[3-[carboxy-(4-isobutylphenyl)methylamino]-benzoyl]-1-indolyl]butyriate was hydrogenated by using Pd-C in 1,4-dioxane to give 4-[3-[3-[carboxy-(4-isobutylphenyl)methyl-amino]benzoyl]-1-indolyl]butyric acid.

^{1}H-NMR ($CDCl_3$, δ) : 8.42 (m, 1H), 7.51 (m, 1H), 7.0 - 7.4 (m, 10H), 6.80 (m, 1H), 5.10 (s, 1H), 4.18 (m, 2H), 2.40 (d, 2H, J=7Hz), 2.1 - 2,4 (m, 4H), 1.80 (m, 1H), 0.85 (d, 6H, J=7Hz)

Example 11

[Step 1]:To a solution of ethyl 4-[3-(4-hydroxybenzoyl)-1-indolyl]butyrate (12.3 g) and diisopropylethylamine (7 ml) in tetrahydrofuran (100 ml) was added chloromethyl methyl ether (5 ml). The mixture was stirred for 4 hours at room temperature, evaporated and dissolved in ethyl acetate (100 ml). The solution was washed with water, dried over magnesium sulfate and evaporated. The residue was chromatographed on silica gel (500 ml) with chloroform as eluent to give ethyl 4-[3-[4-(methoxymethoxy)benzoyl]-1-indolyl]butyrate as a yellow oil

(9.27 g).

[Step 2]:To a solution of ethyl 4-[3-(4-methoxymethoxy)-benzoyl]-1-indolyl]butyrate (9.20 g) in ethanol (50 ml) was added 1N aqueous solution of sodium hydroxide (30 ml). The mixture was stirred for 1 hour at room temperature, evaporated and dissolved in ethyl acetate (100 ml). The solution was washed with 5% aqueous solution of citric acid and water, and dried over magnesium sulfate. The solvent was removed under reduced pressure to give 4-[3-[4-(methoxymethoxy)benzoyl]-1-indolyl]butyric acid as a yellow gum (7.50 g).

[Step 3]:To a solution of 4-[3-[4-(methoxymethoxy)benzoyl]-1-indolyl]butyric acid (3.67 g) in dichloromethane (30 ml) were added diisopropylethylamine (3 ml) and benzyl bromide (1.2ml). The mixture was stirred for 16 hours at room temperature, evaporated and dissolved in ethyl acetate (50 ml). The solution was washed with 5% aqueous solution of citric acid and water, dried over magnesium sulfate and evaporated. The residue was chromatographed on silica gel (100 g) eluting with a mixture of n-hexane and ethyl acetate to give benzyl 4-[3-[4-(methoxymethoxy)benzoyl]-1-indolyl]butyrate as a yellow oil (4.50 g).

[Step 4]:Trifluoroacetic acid (10 ml) and water (10 ml) were added to benzyl 4-[3-[4-(methoxymethoxy)benzoyl]-1-indolyl]butyrate (4.50 g) in dichloromethane (50 ml). The mixture was stirred for three days at room temperature. The mixture was washed with water and an aqueous sodium bicarbonate

solution, dried over magnesium sulfate and evaporated. The residue was chromatographed on silica gel (100 g) eluting with chloroform to give benzyl 4-[3-(4-hydroxybenzoyl)-1-indolyl]-butyrate as a yellow oil (2.56 g).

[Step 5]:Separately, to a solution of 2-hydroxy-2-(4-isobutylphenyl)acetic acid (1.0 g) in N,N-dimethyl-formamide (10 ml) were added potassium carbonate (2.0 g) and iodoethane (0.5 ml). The mixture was stirred at room temperature for 16 hours and poured into 7% hydrochloric acid in ice water. The organic layer was extracted with ethyl acetate (20 ml), washed with an aqueous sodium bicarbonate solution and water, and dried over magnesium sulfate. The solvent was removed in vacuo to give ethyl 2-hydroxy-2-(4-isobutylphenyl)acetate as an oil (1.00 g).

[Step 6]:To a solution of benzyl 4-[3-(4-hydroxybenzoyl)-1-indolyl]butyrate (0.41 g), ethyl 2-hydroxy-2-(4-isobutyl-phenyl)acetate (0.24 g) and triphenylphosphine (0.26 g) in a mixture of toluene (8 ml) and tetrahydrofuran (2 ml) was added diethyl azodicarboxylate (0.71 g) at -20℃. The mixture was stirred at -20℃ for 4 hours, and acetic acid (0.1 ml) was added to the mixture. After filtration, the solvent was removed under reduced pressure. The residue was chromatographed on silica gel (50 g) eluting with a mixture of n-hexane and ethyl acetate to give benzyl 4-[3-[4-[ethoxycarbonyl(4-isobutylphenyl)methoxy]benzoyl]-1-indolyl]butyrate (0.26 g).

[Step 7]:Benzyl 4-[3-[4-[ethoxycarbonyl(4-isobutylphenyl)-methoxy]benzoyl]-1-indolyl]butyrate (o.20 g) was dissolved in

ethanol (15 ml) and 10% palladium on carbon was added. The mixture was stirred at room temperature for 2 hours under hydrogen atmosphere. Filtration of catalyst and evaporation of the solvent gave a yellow oil. The oil was chromatographed on silica gel eluting with chloroform to give 4-[3-[4-[ethoxy-carbonyl(4-isobutylphenyl)methoxy]benzoyl]-1-indolyl]-butyric acid as a white powder (0.10 g).

^{1}H-NMR ($CDCl_3$, δ) : 8.37 (m, 1H), 7.82 (d, 2H, J=9Hz), 7.56 (s, 1H), 7.50 (d, 2H, J=9Hz), 7.25 - 7.45 (m, 3H), 7.20 (d, 2H, J=9Hz), 7.03 (d, 2H, J=9Hz), 5.68 (s, 1H), 4.1 - 4.35 (m, 4H), 2.49 (d, 2H, J=7Hz), 2.38 (t, 2H, 7Hz), 2.22 (m, 2H), 1.87 (m, 1H), 1.22 (t, 3H, J=7Hz), 0.90 (d, 6H, J=7Hz)

Example 12

[Step 1]:To a solution of benzylmagnesium chloride (2.26 g) in diethyl ether was added 4'-isobutylbutyrophenone (3.06 g). The mixture was stirred at room temperature for 1 hour, and then aqueous ammonium chloride was added. The organic layer was separated, washed with water and brine, dried over magnesium sulfate and concentrated. The residue was chromatographed on silica gel column eluting with a mixture of hexane and ethyl acetate to give 2-(4-isobutylphenyl)-1-phenyl-2-pentanol as an oil (2.73 g).

[Step 2]:To a solution of 2-(4-isobutylphenyl)-1-phenyl-2-pentanol (2.72 g) in pyridine (30 ml) was added thionyl chloride (5 ml) at 0℃. The mixture was stirred at 0℃ for 1 hour,

poured into ice water and extracted with diethyl ether. The organic layer was washed with 0.5N hydrochloric acid and water, dried over magnesium sulfate and concentrated. The residue was dissolved in a mixture of methanol (15 ml) and 1,4-dioxane (30 ml), and 10% palladium on carbon was added. The mixture was stirred under hydrogen atmosphere at room temperature for 1 hour. Removal of catalyst and evaporation of solvent gave 2-(isobutylphenyl)-1-phenylpentane as an oil (1.64 g).

[Step 3]:To a suspension of aluminum chloride (755 mg) in dichloromethane (10 ml) was added oxalyl chloride (0.51 ml) at 0℃. The mixture was stirred at 0℃ for 1 hour, and then 2-(isobutylphenyl)-1-phenylpentane (1.63 g) was added. After stirring for 2 hours, the mixture was poured into ice water, and extracted with dichloromethane. The organic layer was dried over magnesium sulfate and concentrated to give 4-[2-(4-isobutylphenyl)pentyl]benzoyl chloride as an oil (1.98 g).

[Step 4]:To a mixture of indole (2.03 g) and tetrahydrofuran (20 ml) was added 3 M solution of methylmagnesium bromide (6.6 ml). The mixture was stirred at room temperature for 1 hour, and then 4-[2-(4-isobutylphenyl)pentyl]benzoyl chloride (1.98 g) in tetrahydrofuran (20 ml) was added. After stirring for 1 hour, the mixture was poured into 0.5N hydrochloric acid in ice water, and extracted with ethyl acetate. The organic layer was washed with water and an aqueous solution of sodium bicarbonate, dried over magnesium sulfate and concentrated. The residue was chromatographed on silica gel column eluting with a

mixture of hexane and ethyl acetate to give 3-[4-[2-(4-isobutylphenyl)-pentyl]benzoyl]indole as a solid (494 mg).

[Step 5]:A mixture of 3-[4-[2-(4-isobutylphenyl)pentyl]-benzoyl]indole (424 mg), ethyl 4-bromobutyrate (234 mg) and potassium carbonate (415 mg) was stirred at room temperature for 6 hours. The insoluble materials were filtered off, and the filtrate was poured into a mixture of ethyl acetate and water. The organic layer was separated, washed with water and brine, dried over magnesium sulfate and concentrated. The residue was chromatographed on silica gel column with a mixture of hexane and ethyl acetate as eluent to give ethyl 4-[3-[4-[2-(4-isobutyl-phenyl)pentyl]benzoyl]-1-indolyl]butyrate as an oil (534 mg).

[Step 6]:4-[3-[4-[2-(4-Isobutylphenyl)pentyl]benzoyl]-1-indolyl]butyric acid was prepared from ethyl 4-[3-[4-[2-(4-isobutylphenyl)pentyl]benzoyl]-1-indolyl]butyrate in a manner similar to that of Ex. 2.

^{1}H-NMR ($CDCl_3$, δ) : 0.75 - 0.95 (m, 9H), 1.05 - 1.3 (m, 2H), 1.55 - 1.95 (m, 3H), 2.1 - 2.3 (m, 2H), 2.35 - 2.5 (m, 4H), 2.7 - 3.0 (m, 3H), 4.25 (t, 2H, J=7Hz), 6.95 - 7.15 (m, 6H), 7.25 - 7.45 (m, 3H), 7.55 (s, 1H), 7.67 (d, 2H, J=8.5Hz), 8.3 - 8.4 (m, 1H)

Example 13

Isoamyl valerophenone was prepared from isoamylbenzene and valeryl chloride in a manner similar to that of Pre. Ex. 2.

1-(4-Isoamylphenyl)pentanol was prepared from the obtained isoamyl valerophenone in a manner similar to that of Pre. Ex. 1.

Ethyl 4-[3-[4-[1-(4-isoamylphenyl)pentyloxy]benzoyl]-1-indolyl]butyrate was prepared from the obtained 1-(4-isoamylphenyl)pentanol and ethyl 4-[3-(4-hydroxybenzoyl)-1-indolyl]-butyrate, in a manner similar to that of Ex. 1.

4-[3-[4-[1-(4-Isoamylphenyl)pentyloxy]benzoyl]-1-indolyl]-butyric acid was prepared by hydrolyzing the obtained ester, in a manner similar to that of Ex. 2.

^{1}H-NMR ($CDCl_3$, δ) : 0.85 - 1.0 (m, 9H), 1.2 - 1.7 (m, 7H), 1.7 - 2.3 (m, 4H), 2.38 (t, 2H, J=6.5Hz), 2.58 (t, 2H, J=7.5Hz), 4.24 (t, 2H, J=7Hz), 5.13 (dd, 1H, J=5Hz, 8Hz), 6.92 (d, 2H, J=9Hz), 7.15 (d, 2H, J=9Hz), 7.2 - 7.45 (m, 5H), 7.54 (s, 1H), 7.73 (d, 2H, J=9Hz), 8.3 - 8.4 (m, 1H)

Example 14

The procedure of Ex. 13 was repeated except that isopropylbenzene was used instead of isoamylbenzene to give 4-[3-[4-[1-(4-isopropylphenyl)pentyloxy]benzoyl]-1-indolyl]-butyric acid.

^{1}H-NMR ($CDCl_3$, δ) : 0.91 (t, 3H, J=7Hz), 1.24 (d, 6H, J=7Hz), 1.25 - 1.65 (m, 4H), 1.7 - 2.3 (m, 4H), 2.38 (t, 2H, J=7Hz), 2.75 - 3.0 (m, 1H), 4.24 (t, 2H, J=7Hz), 5.14 (dd, 1H, J=5Hz, 7.5Hz), 6.93 (d, 2H, J=9Hz), 7.15 - 7.45 (m, 7H) 7.54 (s, 1H), 7.73 (d, 2H, J=9Hz), 8.3 - 8.4 (m, 1H)

Example 15

The procedure of Ex. 13 was repeated except that 2,2-dimethylpropylbenzene was used instead of isoamylbenzene to give 4-[3-[4-[1-[4-(2,2-dimethylpropyl)phenyl]pentyloxy]benzoyl]-

1-indolyl]butyric acid.

^{1}H-NMR ($CDCl_3$, δ) : 0.8 - 0.95 (m, 12H), 1.25 - 1.6 (m, 4H), 1.75 - 2.3 (m, 4H), 2.38 (t, 2H, J=7Hz), 2.47 (s, 1H), 4.23 (t, 2H, J=7Hz), 5.15 (dd, 1H, J=5Hz, 7.5Hz), 6.92 (d, 2H, J=9Hz), 7.09 (d, 2H, J=9Hz), 7.2 - 7.45 (m, 5H), 7.54 (s, 1H), 7.73 (d, 2H, J=9Hz), 8.3 - 8.4 (m, 1H)

Example 16

The procedure of Ex. 13 was repeated except that butylbenzene was used instead of isoamylbenzene to give 4-[3-[4-[1-(4-butylphenyl)pentyloxy]benzoyl]-1-indolyl]butyric acid.

^{1}H-NMR ($CDCl_3$, δ) : 0.8 - 1.0 (m, 6H), 1.2 - 1.65 (m, 8H), 1.7 - 2.3 (m, 4H), 2.38 (t, 2H, J=7Hz), 2.48 (t, 2H, J=7.5Hz), 4.23 (t, 2H, J=7Hz), 5.12 (dd, 1H, J=5Hz, 8Hz), 6.92 (d, 2H, J=9Hz), 7.14 (d, 2H, J=8.5Hz), 7.2 - 7.45 (m, 5H), 7.53 (s, 1H), 7.72 (d, 2H, J=9Hz), 8.3 - 8.4 (m, 1H)

Example 17

The procedure of Ex. 13 was repeated except that propylbenzene was used instead of isoamylbenzene to give 4-[3-[4-[1-(4-propylphenyl)pentyloxy]benzoyl]-1-indolyl]butyric acid.

^{1}H-NMR ($CDCl_3$, δ) : 0.8 - 1.0 (m, 6H), 1.2 - 2.3 (m, 10H), 2.38 (t, 2H, J=7Hz), 2.56 (t, 2H, J=7.5Hz), 4.24 (t, 2H, J=7Hz), 5.15 (dd, 1H, J=5Hz, 8Hz), 6.92 (d, 2H, J=9Hz), 7.15 (d, 2H, J=8.5Hz), 7.2 - 7.45 (m, 5H), 7.53 (s, 1H), 7.73 (d, 2H, J=9Hz), 8.3 - 8.4 (m, 1H)

Example 18

To a suspension of aluminum chloride (4.0 g) in dichloromethane (50 ml) was added valeryl chloride (3.56 ml) at 0℃. After the mixture was stirred at 0℃ for 30 minutes, chlorobenzene (3.68 g) was added to the mixture. The mixture was heated under reflux for 4 hours, then cooled to room temperature, and poured into ice water. The organic layer was separated, washed with water, aqueous sodium bicarbonate solution and brine, and dried over magnesium sulfate. Evaporation of the solvent gave 4'-chlorovalerophenone as an oil (780 mg).

1-(4-Chlorophenyl)pentanol was prepared from the obtained 4'-chlorovalerophenone in a manner similar to that of Pre. Ex. 1.

Ethyl 4-[3-[4-[1-(4-chlorophenyl)pentyloxy]benzoyl]-1-indolyl]butyrate was prepared from the obtained 1-(4-chlorophenyl)pentanol and ethyl 4-[3-(4-hydroxybenzoyl)-1-indolyl]butyrate in a manner similar to that of Ex. 1.

4-[3-[4-[1-(4-Chlorophenyl)pentyloxy]benzoyl]-1-indolyl]butyric acid was prepared from the obtained ester in a manner similar to that of Ex. 2.

^{1}H-NMR ($CDCl_3$, δ) : 0.90 (t, 3H, J=7Hz), 1.2 - 1.6 (m, 4H), 1.7 - 2.3 (m, 4H), 2.38 (t, 2H, J=7Hz), 4.24 (t, 2H, J=7Hz), 5.14 (dd, 1H, J=5.5Hz, 7.5Hz), 6.89 (d, 2H, J=9Hz), 7.2 - 7.45 (m, 7H), 7.53 (s, 1H), 7.73 (d, 2H, J=9Hz), 8.3 - 8.4 (m, 1H)

Example 19

A mixture of ethyl 4-[3-(4-hydroxybenzoyl)-1-indolyl]-

butyrate (246 mg), 4-isobutylbenzyl chloride (256 mg) and potassium carbonate (290 mg) in N,N-dimethylformamide (5 ml) was stirred at 50℃ for 2 hours. The reaction mixture was filtered and the filtrate was poured into a mixture of ethyl acetate and water. The organic layer was separated, washed with water and brine, dried over magnesium sulfate and concentrated. The residue was chromatographed on silica gel column eluting with a mixture of n-hexane and ethyl acetate to give ethyl 4-[3-[4-(4-isobutylbenzyloxy)benzoyl]-1-indolyl]butyrate as an oil (284 mg).

^{1}H-NMR ($CDCl_3$, δ) : 0.91 (d, 6H, J=7Hz), 1.75 - 2.0 (m, 1H), 2.1 - 2.3 (m, 2H), 2.39 (t, 2H, J=7Hz), 2.49 (d, 2H, J=7Hz), 4.25 (t, 2H, J=7Hz), 5.08 (s, 2H), 7.06 (d, 2H, J=9Hz), 7.1 - 7.5 (m, 7H), 7.58 (s, 1H), 7.85 (d, 2H, J=9Hz), 8.3 - 8.4 (m, 1H)

Example 20

Ethyl 4-[3-[4-[4,4,4-trifluoro-1-(4-isobutylphenyl)butoxy]-benzoyl]-1-indolyl]butyrate was obtained according to a method similar to that of Example 1.

^{1}H-NMR ($CDCl_3$, δ) : 0.89 (6H, d, J=7Hz), 1.20 (3H, t, J=7Hz), 1.7 - 2.0 (1H, m), 2.05 - 2.5 (10H, m), 4.10 (2H, q, J=7Hz), 4.24 (2H, t, J=7Hz), 5.24 (1H, t, J=5.5Hz), 6.91 (2H, d, J=9Hz), 7.13 (2H, d, J=8Hz), 7.2 - 7.45 (5H, m), 7.52 (1H, s), 7.74 (2H, d, J=9Hz), 8.3 - 8.4 (1H, m)

Example 21

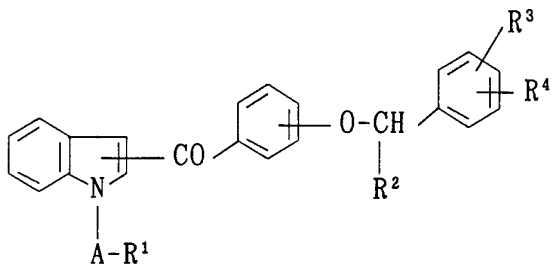
4-[3-[4-[4,4,4-Trifluoro-1-(4-isobutylphenyl)butoxy]-

benzoyl]-1-indolyl]butyric acid was obtained according to a method similar to that of Example 2.

^{1}H-NMR ($CDCl_3$, δ) : 0.89 (6H, d, J=7Hz), 1.7 - 2.0 (1H, m), 2.05 - 2.5 (10H, m), 4.24 (2H, t, J=7Hz), 5.23 (1H, t, J=5.5Hz), 6.91 (2H, d, J=9Hz), 7.13 (2H, d, J=8.5Hz), 7.2 - 7.45 (5H, m), 7.53 (1H, s), 7.74 (2H, d, J=9Hz), 8.3 - 8.4 (1H, m).

CLAIMS

1. A compound of the formula (I) :



(I)

wherein R^1 is a carboxy or protected carboxy,

R^2 is a lower alkyl, halo(lower)alkyl or phenyl,

R^3 is a lower alkyl,

R^4 is a hydrogen or halogen, and

A is a lower alkylene,

with the proviso that

when R^2 is a lower alkyl, R^4 is a halogen,

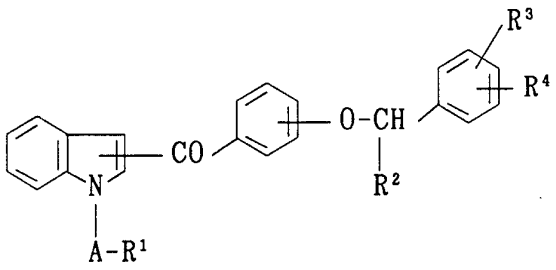
or a pharmaceutically acceptable salt thereof.

2. A compound of claim 1, wherein

R^1 is a carboxy or lower alkoxycarbonyl.

3. A compound of claim 2, which is 4-[3-[4-[1-(4-isobutyl-phenyl)-3-chloropropoxy]benzoyl]-1-indolyl]butyric acid.

4. A process for preparing a compound of the formula (I) :



(I)

wherein R^1 is a carboxy or protected carboxy,

R^2 is a lower alkyl, halo(lower)alkyl or phenyl,

R^3 is a lower alkyl,

R^4 is a hydrogen or halogen, and

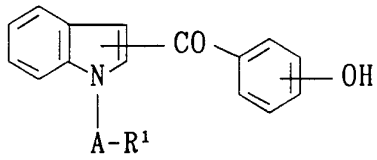
A is a lower alkylene,

with the proviso that

when R^2 is a lower alkyl, R^4 is a halogen,

or a salt thereof, which comprises:

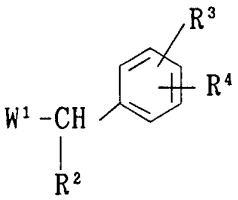
(1) reacting a compound of the formula (II) :



(II)

wherein R^1 and A are as defined above,

or a salt thereof, with a compound of the formula (III) :



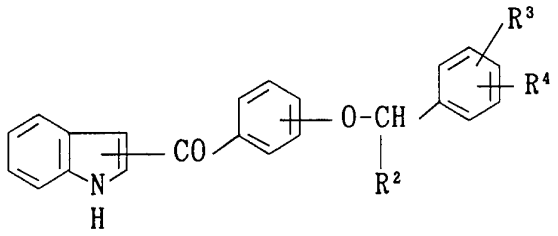
(III)

wherein R^2, R^3 and R^4 are as defined above, and

W^1 is a leaving group,

or a salt thereof;

(2) reacting a compound of the formula (IV) :



(IV)

wherein R^2, R^3 and R^4 are as defined above,

or a salt thereof, with a compound of the formula (V):

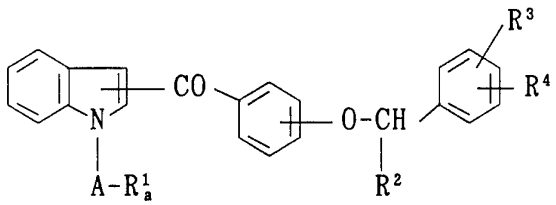
$$W^2\text{-}A\text{-}R^1 \qquad (V)$$

wherein R^1 and A are as defined above, and

W^2 is an acid residue,

or a salt thereof ;

(3) subjecting a compound of the formula (I-a) :

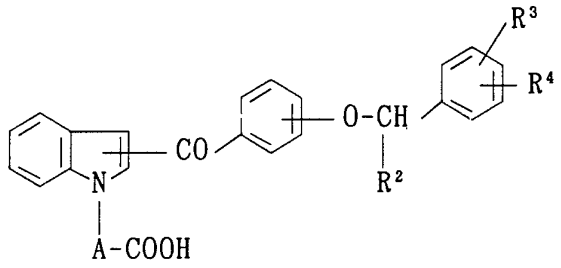


(I-a)

wherein R^2, R^3, R^4 and A are as defined above, and

R^1_a is a protected carboxy,

or a salt thereof, to an elimination reaction of the carboxy-protective group, to give a compound of the formula (I-b) :

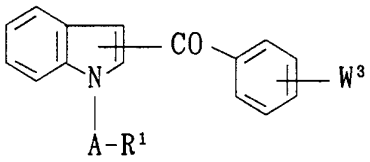


(I-b)

wherein R^2, R^3, R^4 and A are as defined above,

or a salt thereof; or

(4) reacting a compound of the formula (VI) :

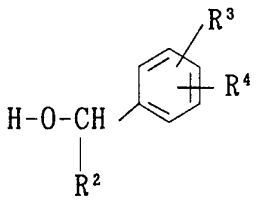


(VI)

wherein R^1 and A are as defined above, and

W^3 is an acid residue,

or a salt thereof, with a compound of the formula (VII) :



(VII)

wherein R^2, R^3 and R^4 are as defined above,

or a salt thereof.

5. A pharmaceutical composition comprising a compound of claim 1 or a pharmaceutically acceptable salt thereof in association with pharmaceutically acceptable carriers or excipients.

6. A method for treating or preventing testosterone 5α-reductase-mediated diseases, which comprises administering a compound of claim 1 or a pharmaceutically acceptable salt thereof to human being or animals.

7. Use of a compound of claim 1 or a pharmaceutically acceptable salt thereof as a medicament.

8. Use of a compound of claim 1 or a pharmaceutically acceptable salt thereof as a testosterone 5α-reductase inhibitor.

9. A process for preparing a pharmaceutical composition which comprises admixing a compound of claim 1 or a pharmaceutically acceptable salt thereof with pharmaceutically acceptable carriers or excipients.

INTERNATIONAL SEARCH REPORT

Internat··nal Application No
PCT/JP 94/00093

A. CLASSIFICATION OF SUBJECT MATTER
IPC 5 C07D209/12 A61K31/40

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 5 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP,A,0 458 207 (FUJISAWA PHARMACEUTICAL CO., LTD.) 27 November 1991 see the whole document	1-9
X,P	WO,A,93 16996 (FUJISAWA PHARMACEUTICAL CO., LTD.) 2 September 1993 see the whole document	1-9
X,P	WO,A,93 05019 (FUJISAWA PHARMACEUTICAL CO., LTD.) 18 March 1993 see page 9, line 23 - line 29; claims 1-12	1-9
A	WO,A,93 02051 (PFIZER) 4 February 1993 see claims; examples 3,8,26	1-9
X	WO,A,93 02050 (PFIZER) 4 February 1993 see page 8; claims; examples 31,37	1-9

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

1

Date of the actual completion of the international search	Date of mailing of the international search report
16 March 1994	25. 03. 94

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax (+31-70) 340-3016	Bosma, P

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

ernational application No.
PCT/JP 94/00093

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claim 6 is directed to a method of treatment of (diagnostic method practised on) the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searches without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

...rmation on patent family members

Internat...al Application No
PCT/JP 94/00093

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
EP-A-0458207	27-11-91	AU-B-	645560	20-01-94
		AU-A-	7711691	21-11-91
		CN-A-	1056685	04-12-91
		JP-A-	4244061	01-09-92
		US-A-	5212320	18-05-93
WO-A-9316996	02-09-93	NONE		
WO-A-9305019	18-03-93	US-A-	5212320	18-05-93
WO-A-9302051	04-02-93	AU-A-	2327092	23-02-93
		AU-A-	2327192	23-02-93
		CN-A-	1068817	10-02-93
		CN-A-	1068816	10-02-93
		WO-A-	9302050	04-02-93
WO-A-9302050	04-02-93	AU-A-	2327092	23-02-93
		AU-A-	2327192	23-02-93
		CN-A-	1068817	10-02-93
		CN-A-	1068816	10-02-93
		WO-A-	9302051	04-02-93