PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 5 :
C07D 471/04, 333/24, 215/22
C07D 231/56, 235/26, C07C 229/44
C07C 59/90, A61K 31/33, 31/215
A61K 31/19 // (C07D 471/04
C07D 235:00, 221:00)
(C07D 471/04, 221:00, 209:00)

A1

(11) International Publication Number: **WO 93/13099**

(43) International Publication Date: 8 July 1993 (08.07.93)

(21) International Application Number: PCT/JP92/01674

(22) International Filing Date: 21 December 1992 (21.12.92)

(30) Priority data:
9127531.3 31 December 1991 (31.12.91) GB

(71) Applicant *(for all designated States except US):* FUJISAWA PHARMACEUTICAL CO., LTD. [JP/JP]; 4-7, Doshomachi 3-chome, Chuo-ku, Osaka-shi, Osaka 541 (JP).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)* : OKADA, Satoshi [JP/JP]; 13-1, Namiki 4-chome, Tsukuba-shi, Ibaraki 305 (JP). SAWADA, Kozo [JP/JP]; 1-602-301, Azuma, Tsukuba-shi, Ibaraki 305 (JP). KURODA, Akio [JP/JP]; 2-221, Gokasho-Hirookadani, Uji-shi, Kyoto 611 (JP). WATANABE, Shinya [JP/JP]; 4-13-1-1-205, Ninomiya, Tsukuba-shi, Ibaraki 300 (JP). TANAKA, Hirokazu [JP/JP]; 1-4-8, Ottominami, Tsuchiura-shi, Ibaraki 300 (JP).

(74) Agent: SEKI, Hideo; Fujisawa Pharmaceutical Co., Ltd., Osaka Factory, 1-6, Kashima 2-chome, Yodogawa-ku, Osaka-shi, Osaka 532 (JP).

(81) Designated States: CA, JP, US, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).

Published
With international search report.

(54) Title: ARYL KETONES AS TESTOSTERONE 5α-REDUCTASE INHIBITORS

$$\overset{\displaystyle R^6}{\overset{|}{-N-}}$$

(a)

(57) Abstract

Heterocyclic compound of the formula: R^1-A-CO-X-Y-R^2, in which R^1 is carboxy(lower)alkyl or protected carboxy(lower)alkyl, R^2 is optionally substituted aralkyl, X is optionally substituted arylene, Y is -O- or (a), wherein R^6 is hydrogen, lower alkyl, optionally substituted aralkyl or amino-protective group, and A is a bivalent radical derived from imidazopyridine, azulene, thiophene, pyrrolo[2,3-b]pyridine, quinolone, indazole or dihydrobenzimidazole, each of which may be substituted by one or more suitable substituent(s), which are useful as a testosterone 5α-reductase inhibitor.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AT	Austria
AU	Australia
BB	Barbados
BE	Belgium
BF	Burkina Faso
BG	Bulgaria
BJ	Benin
BR	Brazil
CA	Canada
CF	Central African Republic
CG	Congo
CH	Switzerland
CI	Côte d'Ivoire
CM	Cameroon
CS	Czechoslovakia
CZ	Czech Republic
DE	Germany
DK	Denmark
ES	Spain
FI	Finland
FR	France
GA	Gabon
GB	United Kingdom
GN	Guinea
GR	Greece
HU	Hungary
IE	Ireland
IT	Italy
JP	Japan
KP	Democratic People's Republic of Korea
KR	Republic of Korea
KZ	Kazakhstan
LI	Liechtenstein
LK	Sri Lanka
LU	Luxembourg
MC	Monaco
MG	Madagascar
ML	Mali
MN	Mongolia
MR	Mauritania
MW	Malawi
NL	Netherlands
NO	Norway
NZ	New Zealand
PL	Poland
PT	Portugal
RO	Romania
RU	Russian Federation
SD	Sudan
SE	Sweden
SK	Slovak Republic
SN	Senegal
SU	Soviet Union
TD	Chad
TG	Togo
UA	Ukraine
US	United States of America
VN	Viet Nam

DESCRIPTION

Aryl Ketones as testosterone 5α - reductase inhibitors

Technical Field

The present invention relates to novel heterocyclic compound. More particularly, it relates to novel heterocyclic compound or a pharmaceutically acceptable salt thereof which has pharmacological activities such as inhibitory activity on testosteron 5α-reductase and the like, to a process for preparation thereof, to a pharmaceutical composition comprising the same and to a use of the same as a medicament.

Disclosure of the Invention

Accordingly, one object of the present invention is to provide novel heterocyclic compound or a pharmaceutically acceptable salt thereof, which is of use as a testosteron 5α-reductase inhibitor.

Another object of the present invention is to provide a process for preparation of said heterocyclic compound or a salt thereof.

A further object of the present invention is to provide a pharmaceutical composition comprising, as an active ingredient, said heterocyclic compound or a pharmaceutically acceptable salt thereof.

Still further object of the present invention is to provide a use of said heterocyclic compound or a pharmaceutically acceptable salt thereof as a medicament such as testosteron 5α-reductase inhibitor useful for treating or preventing testosteron 5α-reductase-mediated diseases such as prostatomegaly, prostatism, alopecia, acnes, and the like in human being or animals.

The heterocyclic compound of the present invention is novel and can be represented by the formula (I) :

$$R^1\text{-A-CO-X-Y-}R^2 \qquad \text{(I)}$$

in which R^1 is carboxy(lower)alkyl or protected carboxy(lower)alkyl,

R^2 is optionally substituted aralkyl,

X is optionally substituted arylene,

Y is -O- or $-\overset{\overset{\displaystyle R^6}{|}}{N}-$,

wherein R^6 is hydrogen, lower alkyl, optionally substituted aralkyl or amino-protective group, and

A is a bivalent radical derived from imidazopyridine, azulene, thiophene, pyrrolo[2,3-b]pyridine, quinolone, indazole or dihydrobenzimidazole, each of which may be substituted by one or more suitable substituent(s).

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

Process 1

R^1-A-CO-X-Y-H + HO-R^2

(II)
or a salt thereof

(III)
or its reactive derivative
at the hydroxy group,
or a salt thereof

$\longrightarrow$ R^1-A-CO-X-Y-R^2

(I)
or a salt thereof

Process 2

R_a^1-A-CO-X-Y-R^2 $\xrightarrow{\text{Removal or the carboxy-protective group in } R_a^1}$

(I-a)
or a salt thereof

R_b^1-A-CO-X-Y-R^2

(I-b)
or a salt thereof

wherein R^1, R^2, A, X and Y are each as defined above,
R_a^1 is protected carboxy(lower)alkyl, and
R_b^1 is carboxy(lower)alkyl.

Suitable salts of the compound (I) are conventional non-toxic, pharmaceutically acceptable salt and may include a salt with a base or an acid addition salt such as a salt with an inorganic base, for example, an alkali metal salt (e.g. sodium salt, potassium salt, cesium salt, etc.), an alkaline earth metal salt (e.g. calcium salt, magnesium salt, etc.), an ammonium salt; a salt with an organic base, for example, an organic amine salt (e.g. triethylamine salt, pyridine salt, picoline salt, ethanolamine salt, triethanolamine salt, dicyclohexylamine salt, N,N'-dibenzylethylenediamine salt, etc.), etc.; an inorganic acid addition salt (e.g. hydrochloride, hydrobromide, sulfate, phosphate, etc.); an organic carboxylic or sulfonic acid addition salt (e.g. formate, acetate, trifluoroacetate, maleate, tartrate, methanesulfonate, benzenesulfonate, p-toluenesulfonate, etc.); a salt with a basic or acidic amino acid (e.g. arginine, aspartic acid, glutamic acid, etc.); and the like, and the preferable example thereof is an acid addition salt.

The compound (I) possesses stereoisomers such as optical isomers due to the presence of asymmetric carbon atom(s), and such isomers are also included within a scope of the present invention.

In the above and subsequent descriptions of the present specification, suitable examples and illustrations of the various definitions which the present invention include within the scope thereof are explained in detail as follows.

The term "lower" is intended to mean 1 to 6 carbon atoms, preferably 1 to 4 carbon atoms, unless otherwise indicated.

Suitable "lower alkyl" may include straight or branched one having 1 to 6 carbon atom(s), such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, t-butyl, pentyl, hexyl, and the like, preferably one having 1 to 4 carbon atoms.

"Carboxy(lower)alkyl" means lower alkyl as explained above, which is substituted by a carboxy group at its optional positions, and suitable example thereof may be carboxymethyl, carboxyethyl, carboxypropyl, carboxybutyl, carboxypentyl, carboxyhexyl, and the like, in which preferable one is carboxy(C_1-C_4)alkyl and the most preferable one is 3-carboxypropyl.

"Protected carboxy(lower)alkyl" means carboxy(lower)alkyl as explained above, in which the carboxy group is protected by a conventional carboxy-protective group, and suitable "protected carboxy" moiety of "protected carboxy(lower)alkyl" may include an esterified carboxy group.

Suitable examples of the ester moiety of an "esterified carboxy" may be a conventional one such as lower alkyl ester (e.g. methyl ester, ethyl ester, propyl ester, isopropyl ester, butyl ester, isobutyl ester, tert-butyl ester, pentyl ester, hexyl ester, etc.) which may have at least one suitable substituent(s), for example, lower cycloalkyl(lower)alkyl ester (e.g. 1-cyclopropylethyl, etc.), lower alkanoyloxy(lower)alkyl ester (e.g. acetoxymethyl ester, propionyloxymethyl ester, butyryloxymethyl ester, valeryloxymethyl ester, pivaloyloxymethyl ester, hexanoyloxymethyl 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 ester, isobutyryloxymethyl ester, 2-ethylbutyryloxymethyl ester, 3,3-dimethylbutyryloxymethyl ester, 1(or 2)-pentanoyloxyethyl ester, etc.) lower alkanesulfonyl(lower)alkyl ester (e.g. 2-mesylethyl ester, etc.), mono(or di or tri)-halo(lower)alkyl ester (e.g. 2-iodoethyl ester, 2,2,2-trichloroethyl ester, etc.), lower alkoxycarbonyloxy(lower)alkyl ester (e.g. methoxycarbonyloxymethyl ester, ethoxycarbonyloxymethyl ester, 2-methoxycarbonyloxyethyl ester, 1-ethoxycarbonyloxyethyl ester, 1-isopropoxycarbonyloxyethyl ester, etc.), 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, etc.; lower alkenyl ester (e.g. vinyl ester, allyl ester, etc.); lower alkynyl ester (e.g. ethynyl ester, propynyl ester, etc.); ar(lower)alkyl ester which may have at least one suitable substituent(s) (e.g. benzyl ester, 4-methoxybenzyl ester, 4-nitrobenzyl ester, phenethyl ester, trityl ester, benzhydryl ester, bis(methoxyphenyl)methyl ester, 3,4-dimethoxybenzyl ester, 4-hydroxy-3,5-di-tert-butylbenzyl ester, etc.); aryl ester which may have at least one suitable substituent(s) (e.g. phenyl ester, 4-chlorophenyl ester, tolyl ester, tert-butylphenyl ester, xylyl ester, mesityl ester, cumenyl ester, etc.); phthalidyl ester; and the like.

Preferable example of "protected carboxy(lower)alkyl" thus defined may be esterified carboxy(lower)alkyl such as lower alkoxycarbonyl(lower)alkyl, more preferably 3-lower alkoxycarbonylpropyl (e.g. 3-methoxycarbonylpropyl, 3-ethoxycarbonylpropyl, 3-propoxycarbonylpropyl, 3-isopropoxycarbonylpropyl, 3-butoxycarbonylpropyl, 3-isobutoxycarbonylpropyl, 3-tert-butoxycarbonylpropyl, 3-pentyloxycarbonylpropyl, 3-tert-pentyloxycarbonylpropyl, 3-hexyloxycarbonylpropyl, etc.).

"Aralkyl" in "optionally substituted aralkyl" means straight or branched C_1-C_{10}, preferably C_1-C_6 alkyl substituted by aryl, and suitable "optionally substituted aralkyl" thus defined may include aralkyl (e.g. trityl, benzhydryl, benzyl, phenethyl, naphthylmethyl, 1-phenylethyl, 1-phenylpropyl, 1-phenylbutyl, 1-phenylpentyl, 1-phenylhexyl, 1-phenylheptyl, 1-phenyloctyl, 1-phenyldecyl, 2,2-dimethyl-1-phenylpropyl, etc.), substituted ar(lower)alkyl, for example, aralkyl substituted by one or more, preferably one to four substituents such as lower alkyl as mentioned above, halogen (e.g. fluoro, chloro, bromo, iodo, etc.), cyano, carboxy, protected carboxy as mentioned above, aryl (e.g. phenyl, tolyl, xylyl, naphthyl, etc.), amidated carboxy such as carbamoyl, mono or di(lower)alkylcarbamoyl (e.g. methylcarbamoyl, dimethylcarbamoyl, ethylcarbamoyl , diethylcarbamoyl, butylcarbamoyl, t-butylcarbamoyl, etc.), lower alkylarylcarbamoyl (e.g. isobutylphenylcarbamoyl, etc.), and the like.

Preferable example of thus defined "optionally substituted aralkyl" may be benzyl, benzhydryl, trityl, phenethyl, 1-phenylethyl, methylbenzyl, isobutylbenzyl, methylphenylethyl, isobutylphenylethyl, methylphenylpropyl, isobutylphenylpropyl, methylphenylpentyl, isobutylphenylpentyl, bis(methylphenyl)methyl, bis(propylphenyl)methyl, bis(butylphenyl)methyl, bis(isobutylphenyl)methyl, bis(chlorophenyl)methyl, (cyano)(isobutylphenyl)methyl, (carboxy)(isobutylphenyl)methyl, (benzyloxycarbonyl)(isobutylphenyl)methyl, (N,N-diethylcarbamoyl)(isobutylphenyl)methyl, (t-butylcarbamoyl)(isobutylphenyl)methyl, (phenylcarbamoyl)(isobutylphenyl)methyl, (isobutylphenylcarbamoyl)(isobutylphenyl)methyl, etc.], and the like, more preferably bis[(lower)alkylphenyl]methyl, and the most preferably bis[isobutylphenyl]methyl.

Suitable "amino-protective group" may be a conventional protective group which is used in the field of peptide chemistry, that is, may include acyl such as lower alkanoyl (e.g. formyl, acetyl, propionyl, butyryl, isobutyryl, valeryl, isovaleryl, pivaloyl, hexanoyl etc.), lower alkoxycarbonyl (e.g. methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, butoxycarbonyl, t-butoxycarbonyl, etc.), ar(lower)alkyl (e.g. benzyl, benzhydryl, trityl, etc.), and the like.

"Optionally substituted arylene" means a bivalent radical derived from arene, preferably C_6-C_{10} arene, such as benzene, toluene, xylene, mesitylene, naphthalene, and the like, which may be substituted by one or more, preferably one or two suitable substituents such as halogen as mentioned above, lower alkoxy (e.g. methoxy, ethoxy, propoxy, isobutoxy, butoxy, etc.), and the like. Suitable example thereof may be 1,2-phenylene, 1,3-phenylene, 1,4-phenylene, 5-methyl-1,3-phenylene, 2,3-dimethyl-1,4-phenylene, 1,2-naphthylene, 3-fluoro-1,4-phenylene, and the like, and more preferably 1,4-phenylene or 1,3-phenylene.

Suitable "a bivalent radical derived from imidazopyridine" may be imidazo[1,5-a]pyridin-diyl such as imidazo[1,5-a]pyridin-1,3-diyl, and the like.

Suitable "a bivalent radical derived from azulene" may be azulen-diyl such as azulen-1,3-diyl, and the like.

Suitable "a bivalent radical derived from thiophene" may be thien-diyl such as thien-2,5-diyl, and the like.

Suitable "a bivalent radical derived from pyrrolo[2,3-b]pyridine" may be 1H-pyrrolo[2,3-b]pyridin-diyl such as 1H-pyrrolo[2,3-b]pyridin-1,3-diyl, and the like.

Suitable "a bivalent radical derived from quinolone" may be 4-(1H)-quinolon-diyl such as

4-(1H)-quinolon-1,3-diyl, and the like.

Suitable "a bivalent radical derived from indazole" may be 1H-imidazol-diyl such as 1H-indazol-1,3-diyl, and the like.

Suitable "a bivalent radical derived from dihydrobenzimidazole" may be 2,3-dihydro-1H-benzimidazol-diyl such as 2,3-dihydro-1H-benzimidazol-1,3-diyl, and the like.

The bivalent radicals mentioned above may be substituted by one or more, preferably one to three suitable substituent(s) such as aryl (e.g. phenyl, tolyl, xylyl, naphthyl, etc.), lower alkyl as mentioned above, halogen as mentioned above, hydroxy, lower alkoxy (e.g. methoxy, ethoxy, propoxy, isopropoxy, etc.), and the like.

Suitable "halogen" may be the same as those given in the above.

Suitable "protected hydroxy" may be lower alkyl, ar(lower)alkyl and acyloxy explained above, and the like.

The processes 1 and 2 for preparing the object compound (I) of the present invention are explained in detail in the following.

Process 1

The object compound (I) or a salt thereof can be prepared by reacting the compound (II) or a salt thereof with the compound (III) or its reactive derivative at the hydroxy group, or a salt thereof.

Suitable salt of the compounds (II) and (III) or its reactive derivative at the hydroxy group may be the same that exemplified for the compound (I).

Suitable "reactive derivative at the hydroxy group" of the compound (III) may include an acid residue such as halo (e.g. bromo, chloro, iodo, etc.), acyloxy (e.g. acetoxy, mesyloxy, tosyloxy, etc.), and the like.

This reaction is usually carried out in a solvent such as chloroform, dichloromethane, benzene, N,N-dimethylformamide, dimethyl sulfoxide, tetrahydrofuran, diethyl ether or any other solvent which does not adversely affect the reaction.

The reaction may be carried out in the presence of an inorganic or an organic base such as an alkali metal hydroxide [e.g. sodium hydroxide, potassium hydroxide, etc.], an alkali metal carbonate [e.g. sodium carboante, potassium carbonate, etc.], an alkali metal bicarbonate [e.g. sodium bicarbonate, potassium bicarbonate, etc.], alkali metal hydride (e.g. sodium hydride, potassium hydride, etc.), tri(lower)alkylamine [e.g. trimethylamine, triethylamine, diisopropylethylamine, etc.], pyridine or its derivative [e.g. picoline, lutidine, 4-dimethylaminopyridine, etc.], or the like. In case that the base to be used is liquid, it can also be used as a solvent.

Also, this reaction can be carried out in the presence of a conventional condensing agent which is capable of condensing alcohols and amines.

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-b) or a salt thereof can be prepared by subjecting the compound (I-a) or a salt thereof to removal reaction of the carboxy-protective group in R_a^1.

Suitable salt of the compounds (I-a) and (I-b) may be the same as that exemplified for the compound (I).

In the present removal reaction, and conventional methods used in the removal of the carboxy-protective group, for example, hydrolysis, reduction, removal using

Lewis acid, etc. are applicable. When the carboxy-protective group is an ester, it can be removed by hydrolysis or removal using Lewis acid. The hydrolysis is preferably carried out in the presence of a base or an acid.

Suitable base may include, for example, an inorganic base such as alkali metal hydroxide (e.g. sodium hydroxide, potassium hydroxide, etc.), alkaline earth metal hydroxide (e.g. magnesium hydroxide, calcium hydroxide, etc.), alkali metal carbonate (e.g. sodium carbonate, potassium carbonate, etc.), alkaline earth metal carboante (e.g. magnesium carbonate, calcium carbonate, etc.), alkali metal bicarbonate (e.g. sodium bicarbonate, potassium bicarbonate, etc.), alkali metal acetate (e.g. sodium acetate, potassium acetate, etc.), alkaline earth metal phosphate (e.g. magnesium phosphate, calcium phosphate, etc.), alkali metal hydrogen phosphate (e.g. disodium hydrogen phosphate, dipotassium hydrogen phosphate, etc.), and the like. The hydrolysis using a base is often carried out in water or a hydrophilic organic solvent or a mixed solvent thereof.

Suitable acid may include an organic acid (e.g. formic acid, acetic acid, propionic acid, benzoic acid etc.) and an inorganic acid (e.g. hydrochloric acid, hydrobromic acid, sulfuric acid, etc.).

The present hydrolysis is usually carried out in an organic solvent such as alcohol (e.g. methanol, ethanol, etc.), tetrahydrofuran, N,N-dimethylformamide, water or a mixed solvent thereof.

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

The removal using Lewis acid is preferably to remove substituted or unsubstituted ar(lower)alkyl ester and carried out by reacting the compound (I-a) or a salt thereof with Lewis acid such as boron trihalide (e.g. boron trichloride, boron trifluoride, etc.), titanium tetrahalide (e.g. titanium tetrachloride, titanium tetrabromide, etc.), tin tetrahalide (e.g. tin tetrachloride, tin tetrabromide, etc.), aluminum halide (e.g. aluminum chloride, aluminum bromide, etc.), trihaloacetic acid (e.g. trichloroacetic acid, trifluoroacetic acid, etc.) or the like. This removal reaction is preferably carried out in the presence of cation trapping agents (e.g. anisole, phenol, etc.) and is usually carried out in a solvent such as nitroalkane (e.g. nitromethane, nitroethane, etc.), alkylene halide (e.g. methylene chloride, ethylene chloride, etc.), diethyl ether, carbon disulfide or any other solvent which does not adversely affect the reaction. These solvents may be used as a mixture thereof.

The reduction can be applied preferably for removing the protective-group such as halo(lower)alkyl (e.g. 2-iodoethyl, 2,2,2-trichloroethyl, etc.) ester, ar(lower)alkyl (e.g. benzyl, etc.) ester or the like.

The reduction method applicable for the removal reaction may include, for example, reduction by using a combination of a metal (e.g. zinc, zinc amalgam, etc.) or a salt of chromium compound (e.g. chromous chloride, chromous acetate, etc.) and an organic or an inorganic acid (e.g. acetic acid, propionic acid, hydrochloric acid, etc.); and conventional catalytic reduction in the pressure of a conventional metallic catalyst (e.g. Palladium carbon, Raney nickel, etc.).

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

The object compound (I) thus prepared can be iolated and purified in a conventional manner, for example, extraction, precipitation, fractional crystallization, recrystallization, chromatography, and the like.

The object compound (I) of the present invention can be converted to its salt by a conventional method.

The optically active compound can be prepared by a conventional optical resolution method or by selecting the optical active starting compound.

The starting compound (II) can be prepared by the following methods, the details of which are shown in Preparations mentioned below, or a conventional manner.

Method A

$$\underset{\substack{\text{(IV)}\\ \text{or a salt thereof}}}{R^1\text{-A-H}} \xrightarrow[\text{Lewis Acid}]{Z^1\text{-CO-X-Ya (V)}} \underset{\substack{\text{(VI)}\\ \text{or a salt thereof}}}{R^1\text{-A-CO-X-Ya}}$$

Method B

$$\underset{\substack{\text{(VII)}\\ \text{or a salt thereof}}}{\text{H-A-CO-X-Ya}} \xrightarrow[\text{or a salt thereof}]{\substack{R^1\text{-}Z^2\\ \text{(VIII)}}} \underset{\substack{\text{(VI)}\\ \text{or a salt thereof}}}{R^1\text{-A-CO-X-Ya}}$$

Method C

$$R^1\text{-A-CO-Z}^3 \xrightarrow{\substack{\text{H-X-Ya} \\ \text{(X)}}} R^1\text{-A-CO-X-Ya}$$

(IX) or a salt thereof → (VI) or a salt thereof

Method D

$$R^1_a\text{-A-CO-X-Ya} \xrightarrow{\substack{\text{Removal of the} \\ \text{carboxy-protective} \\ \text{group}}} R^1_b\text{-A-CO-X-Ya}$$

(VI-a) or a salt thereof → (VI-b) or a salt thereof

Method E

$$R^1\text{-A-CO-X-NO}_2 \xrightarrow{\text{Reduction}} R^1\text{-A-CO-X-NH}_2$$

(VI-c) or a salt thereof → (III-a) or a salt thereof

Method F

$$R^1\text{-A-CO-X-Yb} \xrightarrow{\substack{\text{Removal of the} \\ \text{hydroxy-protective} \\ \text{group in Yb}}} R^1\text{-A-CO-X-OH}$$

(VI-d) or a salt thereof → (III-b) or a salt thereof

wherein R^1, R^1_a, R^1_b, A and X are each as defined above,
Z^1, Z^2 and Z^3 are each hydrogen,
Ya is nitro or protected hydroxy, and
Yb is protected hydroxy.

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

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

In order to illustrate the usefulness of the object compounds (I), pharmacological activity of representative compounds of the present invention is shown below.

[1] Test compound :

4-[3-[4-[Bis(4-isobutylphenyl)methylamino]benzoyl]-imidazo[1,5-a]pyridin-1-yl]butyric acid

[2] Inhibitory activity on testosterone 5α-reductase in rats :

Test Methods

i) Materials

1,2,6,7-^{3}H-Testosterone (85-105 Ci/mmol) :

1,2,6,7-^{3}H-Testosterone (85-105 Ci/mmol) is a mixture of 1,2,6,7-^{3}H-testosterone and testosterone which includes 85-105 Ci of 1,2,6,7-^{3}H-testosterone per mmol of testosterone and is purchased from New England Nuclear, Boston, Mass., U.S.A..

Aquazol-2 (Aquazol-2-Universal LSC Cocktail) : trademark, purchased from New England Nuclear, Boston, Mass., U.S.A.

ii) Preparation of prostatic testosterone 5α-reductase

Mature Spraque-Dawley male rats (7-8 weeks old) were sacrificed by diethyl ether. The ventral prostates were dissected to be free of their capsules and their combined volume was measured by displacement in several milliliters of ice-cold medium A (0.32 M sucrose, 0.1 mM dithiothreitol and 20 mM sodium phosphate, pH 6.5). Unless specified, all the following procedures were carried out at 0-4°C. The prostates were drained, minced, and then homogenized in 3-4 tissue volumes of medium A with Pyrex-glass homogenizer. The homogenate was fractioned by differential centrifugations at 3,000 g for 15 minutes. The resulting pellets were resuspended in medium A. The suspension (20-30 mg protein/ml) was stored at -80°C.

iii) Testosterone 5α-reductase assay

The reaction solution contains 1 mM dithiothreitol, 40 mM sodium phosphate pH 6.5, 50 μM NADPH, 1,2,6,7-^{3}H-testosterone/testosterone (2.2×10^{-9} M) and the suspension prepared above (0.8 mg of protein) in a total volume of 565 μl. Test Compound was added in 10 μl of 10% ethanol whereas control tubes received the same volume of 10% ethanol. The reaction was started with the addition of the enzyme suspension. After incubation at

37°C for 30 minutes, the reaction was extracted with 1 ml of ethyl acetate. Fifty μl of ethyl acetate phase was chromatographed on a Merck silica plastic sheet Kieselgel 60 F_{254}, using ethyl acetate : cyclohexane (1:1) as the developing solvent system. The plastic sheet was air dried and cut the testosterone and the 5α-dihydrotestosterone areas. The radioactivity was counted in 5 ml of Aquazol-2 in Packard scintillation counter (PACKARD TRI - CARB 4530), and an inhibitory ratio was calculated.

[3] <u>Test Results</u> :

$$IC_{50} : 3.0 \times 10^{-9} \text{ (M)}$$

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

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, ethylene glycol, and the like.

While the dosage of the compound (I) may very from and also depend upon the age, conditions of the patient, a kind of diseases, a kind of the compound (I) to be applied, etc. In general amounts between 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 in treating diseases.

The following Preparations and Example are given for the purpose of illustrating the present invention.

to be continued on the next page

Preparation 1

(1) To a solution of 2-(aminomethyl)pyridine (1.74 g) in pyridine (5 ml) was added glutaric anhydride (1.84 g) at ambient temperature. After stirring for 2 hours, the resulting solid was collected and washed with dichloromethane to give 4-[N-(2-pyridylmethyl)carbamoyl]-butyric acid (3.38 g).

^{1}H-NMR (DMSO-d_6, δ) : 1.55 (2H, m), 2.15-2.3 (4H, m), 4.32 (2H, d, J=6Hz), 7.15-7.3 (2H, m), 7.75 (1H, dt, J=2, 8Hz), 8.35-8.55 (2H, m)

(2) To a suspension of 4-[N-(2-pyridylmethyl)carbamoyl]-butyric acid (3.38 g) in ethanol (100 ml) was added camphorsulfonic acid (3.8 g). After 10 minutes, the mixture was heated under reflux using a reflux condenser containing 3Å molecular sieves. After 3 hours, the mixture was evaporated, diluted with saturated aqueous sodium hydrogencarbonate and then extracted with ethyl acetate. The organic layer was washed with brine, dried over sodium sulfate and evaporated in vacuo to give ethyl 4-[N-(2-pyridylmethyl)carbamoyl]butyrate (3.22 g).

^{1}H-NMR ($CDCl_3$, δ) : 1.25 (3H t, J=7Hz), 2.01 (2H, m), 2.3-2.5 (4H, m), 4.13 (2H, q, J=7Hz), 4.59 (2H, d, J=2Hz), 6.95 (1H, m), 7.2-7.4 (2H, m), 7.75 (1H, dt, J=1, 7Hz), 8.57 (1H, m)

(3) A solution of ethyl 4-[N-(2-pyridylmethyl)carbamoyl]-butyrate (692 mg) and phosphorus oxychloride (1.4 ml) in benzene (5 ml) were heated under reflux for 5 hours. Water was then added to the cooled mixture, and the resulting solution was made basic and extracted with ether. The separated organic layer was washed with brine, dried over sodium sulfate and evaporated in vacuo. The residue was chromatographed on silica gel (eluent : ethyl acetate to give ethyl 4-(imidazo[1,5-a]pyridin-3-yl)-

butyrate (638 mg).

^{1}H-NMR ($CDCl_3$, δ) : 1.25 (3H, t, J=7Hz), 2.26 (2H, m), 2.48 (2H, t, J=7Hz), 3.11 (2H, t, J=7Hz), 4.14 (2H, q, J=7Hz), 6.55-6.8 (2H, m), 7.48 (1H, s), 7.43 (1H, dt, J=9, 1Hz), 7.88 (1H, dd, J=7Hz)

Preparation 2

(1) To a solution of (2-carboxyethyl)triphenylphosphonium chloride (6.87 g) in dimethylformamide (20 ml) was added sodium hydride (1.48 g, 60% in mineral oil) at ambient temperature. After 20 minutes, 1-formylimidazo[1,5-a]-pyridine (2.46 g) was added thereto and the mixture was stirred at 30°C for 1 hour. Ice was added to the mixture, followed by acidifying it to pH 5 with 1N hydrochloric acid, and then extraction with ethyl acetate. The organic layer was washed with brine, dried and evaporated. The residue was chromatographed on silica gel (eluent : a mixture of chloroform and methanol, 9:1) to give 4-(imidazo[1,5-a]pyridin-1-yl)-trans-3-butenoic acid (613 mg).

^{1}H-NMR (DMSO-d_6, δ) : 3.20 (2H, dd, J=1, 7Hz), 6.32 (1H, dt, J=16, 7Hz), 6.63 (1H, dt, J=1, 7Hz), 6.74 (1H, d, J=16Hz), 6.78 (1H, m), 7.65 (1H, d, J=9Hz), 8.27 (1H, d, J=7Hz), 8.33 (1H, s)

(2) To a solution of 4-(imidazo[1,5-a]pyridin-1-yl)-trans-3-butenoic acid (1.91 g) in ethanol (100 ml) was added camphorsulfonic acid (2.4 g), and the mixture was heated under reflux using reflux condenser containing 3Å molecular sieves. After 2 hours, the mixture was evaporated, diluted with saturated aqueous sodium hydrogencarbonate, and then extracted with ethyl acetate. The organic layer was washed with brine, dried over sodium sulfate and, evaporated in vacuo. The residue was

chromatographed on silica gel (eluent : ethyl acetate) to give ethyl 4-(imidazo[1,5-a]pyridin-1-yl)-trans-3-butenoate (1.2 g).

^{1}H-NMR ($CDCl_3$, δ) : 1.28 (3H, t, J=7Hz), 3.30 (2H, dd, J=1, 7Hz), 4.18 (2H, q, J=7Hz), 6.4-6.6 (2H, m), 6.65-6.8 (2H, m), 7.49 (1H, d, J=9Hz), 7.85 (1H, d, J=7Hz), 8.04 (1H, s)

(3) To a solution of ethyl 4-(imidazo[1,5-a]pyridin-1-yl)-trans-3-butenoate (1.2 g) in ethanol (5 ml) was added 10% palladium on carbon (200 mg), and the mixture was stirred for 2 hours under hydrogen atmosphere (4 atm). The reaction mixture was filtered through a celite pad, and removal of the solvent from the filtrate in vacuo gave ethyl 4-(imidazo[1,5-a]pyridin-1-yl)butyrate (1.05 g).

^{1}H-NMR ($CDCl_3$, δ) : 1.24 (3H, t, J=7Hz), 2.10 (2H, m), 2.36 (2H, t, J=7Hz), 2.94 (2H, t, J=7Hz), 4.12 (2H, q, J=7Hz), 6.50 (1H, dt, J=1,7Hz), 6.63 (1H, m), 7.38 (1H, d, J=9Hz), 7.87 (1H, d, J=7Hz), 8.12 (1H, s)

Preparation 3

(1) To a stirred solution of ethyl succinyl chloride (836 mg) in dichloromethane (30 ml) was added aluminum chloride (831 mg) at ambient temperature. After 10 minutes, a solution of azulene (503 mg) in dichloromethane was added. After one hour, ice was added thereto, and the mixture was extracted with chloroform. The organic layer was washed with water, aqueous sodium hydrogencarbonate and brine, dried over sodium sulfate and then evaporated in vacuo. The residue was chromatographed on silica gel to give ethyl 4-(azulen-1-yl)-4-oxobutyrate (422 mg).

^{1}H-NMR ($CDCl_3$, δ) : 1.28 (3H, t, J=7Hz), 2.81 (2H, t, J=7Hz), 3.48 (2H, t, J=7Hz), 4.18 (2H, q, J=7Hz), 7.29 (1H, d, J=4Hz), 7.49 (1H, t, J=9Hz), 7.60 (1H, t, J=9Hz), 7.83 (1H, t, J=9Hz), 8.37 (1H, d, J=4Hz), 8.50 (1H, d, J=9Hz), 9.88 (1H, d, J=9Hz)

(2) To a stirred solution of ethyl 4-(azulen-1-yl)-4-oxobutyrate (206 mg) in tetrahydrofuran (3 ml) was added 1M tetrahydrofuran solution of diborane (1.37 ml) at 0°C. After stirring at ambient temperature for 20 minutes and 50°C for additional 20 minutes, the reaction was quenched by aqueous potassium dihydrogen phosphate at 0°C. The reaction mixture was extracted with ether. The separated organic layer was washed with aqueous sodium hydrogencarbonate and brine, dried over sodium sulfate and evaporated in vacuo. The residue was chromatographed on silica gel (eluent : a mixture of hexane and ethyl acetate, 2:1) to give ethyl 4-(azulen-1-yl)butyrate (96 mg).

^{1}H-NMR ($CDCl_3$, δ) : 1.25 (3H, t, J=7Hz), 2.08 (2H, m), 2.36 (2H, t, J=7Hz), 3.12 (2H, t, J=7Hz), 4.11 (2H, q, J=7Hz), 7.08 (2H, m), 7.34 (1H, br s), 7.54 (1H, t, J=9Hz), 7.79 (1H, br s), 8.27 (2H, m)

Preparation 4

To a solution of 3-nitrobenzoyl chloride (713 mg) in 1,2-dichloroethane (5 ml) was added aluminum chloride (650 mg). After 10 minutes, ethyl 4-(imidazo[1,5-a]pyridin-3-yl)butyrate (405 mg) in 1,2-dichloroethane (5 ml) was added thereto. The resultant mixture was heated under reflux for 6 hours. The mixture was diluted with ethyl acetate and then washed with water, saturated aqueous sodium hydrogencarbonate, and brine. The solution was dried over sodium sulfate, and the solvent was removed by evaporation in vacuo. The residue was chromatographed on silica gel (eluent : a mixture of hexane and ethyl acetate, 1:2) to give ethyl 4-[1-(3-nitrobenzoyl)imidazo[1,5-a]pyridin-3-yl]butyrate (240 mg).

^{1}H-NMR (CDCl$_3$, δ) : 1.27 (3H, t, J=7Hz), 2.24 (2H, m), 2.59 (2H, t, J=7Hz), 3.14 (2H, t, J=7Hz), 4.16 (2H, t, J=7Hz), 6.99 (1H, dt, J=1, 7Hz), 7.32 (1H, m), 7.68 (1H, t, J=8Hz), 8.16 (1H, m), 8.38 (1H, m), 8.55 (1H, dt, J=1, 8Hz), 8.72 (1H, m), 9.43 (1H, m)

The compounds described in the following Preparations 5 to 11 could be obtained in accordance with a similar manner to that of Preparation 4.

Preparation 5

Ethyl 4-[1-(4-nitrobenzoyl)imidazo[1,5-a]pyridin-3-yl]butyrate

^{1}H-NMR (CDCl$_3$, δ) : 1.27 (3H, t, J=7Hz), 2.20 (2H, m), 2.55 (2H, t, J=7Hz), 3.13 (2H, t, J=7Hz), 4.15 (2H, q, J=7Hz), 7.00 (1H, dt, J=1, 7Hz), 7.34 (1H, ddd, J=1, 7, 9Hz), 8.18 (1H, dt, J=7, 1Hz), 8.33 (2H, m), 8.5-8.6 (3H, m)

Preparation 6

Ethyl 4-[3-(3-nitrobenzoyl)imidazo[1,5-a]pyridin-1-yl]butyrate

^{1}H-NMR (CDCl$_3$, δ) : 1.25 (3H, t, J=7Hz), 2.19 (2H, m), 2.48 (2H, t, J=7Hz), 3.04 (2H, t, J=7Hz), 4.14 (2H, q, J=7Hz), 7.11 (1H, dt, J=7.1Hz), 7.28 (1H, m), 7.70 (1H, t, J=8Hz), 7.76 (1H, m), 8.51 (1H, m), 8.79 (1H, dt, J=8Hz), 9.41 (1H, m), 9.86 (1H, dt, J=7, 1Hz)

Preparation 7

Ethyl 4-[3-(4-nitrobenzoyl)imidazo[1,5-a]pyridin-1-yl]butyrate

^{1}H-NMR ($CDCl_3$, δ) : 1.25 (3H, t, J=7Hz), 2.17 (2H, m), 2.47 (2H, t, J=7Hz), 3.04 (2H, t, J=7Hz), 4.14 (2H, q, J=7Hz), 7.11 (1H, dt, J=7,1Hz), 7.29 (1H, m), 7.77 (1H, dt, J=9,1Hz), 8.36 (2H, d, J=9Hz), 8.60 (2H, d, J=9Hz), 9.87 (1H, dt, J=7,1Hz)

<u>Preparation 8</u>

Ethyl 4-[3-(3-nitrobenzoyl)azulen-1-yl]butyrate

^{1}H-NMR ($CDCl_3$, δ) : 1.22 (3H, t, J=7Hz), 2.05 (2H, m), 2.38 (2H, t, J=7Hz), 3.09 (2H, t, J=7Hz), 4.11 (2H, q, J=7Hz), 7.58 (1H, t, J=9Hz), 7.68 (1H, d, J=9Hz), 7.72 (1H, t, J=9Hz), 7.85 (1H, s), 7.90 (1H, t, J=9Hz), 8.17 (1H, m), 8.42 (1H, m), 8.53 (1H, d, J=9Hz), 8.57 (1H, m), 9.71 (1H, d, J=9Hz)

<u>Preparation 9</u>

Ethyl 4-[3-(4-nitrobenzoyl)azulen-1-yl]butyrate

^{1}H-NMR ($CDCl_3$, δ) : 1.22 (3H, t, J=7Hz), 2.05 (2H, m), 2.37 (2H, t, J=7Hz), 3.08 (2H, t, J=7Hz), 4.11 (2H, q, J=7Hz), 7.58 (1H, t, J=9Hz), 7.68 (1H, t, J=9Hz), 7.81 (1H, s), 7.90 (1H, m), 7.96 (2H, d, J=8Hz), 8.38 (2H, d, J=8Hz), 8.53 (1H, d, J=9Hz), 9.77 (1H, d, J=9Hz)

<u>Preparation 10</u>

Ethyl 4-[1-(4-methoxybenzoyl)imidazo[1,5-a]pyridin-3-yl]butyrate

^{1}H-NMR ($CDCl_3$, δ) : 1.27 (3H, t, J=7Hz), 2.21 (2H, m), 2.55 (2H, t, J=7Hz), 3.13 (2H, t, J=7Hz), 3.90 (3H, s), 4.15 (2H, q, J=7Hz), 6.88 (1H, dt, J=1, 7Hz), 7.00 (2H, d, J=9Hz), 7.19 (1H, m), 8.07 (1H, dt, J=7, 1Hz), 8.49 (2H, d, J=9Hz), 8.45-8.55 (1H, m)

Preparation 11

Ethyl 4-[1-(3-methoxybenzoyl)imidazo[1,5-a]pyridin-3-yl]butyrate

^{1}H-NMR ($CDCl_3$, δ) : 1.26 (3H, t, J=7Hz), 2.21 (2H, m), 2.55 (2H, t, J=7Hz), 3.12 (2H, t, J=7Hz), 3.90 (3H, s), 4.15 (2H, q, J=7Hz), 6.92 (1H, dt, J=7, 1Hz), 7.10 (1H, m), 7.23 (1H, m), 7.41 (1H, t, J=8Hz), 7.95 (1H, m), 8.03 (1H, m), 8.10 (1H, m), 8.51 (1H, m)

Preparation 12

To a solution of ethyl 4-[1-(3-nitrobenzoyl)imidazo-[1,5-a]pyridin-3-yl]butyrate in ethanol (10 ml) was added 4N sodium hydroxide (1.9 ml), and the mixture was heated under reflux for 40 minutes. After removal of the organic solvent in vacuo, the resulting aqueous solution was made acidic with saturated aqueous potassium dihydrogen phosphate and extracted with ethyl acetate. The organic layer was washed with brine and dried over sodium sulfate. The solvent was removed in vacuo to give 4-[1-(3-nitrobenzoyl)imidazo[1,5-a]pyridin-3-yl]butyric acid (638 mg).

^{1}H-NMR (DMSO-d_6, δ) : 2.05 (2H, m), 2.48 (2H, t, J=7Hz), 3.13 (2H, t, J=7Hz), 7.17 (1H, dt, J=1, 7Hz), 7.52 (1H, dd, J=7, 9Hz), 7.84 (1H, t, J=8Hz), 8.3-8.5 (2H, m), 8.59 (1H, d, J=7Hz), 8.78 (1H, m), 9.28 (1H, m)

Preparation 13

To a solution of 4-[1-(3-nitrobenzoyl)imidazo[1,5-a]-pyridin-3-yl]butyric acid (93 mg) in dioxane and ethanol (5 ml; 1:1) was added 10% palladium on carbon (15 mg), and the mixture was stirred for 3 hours under hydrogen atmosphere (4 atms). The reaction mixture was then filtered through a celite pad. Removal of the solvent in vacuo gave 4-[1-(3-aminobenzoyl)imidazo[1,5-a]pyridin-3-yl]butyric acid (94 mg).

^{1}H-NMR ($CDCl_3$-CD_3OD, δ) : 2.23 (2H, m), 2.56 (2H, t, J=7Hz), 3.13 (2H, t, J=7Hz), 6.96 (1H, m), 7.05-7.5 (3H, m), 7.8 (1H, m), 7.92 (1H, m), 8.13 (1H, m), 8.42 (1H, d, J=9Hz)

The compounds described in the following Preparations 14 to 16 could be obtained in accordance with a similar manner to that of Preparation 13.

Preparation 14

Ethyl 4-[1-(4-aminobenzoyl)imidazo[1,5-a]pyridin-3-yl]butyrate

^{1}H-NMR ($CDCl_3$, δ) : 1.27 (3H, t, J=7Hz), 2.20 (2H, m), 2.53 (2H, t, J=7Hz), 3.14 (2H, t, J=7Hz), 4.15 (2H, q, J=7Hz), 6.75 (2H, d, J=9Hz), 6.87 (1H, dt, J=1, 7Hz), 7.17 (1H, m), 8.06 (1H, d, J=7Hz), 8.37 (2H, d, J=9Hz), 8.48 (1H, dt, J=9, 1Hz)

Preparation 15

Ethyl 4-[3-(3-aminobenzoyl)imidazo[1,5-a]pyridin-1-yl]butyrate

^{1}H-NMR ($CDCl_3$, δ) : 1.25 (3H, t, J=7Hz), 2.17 (2H, m), 2.47 (2H, t, J=7Hz), 3.03 (2H, t, J=7Hz), 4.15 (2H, q, J=7Hz), 6.89 (1H, m), 7.01 (1H, dt, J=1, 7Hz), 7.16 (1H, m), 7.29 (1H, t, J=8Hz), 7.6-7.9 (3H, m), 9.92 (1H, dt, J=7Hz)

Preparation 16

Ethyl 4-[3-(4-aminobenzoyl)imidazo[1,5-a]pyridin-1-yl]butyrate

^{1}H-NMR ($CDCl_3$, δ) : 1.25 (3H, t, J=7Hz), 2.17 (2H, m), 2.44 (2H, t, J=7Hz), 3.03 (2H, t, J=7Hz), 4.13 (2H, q, J=7Hz), 6.72 (2H, d, J=9Hz), 6.92 (1H, dt, J=1, 7Hz), 7.09 (1H, m), 7.64 (1H, dt, J=8, 1Hz), 8.42 (2H, d, J=9Hz), 9.76 (1H, dt, J=7, 1Hz)

Preparation 17

To a stirred suspension of ethyl 4-[3-(3-nitrobenzoyl)azulen-1-yl]butyrate (200 mg) in ethanol (2.5 ml) and water (2 ml) was added iron powder (166 mg) and ferrous sulfate 7 hydrate (16 mg), and the mixture was heated under reflux for an hour. The reaction mixture was cooled and extracted with chloroform. The organic layer was washed with water, aqueous sodium hydrogencarbonate and brine, and then evaporated in vacuo to give ethyl 4-[3-(3-aminobenzoyl)azulen-1-yl]butyrate (179 mg).

^{1}H-NMR ($CDCl_3$, δ) : 1.22 (3H, t, J=7Hz), 2.07 (2H, m), 2.36 (2H, t, J=7Hz), 3.08 (2H, t, J=7Hz), 4.10 (2H, q, J=7Hz), 6.88 (1H, m), 7.1-7.35 (3H, m), 7.47 (1H, t, J=9Hz), 7.55 (1H, t, J=9Hz), 7.81 (1H, t, J=9Hz), 7.99 (1H, s), 8.45 (1H, d, J=9Hz), 9.62 (1H, d, J=9Hz)

Preparation 18

Ethyl 4-[3-(4-aminobenzoyl)azulen-1-yl]butyrate could be obtained in accordance with a similar manner to that of Preparation 17.

^{1}H-NMR ($CDCl_3$, δ) : 1.23 (3H, t, J=7Hz), 2.08 (2H, m), 2.37 (2H, t, J=7Hz), 3.09 (2H, t, J=7Hz), 4.12 (2H, q, J=7Hz), 6.73 (2H, d, J=8Hz), 7.40 (1H, t, J=9Hz), 7.47 (1H, t, J=9Hz), 7.7-7.85 (1H, m), 7.76 (2H, t, J=8Hz), 7.99 (1H, s), 8.43 (1H, d, J=9Hz), 9.45 (1H, d, J=9Hz)

Preparation 19

To a solution of ethyl 4-[1-(4-methoxybenzoyl)-

imidazo[1,5-a]pyridin-3-yl]butyrate in dichloromethane (10 ml) and ethanethiol (1.0 ml) was added aluminum chloride (1.5 g) at 0°C. After stirring for 40 minutes, the solvent was removed by evaporation and the residue was poured into ice. The resulting solid was collected, washed successively with water, ethanol and dichloromethane, and then dried in vacuum desicator to give ethyl 4-[1-(4-hydroxybenzoyl)imidazo[1,5-a]pyridin-3-yl]butyrate (618 mg).

^{1}H-NMR (DMSO-d_6, δ) : 1.16 (3H, t, J=7Hz), 2.07 (2H, m), 2.50 (2H, t, J=7Hz), 3.11 (2H, t, J=7Hz), 4.02 (2H, q, J=7Hz), 6.87 (2H, d, J=9Hz), 7.04 (1H, dt, J=1, 7Hz), 7.33 (1H, m), 8.35 (1H, d, J=9Hz), 8.38 (2H, d, J=9Hz), 8.48 (1H, d, J=7Hz)

Preparation 20

Ethyl 4-[1-(3-hydroxybenzoyl)imidazo[1,5-a]pyridin-3-yl]butyrate could be obtained in accordance with a similar manner to that of Preparation 19.

^{1}H-NMR ($CDCl_3$, δ) : 1.24 (3H, t, J=7Hz), 2.18 (2H, m), 2.51 (2H, t, J=7Hz), 3.09 (2H, t, J=7Hz), 4.16 (2H, q, J=7Hz), 6.92 (1H, dt, J=1, 7Hz), 7.01 (1H, m), 7.24 (1H, m), 7.36 (1H, t, J=8Hz), 7.77 (1H, d, J=7Hz), 8.05-8.15 (2H, m), 8.52 (1H, d, J=9Hz)

Preparation 21

(1) A mixture of ethyl 3-(3-nitrophenyl)-3-oxopropionate (4.0 g), triethyl orthoformate (4.21 ml) and acetic anhydride (4.77 ml) was heated at 120°C for 4 hours. After evaporation of the solvent, the residue was chromatographed on silica gel eluting with a mixture of hexane and ethyl acetate (4:1) to give ethyl 2-(ethoxymethylene)-3-(3-nitrophenyl)-3-oxopropionate (3.73 g) as an oil.

^{1}H-NMR ($CDCl_3$, δ) : 1.18 (3H, t, J=8Hz), 1.28 (3H, t, J=8Hz), 4.15 (2H, q, J=8Hz), 4.18 (2H, q, J=8Hz), 7.67 (1H, t, J=8Hz), 7.82 (1H, s), 8.22 (1H, dt, J=8, 1Hz), 8.44 (1H, dt, J=8, 1Hz), 8.67 (1H, t, J=1Hz)

(2) A mixture of ethyl 2-(ethoxymethylene)-3-(3-nitrophenyl)-3-oxopropionate (3.65 g) and aniline (1.13 ml) in chloroform (20 ml) was stirred at 25°C for 1 hour. The precipitated crystals were collected by filtration to give ethyl 3-(3-nitrophenyl)-3-oxo-2-(phenylaminomethylene)propionate (3.4 g).

^{1}H-NMR ($CDCl_3$, δ) : 0.90 (2/3H, t, J=8Hz), 1.06 (4/3H, t, J=8Hz), 4.00-4.14 (2H, m), 7.20-7.64 (6H, m), 7.82 (2/3H, dt, J=8, 1Hz), 7.95 (3/1H, dt, J=8, 1Hz), 8.25-8.40 (2H, m), 8.48 (1/3H, d, J=14Hz), 8.66 (2/3H, d, J=14Hz)

(3) A solution of ethyl 3-(3-nitrophenyl)-3-oxo-2-(phenylaminomethylene)propionate (1.0 g) in diphenyl ether (10 ml) was heated at 180°C for 4 hours, and the reaction mixture was allowed to cool to 25°C. The precipitates were collected by filtration to give 3-(3-nitrobenzoyl)-4-quinolone (315 mg).

^{1}H-NMR (DMSO-d_6, δ) : 7.47 (1H, dt, J=2, 8Hz), 7.68-7.84 (3H, m), 8.12 (2H, d, J=8Hz), 8.38-8.46 (2H, m), 8.51 (1H, s)

Preparation 22

(1) Ethyl 2-(ethoxymethylene)-3-(4-nitrophenyl)-3-oxopropionate could be obtained in accordance with a similar manner to that of Preparation 21-(1).

^{1}H-NMR ($CDCl_3$, δ) : 1.15 (3H, t, J=8Hz), 1.28 (3H, t, J=8Hz), 4.04-4.22 (4H, m), 8.02 (2H, d, J=10Hz), 8.30 (2H, d, J=10Hz)

(2) Ethyl 3-(4-nitrophenyl)-3-oxo-2-(phenylaminomethylene)propionate could be obtained in accordance with a similar manner to that of Preparation 21-(2).

^{1}H-NMR ($CDCl_3$, δ) : 0.88 (3/3H, t, J=8Hz), 1.02 (6/3H, t, J=8Hz), 4.04 (2/3H, q, J=8Hz), 4.06 (4/3H, q, J=8Hz), 7.20-7.34 (3H, m), 7.45 (2H, q, J=8Hz), 7.60 (4/3H, d, J=10Hz), 7.75 (2/3H, d, J=10Hz), 8.26 (2H, d, J=10Hz), 8.50 (1/3H, d, J=16Hz), 8.66 (1/3H, d, J=16Hz)

(3) 3-(4-Nitrobenzoyl)-4-quinolone could be obtained in accordance with a similar manner to that of Preparation 21-(3).

^{1}H-NMR (DMSO-d_6, δ) : 7.47 (1H, dt, J=2, 8Hz), 7.19 (1H, dd, J=2, 8Hz), 7.76 (2H, dq, J=2, 8Hz), 7.88 (2H, d, J=10Hz), 8.12 (1H, d, J=8Hz), 8.30 (2H, d, J=10Hz), 8.52 (1H, s)

Preparation 23

A mixture of 3-(3-nitrobenzoyl)-4-quinolone (300 mg), ethyl 4-bromobutyrate (0.29 ml) and potassium carbonate (423 mg) in N,N-dimethylformamide (10 ml) was stirred at 50°C for 4 hours. The reaction mixture was poured into a mixture of ethyl acetate and 1N hydrochloric acid. The organic layer was separated, washed with water and brine, dried over magnesium sulfate, and evaporated. The residue was chromatographed on silica gel (30 g) eluting with a mixture of ethyl acetate and hexane (1:4) to give ethyl 4-[3-(3-nitrobenzoyl)-4-quinolon-1-yl]butyrate (358 mg) as yellow crystals.

^{1}H-NMR ($CDCl_3$, δ) : 1.32 (3H, t, J=8Hz), 2.23-2.48 (2H, m), 2.53 (2H, t, J=8Hz), 4.22 (2H, q, J=8Hz), 4.38 (2H, t, J=8Hz), 7.50 (1H, dt, J=2, 8Hz), 7.64 (2H, t, J=8Hz), 7.70-7.85 (2H, m), 8.12 (2H, dd, J=2, 8Hz), 8.36-8.50 (3H, m), 8.62 (1H, t, J=2Hz)

The compounds of the following Preparations 24 to 27 could be obtained by reacting the corresponding starting compounds with ethyl 4-bromobutyrate in accordance with a similar manner to that of Preparation 23.

Preparation 24

Ethyl 4-[3-(4-nitrobenzoyl)-4-quinolon-1-yl]butyrate

^{1}H-NMR ($CDCl_3$, δ) : 1.30 (3H, t, J=8Hz), 2.20-2.35 (2H, m), 2.52 (2H, t, J=8Hz), 4.23 (2H, q, J=8Hz), 4.38 (2H, t, J=8Hz), 7.51 (1H, dt, J=2, 8Hz), 7.73-7.82 (2H, m), 7.90 (2H, d, J=10Hz), 8.30 (2H, d, J=10Hz), 8.42 (1H, t, J=2Hz), 8.46 (1H, dd, J=2, 8Hz)

Preparation 25

Ethyl 4-[3-(3-nitrobenzoyl)-1H-pyrrolo[2,3-b]pyridin-1-yl]butyrate

^{1}H-NMR ($CDCl_3$, δ) : 1.20 (3H, t, J=8Hz), 2.20-2.44 (2H, m), 2.38 (2H, t, J=8Hz), 4.08 (2H, q, J=8Hz), 4.48 (2H, t, J=8Hz), 7.35 (1H, dd, J=5, 8Hz), 7.73 (1H, s), 7.74 (1H, t, J=7Hz), 8.18 (1H, dd, J=1, 7Hz), 8.40-8.52 (2H, m), 8.65-8.72 (2H, m)

Preparation 26

Ethyl 4-(3-carboxy-1H-indazol-1-yl)butyrate

^{1}H-NMR (DMSO-d_6, δ) : 1.12 (3H, t, J=8Hz), 2.00-2.20 (2H, m), 2.32 (2H, t, J=8Hz), 3.97 (2H, q, J=8Hz), 4.56 (2H, t, J=8Hz), 7.23 (1H, t, J=8Hz), 7.44 (1H, t, J=8Hz), 7.60 (1H, d, J=8Hz), 8.20 (1H, d, J=8Hz)

Preparation 27

Benzyl 4-[3-(1-methylvinyl)-2,3-dihydro-2-oxo-1H-benzimidazol-1-yl]butyrate

^{1}H-NMR ($CDCl_3$, δ) : 2.05-2.21 (2H, m), 2.24 (3H, d, J=1Hz), 2.48 (2H, t, J=8Hz), 3.94 (2H, t, J=8Hz), 3.94 (2H, t, J=8Hz), 5.13 (2H, s), 5.19 (1H, s), 5.25 (1H, q, J=1Hz), 6.96-7.14 (4H, m), 7.36 (5H, s)

Preparation 28

To a solution of benzyl 4-[3-(1-methylvinyl)-2,3-dihydro-2-oxo-1H-benzimidazol-1-yl)butyrate (980 mg) in tetrahydrofuran (10 ml) were added water (10 ml) and sulfuric acid (2 ml), and the mixture was stirred at 25°C for 2 hours. The reaction mixture was partitioned between ether and water. The organic layer was separated, washed with water and brine, and dried over magnesium sulfate. After evaporation of the solvent, the residue was chromatographed on silica gel eluting with 20% ethyl acetate in hexane to give benzyl 4-(2,3-dihydro-2-oxo-1H-benzimidazol-1-yl)butyrate (342 mg) as an oil.

^{1}H-NMR ($CDCl_3$, δ) : 2.13 (2H, quintet, J=8Hz), 2.49 (2H, t, J=8Hz), 3.96 (2H, t, J=8Hz), 5.12 (2H, s), 6.96-7.10 (4H, m), 7.36 (5H, s)

Preparation 29

A solution of 3-nitrobenzyl chloride (230 mg) in dichloromethane (5 ml) was added to a mixture of benzyl 4-(2,3-dihydro-2-oxo-1H-benzimidazol-1-yl)butyrate (320 mg), diisopropylethylamine (0.36 ml) and 4-(dimethylamino)pyridine (25 mg) in dichloromethane (10 ml) at 25°C. After stirred at 25°C overnight, the reaction mixture was poured into a mixture of ethyl acetate and 1N hydrochloric acid. The organic layer was separated, washed with water and brine, and dried over magnesium sulfate. After evaporation of the solvent, the residue was chromatogrpahed on silica gel eluting with 20% ethyl acetate in hexane to give benzyl 4-[3-(3-nitrobenzyl)-2,3-dihydro-2-oxo-1H-benzimidazol-1-yl]butyrate (331 mg) as an oil.

^{1}H-NMR ($CDCl_3$, δ) : 2.10 (2H, quin, J=8Hz), 2.47 (2H, t, J=8Hz), 3.89 (2H, t, J=8Hz), 5.08 (2H, s), 7.04 (1H, dd, J=1, 8Hz), 7.20-7.30 (2H, m), 7.35 (5H, s), 7.67 (1H, t, J=8Hz), 8.02-8.08 (2H, m), 8.40-8.46 (1H, m), 8.58 (1H, t, J=1Hz)

Preparation 30

(1) To a solution of ethyl 4-(3-carboxy-1H-indazol-1-yl)-butyrate (990 mg) in dichloromethane (20 ml) were added oxalyl chloride (0.33 ml) and N,N-dimethylformamide (1 drop), and the mixture was stirred at 25°C for 2 hours. Evaporation of the solvent gave ethyl 4-[3-(chloroformyl)-1H-indazol-1-yl]butyrate (1.02 g) as yellow solid, which was used for the next step without further purification.

(2) To a solution of ethyl 4-[3-(chloroformyl)-1H-indazol-1-yl]butyrate (350 mg) in anisol (10 ml) was added aluminum chloride (475 mg) at 25°C, and the mixture was stirred at the same temperature for 30 minutes. The reaction mixture was poured into a mixture of ethyl acetate and 1N hydrochloric acid. The organic layer was separated, washed with water and brine, and dried over

magnesium sulfate. After evaporation of the solvent, the residue was chromatographed on silica gel eluting with a mixture of ethyl acetate and hexane (1:4) to give ethyl 4-[3-(4-methoxybenzoyl)-1H-indazol-1-yl]butyrate (224 mg) as an oil.

^{1}H-NMR ($CDCl_3$, δ) : 1.22 (3H, t, J=8Hz), 2.26-2.42 (4H, m), 3.91 (3H, s), 4.13 (2H, q, J=8Hz), 4.58 (2H, t, J=8Hz), 7.03 (2H, d, J=9Hz), 7.30-7.56 (3H, m), 8.42 (2H, d, J=9Hz), 8.44 (1H, dd, J=1, 8Hz)

Preparation 31

3-(3-Nitrobenzoyl)-1H-pyrrolo[2,3-b]pyridine could be obtained by reacting 1H-pyrrolo[2,3-b]pyridine with 3-nitrobenzoyl chloride in accordance with a similar manner to that of Preparation 4.

^{1}H-NMR (DMSO-d_6, δ) : 7.36 (1H, dd, J=5, 8Hz), 7.87 (1H, t, J=7Hz), 8.26 (1H, d, J=7Hz), 8.35-8.66 (5H, m)

The compounds of the following Preparations 32 to 35 could be obtained from the corresponding ethyl esters in accordance with a similar manner to that of Preparation 12.

Preparation 32

4-[3-(3-Nitrobenzoyl)-4-quinolon-1-yl]butyric acid

^{1}H-NMR (DMSO-d_6, δ) : 1.92-2.15 (2H, m), 2.46 (2H, t, J=8Hz), 4.46 (2H, t, J=8Hz), 7.53 (1H, t, J=8Hz), 7.74 (1H, t, J=8Hz), 7.86 (2H, dt, J=1, 8Hz), 7.98 (1H, d, J=8Hz), 8.15 (1H, dd, J=2, 8Hz), 8.23 (1H, dd, J=2, 8Hz), 8.38-8.46 (2H, m), 8.63 (1H, s)

Preparation 33

4-[3-(4-Nitrobenzoyl)-4-quinolon-1-yl]butyric acid

^{1}H-NMR ($CDCl_3$:CD_3OD = 1:1, δ) : 2.12-2.38 (2H, m), 2.45 (2H, t, J=8Hz), 4.38 (2H, t, J=8Hz), 7.45 (1H, dt, J=2, 8Hz), 7.70-7.85 (2H, m), 7.85 (2H, d, J=10Hz), 8.22 (2H, d, J=10Hz), 8.35 (2H, dd, J=2, 8Hz), 8.45 (1H, s)

Preparation 34

4-[3-(4-Hydroxybenzoyl)-1H-indazol-1-yl]butyric acid

^{1}H-NMR ($CDCl_3$:CD_3OD = 1:1, δ) : 2.28-2.46 (4H, m), 4.60 (2H, t, J=8Hz), 6.93 (2H, d, J=9Hz), 7.30-7.60 (3H, m), 8.30 (2H, d, J=9Hz), 8.40 (1H, dd, J=1, 8Hz)

Preparation 35

4-[3-(3-Nitrobenzoyl)-1H-pyrrolo[2,3-b]pyridin-1-yl]-butyric acid

^{1}H-NMR (DMSO-d_6, δ) : 2.0-2.40 (2H, m), 2.26 (2H, t, J=8Hz), 4.38 (2H, t, J=8Hz), 7.38 (1H, dd, J=5, 8Hz), 7.88 (1H, t, J=8Hz), 8.28 (1H, dd, J=2, 8Hz), 8.42 (1H, s), 8.44-8.56 (3H, m), 8.58 (1H, dd, J=2, 8Hz)

The compounds of the following Preparations 36 to 38 could be obtained by reducing the corresponding nitro compounds with palladium on carbon in accordance with a similar manner to that of Preparation 13.

Preparation 36

4-[3-(3-Aminobenzoyl)-4-quinolon-1-yl]butyric acid

^{1}H-NMR (DMSO-d_6, δ) : 1.92-2.10 (2H, m), 2.38 (2H, t, J=8Hz), 4.40 (2H, t, J=8Hz), 6.78 (1H, dd, J=2, 8Hz), 6.92 (1H, d, J=8Hz), 6.98 (1H, t, J=2Hz), 7.10 (1H, t, J=8Hz), 7.50 (2H, t, J=8Hz), 7.78-8.02 (2H, m), 8.23 (2H, dd, J=2, 8Hz), 8.35 (1H, s)

Preparation 37

4-[3-(4-Aminobenzoyl)-4-quinolon-1-yl]butyric acid

^{1}H-NMR (DMSO-d_6, δ) : 1.92-2.10 (2H, m), 2.38 (2H, t, J=8Hz), 4.36 (2H, t, J=8Hz), 6.54 (2H, d, J=8Hz), 7.30-7.50 (1H, m), 7.54 (2H, d, J=14Hz), 7.70-7.95 (3H, m), 8.22 (1H, s)

Preparation 38

4-[3-(3-Aminobenzoyl)-1H-pyrrolo[2,3-b]pyridin-1-yl]-butyric acid

^{1}H-NMR ($CDCl_3$:CD_3OD = 1:1, δ) : 2.20-2.32 (2H, m), 2.38 (2H, t, J=8Hz), 4.42 (2H, t, J=8Hz), 6.90-7.40 (5H, m), 7.86 (1H, s), 8.40 (1H, dd, J=1, 5Hz), 8.65 (1H, dd, J=1, 8Hz)

Preparation 39

4-[3-(3-Aminobenzoyl)-2,3-dihydro-2-oxo-1H-benzimidazol-1-yl]butyric acid could be obtained by reducing benzyl 4-[3-(3-nitrobenzoyl)-2,3-dihydro-2-oxo-1H-benzimidazol-1-yl]butyrate with palladium on carbon in accordance with a similar manner to that of Preparation 13.

^{1}H-NMR (DMSO-d_6, δ) : 1.80-2.00 (2H, m), 2.33 (2H, t, J=8Hz), 3.86 (2H, t, J=8Hz), 6.75-7.40 (7H, m), 7.68 (1H, dd, J=1, 8Hz)

Preparation 40

Ethyl 4-[3-(4-hydroxybenzoyl)-1H-indazol-1-yl]-butyrate could be obtained in accordance with a similar manner to that of Preparation 19.

^{1}H-NMR ($CDCl_3$, δ) : 1.24 (3H, t, J=8Hz), 2.26-2.42 (4H, m), 4.15 (2H, q, J=8Hz), 4.58 (2H, t, J=8Hz), 6.18 (1H, s), 6.96 (2H, d, J=9Hz), 7.30-7.56 (3H, m), 8.35 (2H, d, J=9Hz), 8.45 (2H, dd, J=1, 8Hz)

Preparation 41

Ethyl 4-(thien-2-yl)butyrate could be obtained by reacting 4-(thien-2-yl)butyric acid with ethanol in accordance with a similar manner to that of Preparation 2-(2).

^{1}H-NMR ($CDCl_3$, δ) : 1.26 (3H, t, J=7Hz), 2.01 (2H, m), 2.35 (2H, t, J=7Hz), 2.89 (2H, t, J=7Hz), 4.13 (2H, q, J=7Hz), 6.79 (1H, m), 6.92 (1H, dd, J=3, 5Hz), 7.12 (1H, dd, J=1, 5Hz)

Preparation 42

Ethyl 4-oxo-4-(3-phenylthien-2-yl)butyrate could be obtained by reacting 3-phenylthiophene with ethyl succinyl chloride in accordance with a similar manner to that of Preparation 3-(1).

^{1}H-NMR ($CDCl_3$, δ) : 1.21 (3H, t, J=7Hz), 2.58 (2H, m), 2.79 (2H, t, J=7Hz), 4.09 (2H, q, J=7Hz), 7.05 (1H, d, J=5Hz), 7.35-7.5 (5H, m), 7.54 (1H, d, J=5Hz)

Preparation 43

To a stirred solution of $HgCl_2$ (0.41 g) in conc. HCl (0.2 ml) and water (5 ml) was added zinc dust (4.1 g). After 10 minutes, the aqueous layer was decanted off. To the residue was added water (3 ml), conc. HCl (5 ml), acetic acid (1 ml) and ethyl 4-oxo-4-(3-phenylthien-2-yl)-butyrate (514 mg) in toluene (5 ml), and the mixture was refluxed for 1.5 hours. After cooling, the reaction mixture was extracted with toluene. The combined organic layer were washed with water, aqueous sodium hydrogencarbonate and brine, dried over sodium sulfate and evaporated in vacuo. The residue was chromatographed on silica gel (hexane:dichloromethane = 1:1) to give ethyl 4-(3-phenylthien-2-yl)butyrate (249 mg).

^{1}H-NMR ($CDCl_3$, δ) : 1.22 (3H, t, J=7Hz), 1.85-2.1 (2H, m), 2.32 (2H, t, J=7Hz), 2.92 (2H, t, J=7Hz), 4.08 (2H, q, J=7Hz), 7.00 (1H, d, J=5Hz), 7.18 (1H, d, J=5Hz), 7.2-7.5 (5H, m)

The compounds of the following Preparations 44 and 45 could be obtained by reacting the corresponding starting compounds with 3-nitrobenzoyl chloride in accordance with a similar manner to that of Preparation 4.

Preparation 44

Ethyl 4-[5-(3-nitrobenzoyl)thien-2-yl]butyrate

^{1}H-NMR ($CDCl_3$, δ) : 1.28 (3H, t, J=7Hz), 2.08 (2H, m), 2.42 (2H, t, J=7Hz), 2.98 (2H, t, J=7Hz), 4.16 (2H, q, J=7Hz), 6.93 (1H, d, J=4Hz), 7.49 (1H, d, J=4Hz), 7.72 (1H, t, J=8Hz), 8.17 (1H, m), 8.43 (1H, m), 8.68 (1H, m)

Preparation 45

Ethyl 4-[5-(3-nitrobenzoyl)-3-phenylthien-2-yl]-butyrate

^{1}H-NMR ($CDCl_3$, δ) : 1.23 (3H, t, J=7Hz), 1.95-2.15 (2H, m), 2.36 (2H,, t, J=7Hz), 3.00 (2H, t, J=7Hz), 4.08 (2H, q, J=7Hz), 7.3-7.5 (5H, m), 7.53 (1H, s), 7.71 (1H, t, J=8Hz), 8.2 (1H, m), 8.43 (1H, m), 8.72 (1H, m)

The compounds of the following Preparations 46 and 47 could be obtained by reducing the corresponding nitro compound in accordance with a similar manner to that of Preparation 17.

Preparation 46

Ethyl 4-[5-(3-aminobenzoyl)thien-2-yl]butyrate

^{1}H-NMR ($CDCl_3$, δ) : 1.28 (3H, t, J=7Hz), 2.05 (2H, m), 2.40 (2H, t, J=7Hz), 2.95 (2H, t, J=7Hz), 4.15 (2H, q, J=7Hz), 6.83-6.94 (2H, m), 7.11 (1H, m), 7.15-7.3 (2H, m), 7.51 (1H, d, J=4Hz)

Preparation 47

Ethyl 4-[5-(3-aminobenzoyl)-3-phenylthien-2-yl]-butyrate

^{1}H-NMR ($CDCl_3$, δ) : 1.21 (3H, t, J=7Hz), 1.9-2.15 (2H, m), 2.34 (2H, t, J=7Hz), 2.98 (2H, t, J=7Hz), 4.08 (2H, q, J=7Hz), 6.8-7.5 (9H, m), 7.58 (1H, s)

to be continued on the next page

Example 1

To a solution of 4-[1-(3-aminobenzoyl)imidazo[1,5-a]-pyridin-3-yl]butyric acid (93 mg) in dichloromethane (6 ml) were added diisopropylethyl amine (0.12 ml) and bis(4-isobutylphenyl)chloromethane (109 mg) in dichloromethane (2 ml). After stirring overnight at ambient temperature, the reaction was quenched by saturated aqueous potassium dihydrogen phosphate and 1N hydrochloric acid (0.29 ml). The mixture was extracted with dichloromethane. The organic layer was washed with brine, dried over sodium sulfate, and concentrated in vacuo. Thin layer chromatography of the concentrate with ethyl acetate furnished 4-[1-[3-[bis(4-isobutylphenyl)-methylamino]benzoyl]imidazo[1,5-a]pyridin-3-yl]butyric acid (77 mg).

^{1}H-NMR ($CDCl_3$, δ) : 0.84 (12H, d, J=7Hz), 1.81 (2H, m), 2.18 (2H, m), 2.52 (4H, d, J=7Hz), 2.54 (2H, t, J=7Hz), 3.10 (2H, t, J=7Hz), 5.52 (1H, s), 6.7-6.9 (2H, m), 7.0-7.85 (10H, m), 7.6-7.7 (2H, m), 7.98 (1H, d, J=7Hz), 8.40 (1H, d, J=8Hz)

The compounds described in the following Examples 2 to 8 could be obtained by reacting the corresponding starting compounds with bis(4-isobutylphenyl)chloromethane in accordance with a similar manner to that of Example 1.

Example 2

Ethyl 4-[1-[4-[bis(4-isobutylphenyl)methylamino]-benzoyl]imidazo[1,5-a]pyridin-3-yl]butyrate

^{1}H-NMR ($CDCl_3$, δ) : 0.88 (12H, d, J=7Hz), 1.25 (3H, t, J=7Hz), 1.85 (2H, m), 2.18 (2H, m), 2.45 (4H, d, J=7Hz), 2.51 (2H, t, J=7Hz), 3.09 (2H, t, J=7Hz), 4.13 (2H, q, J=7Hz), 4.64 (1H, br d, J=4Hz), 5.59 (1H, br d, J=4Hz), 6.58 (2H, d, J=9Hz), 6.83 (1H, dt, J=1, 7Hz), 7.05-7.17 (5H, m), 7.34 (4H, d, J=8Hz), 8.02 (1H, d, J=7Hz), 8.36 (2H, d, J=9Hz), 8.49 (1H, d, J=9Hz)

Example 3

Ethyl 4-[3-[3-[bis(4-isobutylphenyl)methylamino]-benzoyl]imidazo[1,5-a]pyridin-1-yl]butyrate

^{1}H-NMR ($CDCl_3$, δ) : 0.88 (12H, d, J=7Hz), 1.24 (3H, t, J=7Hz), 1.83 (2H, m), 2.13 (2H, m), 2.41 (2H, t, J=7Hz), 2.43 (4H, d, J=7Hz), 3.01 (2H, t, J=7Hz), 4.10 (2H, q, J=7Hz), 5.57 (1H, s), 6.70 (1H, m), 6.96 (1H, dt, J=1, 7Hz), 7.09 (4H, d, J=8Hz), 7.0-7.3 (2H, m), 7.27 (4H, d, J=8Hz), 7.55-7.75 (3H, m), 9.76 (1H, d, J=7Hz)

Example 4

Ethyl 4-[3-[4-[bis(4-isobutylphenyl)methylamino]-benzoyl]imidazo[1,5-a]pyridin-1-yl]butyrate

^{1}H-NMR ($CDCl_3$, δ) : 0.89 (12H, d, J=7Hz), 1.24 (3H, t, J=7Hz), 1.85 (2H, m), 2.13 (2H, m), 2.40 (2H, t, J=7Hz), 2.46 (4H,, d, J=7Hz), 3.0 (2H, t, J=7Hz), 4.12 (2H, q, J=7Hz), 4.70 (1H, br d, J=4Hz), 5.50(1H, br d, J=4Hz), 6.60 (2H, d, J=9Hz), 6.89 (1H, dt, J=1, 7Hz), 7.06 (1H, m), 7.10 (4H, d, J=8Hz), 7.23 (4H, d, J=8Hz), 7.62 (1H, dt, J=9, 1Hz), 8.38 (2H, d, J=9Hz), 9.72 (1H, d, J=7Hz)

Example 5

Ethyl 4-[3-[3-[bis(4-isobutylphenyl)methylamino]-benzoyl]azulen-1-yl]butyrate

^{1}H-NMR ($CDCl_3$, δ) : 0.85 (12H, d, J=7Hz), 1.20 (3H, t, J=7Hz), 1.81 (2H, m), 2.03 (2H, m), 2.32 (2H, t, J=7Hz), 2.41 (4H, d, J=7Hz), 3.04 (2H, t, J=7Hz), 4.08 (2H, q, J=7Hz), 5.51 (1H, s), 6.8-7.2 (4H, m), 7.06 (4H, d, J=8Hz), 7.28 (4H, d, J=8Hz), 7.43 (1H, t, J=9Hz), 7.52 (1H, t, J=9Hz), 7.79 (1H, t, J=9Hz), 7.92 (1H, s), 8.43 (1H, d, J=9Hz), 9.60 (1H, d, J=9Hz)

Example 6

Ethyl 4-[3-[4-[bis(4-isobutylphenyl)methylamino]-benzoyl]azulen-1-yl]butyrate

^{1}H-NMR ($CDCl_3$, δ) : 0.89 (12H, d, J=7Hz), 1.23 (3H, t, J=7Hz), 1.84 (2H, m), 2.06 (2H, m), 2.35 (2H, t, J=7Hz), 2.45 (4H, d, J=7Hz), 3.08 (2H, t, J=7Hz), 4.11 (2H, q, J=7Hz), 4.68 (1H, br d, J=4Hz), 5.59 (1H, br d, J=4Hz), 6.60 (2H, d, J=8Hz), 7.11 (4H, d, J=8Hz), 7.25 (4H, d, J=8Hz), 7.38 (1H, t, J=9Hz), 7.43 (1H, t, J=9Hz), 7.73 (2H, d, J=8Hz), 7.68-7.8 (1H, m), 7.98 (1H, s), 8.41 (1H, d, J=9Hz), 9.41 (1H, d, J=9Hz)

Example 7

Ethyl 4-[1-[4-[bis(4-isobutylphenyl)methoxy]benzoyl]-imidazo[1,5-a]pyridin-3-yl]butyrate

^{1}H-NMR ($CDCl_3$, δ) : 0.88 (12H, d, J=7Hz), 1.26 (3H, t, J=7Hz), 1.84 (2H, m), 2.17 (2H, m), 2.44 (4H, d, J=7Hz), 2.51 (2H, t, J=7Hz), 3.09 (2H, t, J=7Hz), 4.13 (2H, q, J=7Hz), 6.28 (1H, s), 6.86 (1H, dt, J=1, 7Hz), 7.03 (2H, d, J=9Hz), 7.11 (4H, d, J=8Hz), 7.17 (1H, m), 7.31 (4H, d, J=8Hz), 8.05 (1H, d, J=7Hz), 8.38 (2H, d, J=9Hz), 8.48 (1H, d, J=9Hz)

Example 8

Ethyl 4-[1-[3-[bis(4-isobutylphenyl)methoxy]benzoyl]-imidazo[1,5-a]pyridin-3-yl]butyrate

^{1}H-NMR ($CDCl_3$, δ) : 0.87 (12H, d, J=7Hz), 1.26 (3H, t, J=7Hz), 1.83 (2H, m), 2.17 (2H, m), 2.42 (4H, d, J=7Hz), 2.53 (2H, t, J=7Hz), 3.10 (2H, t, J=7Hz), 4.14 (2H, q, J=7Hz), 6.32 (1H, s), 6.88 (1H, dt, J=1, 7Hz), 7.09 (4H, d, J=8Hz), 7.05-7.4 (3H, m), 7.33 (4H, d, J=8Hz), 7.9-8.0 (2H, m), 8.09 (1H, d, J=7Hz), 8.46 (1H, dt, J=8, 1Hz)

Example 9

To a solution of ethyl 4-[1-[4-[bis(4-isobutylphenyl)methylamino]benzoyl]imidazo[1,5-a]pyridin-3-yl]butyrate (120 mg) in ethanol (5 ml) was added 1N sodium hydroxide (0.8 ml). After stirring for 40 minutes, the reaction mixture was evaporated in vacuo. To the residual solution were then added a solution of aqueous potassium dihydrogen phosphate (1 ml) and 1N hydrochloric acid (0.8 ml), and extracted with ethyl acetate. The organic layer was dried over sodium sulfate. After evaporation of the solvent the residue was chromatographed on silica gel (eluent : ethyl acetate) to give 4-[1-[4-[bis(4-isobutylphenyl)methylamino]benzoyl]imidazo-[1,5-a]pyridin-3-yl]butyric acid (78 mg).

^{1}H-NMR ($CDCl_3$, δ) : 0.88 (12H, d, J=7Hz), 1.83 (2H, m), 2.19 (2H, m), 2.44 (4H, d, J=7Hz), 2.55 (2H, t, J=7Hz), 3.14 (2H, t, J=7Hz), 5.59 (1H, s), 6.59 (2H, d, J=9Hz), 6.83 (1H, t, J=7Hz), 7.05-7.18 (5H, m), 7.22 (1H, d, J=7Hz), 7.98 (1H, d, J=7Hz), 8.26 (2H, d, J=9Hz), 8.44 (1H, d, J=9Hz)

The compounds described in the following Examples 10 to 15 could be obtained by hydrolyzing the corresponding ethyl ester with aqueous sodium hydroxide in accordance with a similar manner to that of Example 9.

Example 10

4-[3-[3-[Bis(4-isobutylphenyl)methylamino]benzoyl]-imidazo[1,5-a]pyridin-1-yl]butyric acid

^{1}H-NMR (CDCl$_3$, δ) : 0.87 (12H, d, J=7Hz), 1.82 (2H, m), 2.13 (2H, m), 2.42 (4H, d, J=7Hz), 2.48 (2H, t, J=7Hz), 3.03 (2H, t, J=7Hz), 5.56 (1H, s), 6.69 (1H, m), 6.96 (1H, dt, J=1, 7Hz), 7.07 (4H, d, J=8Hz), 7.05-7.3 (2H, m), 7.27 (4H, d, J=8Hz), 7.53 (1H, m), 7.6-7.7 (2H, m), 9.75 (1H, d, J=7Hz)

Example 11

4-[3-[4-[Bis(4-isobutylphenyl)methylamino]benzoyl]-imidazo[1,5-a]pyridin-1-yl]butyric acid

^{1}H-NMR (CDCl$_3$, δ) : 0.89 (12H, d, J=7Hz), 1.84 (2H, m), 2.13 (2H, m), 2.45 (4H, d, J=7Hz), 2.48 (2H, t, J=7Hz), 3.05 (2H, t, J=7Hz), 5.59 (1H, s), 6.59 (2H, d, J=9Hz), 6.90 (1H, dt, J=7, 1Hz), 7.07 (1H, m), 7.10 (4H, d, J=8Hz), 7.23 (4H, d, J=8Hz), 7.60 (1H, dt, J=9, 1Hz), 8.28 (2H, d, J=9Hz), 9.71 (1H, dt, J=7, 1Hz)

Example 12

4-[3-[3-[Bis-(4-isobutylphenyl)methylamino]benzoyl]-azulen-1-yl]butyric acid

^{1}H-NMR (CDCl$_3$, δ) : 0.85 (12H, d, J=7Hz), 1.82 (2H, m), 2.05 (2H, m), 2.40 (2H, t, J=7Hz), 2.42 (4H, d, J=7Hz), 3.06 (2H, t, J=7Hz), 5.51 (1H, s), 6.68 (1H, m), 7.08 (4H, d, J=8Hz), 7.0-7.3 (3H, m), 7.25 (4H, d, J=7Hz), 7.42 (1H, t, J=9Hz), 7.51 (1H, t, J=9Hz), 7.78 (1H, t, J=9Hz), 7.92 (1H, s), 8.41 (1H, d, J=9Hz), 9.59 (1H, d, J=9Hz)

Example 13

4-[3-[4-[Bis(4-isobutylphenyl)methylamino]benzoyl]-azulen-1-yl]butyric acid

^{1}H-NMR ($CDCl_3$, δ) : 0.88 (12H, d, J=7Hz), 1.84 (2H, m), 2.07 (2H, m), 2.51 (2H, t, J=7Hz), 2.45 (4H, d, J=7Hz), 3.09 (2H, t, J=7Hz), 5.58 (1H, s), 6.58 (2H, d, J=8Hz), 7.11 (4H, d, J=8Hz), 7.23 (4H, d, J=8Hz), 7.35 (1H, t, J=9Hz), 7.42 (1H, t, J=9Hz), 7.72 (2H, d, J=8Hz), 7.65-7.8 (1H, m), 7.97 (1H, s), 8.39 (1H, d, J=9Hz), 9.40 (1H, d, J=9Hz)

Example 14

4-[1-[4-[Bis(4-isobutylphenyl)methoxy]benzoyl]-imidazo[1,5-a]pyridin-1-yl]butyric acid

^{1}H-NMR ($CDCl_3$, δ) : 0.88 (12H, d, J=7Hz), 1.83 (2H, m), 2.18 (2H, m), 2.43 (4H, d, J=7Hz), 2.56 (2H, t, J=7Hz), 3.11 (2H, t, J=7Hz), 6.28 (1H, s), 6.84 (1H, dt, J=1, 7Hz), 7.04 (2H, d, J=9Hz), 7.10 (4H, d, J=8Hz), 7.13 (1H, m), 7.30 (4H, d, J=8Hz), 7.98 (1H, d, J=7Hz), 8.33 (2H, d, J=9Hz), 8.46 (1H, d, J=9Hz)

Example 15

4-[1-[3-[Bis(4-isobutylphenyl)methoxy]benzoyl]-imidazo[1,5-a]pyridin-3-yl]butyric acid

^{1}H-NMR ($CDCl_3$, δ) : 0.85 (12H, d, J=7Hz), 1.81 (2H, m), 2.19 (2H, m), 2.41 (4H, d, J=7Hz), 2.57 (2H, t, J=7Hz), 3.11 (2H, t, J=7Hz), 6.29 (1H, s), 6.86 (1H, dt, J=1, 7Hz), 7.08 (4H, d, J=8Hz), 7.05-7.4 (3H, m), 7.31 (4H, d, J=8Hz), 7.88-7.95 (2H, m), 7.99 (1H, d, J=7Hz), 8.43 (1H, d, J=9Hz)

The compounds of the following Examples 16 to 24 could be obtained by reacting the corresponding amino or hydroxy compounds with bis(4-isobutylphenyl)chloromethane in accordance with a similar manner to that of Example 1.

Example 16

4-[3-[3-[Bis(4-isobutylphenyl)methylamino]benzoyl]-4-quinolon-1-yl]butyric acid

^{1}H-NMR ($CDCl_3$, δ) : 0.85 (12H, d, J=8Hz), 1.70-1.90 (2H, m), 2.10-2.30 (2H, m), 2.42 (4H, d, J=8Hz), 2.40-2.50 (2H, m), 4.25-4.40 (2H, m), 5.46 (1H, s), 6.80-7.80 (15H, m), 8.14 (1H, s), 8.46 (1H, d, J=8Hz)

Example 17

4-[3-[4-Bis(4-isobutylphenyl)methylamino]benzoyl]-4-quinolon-1-yl]butyric acid

^{1}H-NMR ($CDCl_3$, δ) : 0.90 (12H, d, J=8Hz), 1.74-1.96 (2H, m), 2.14-2.32 (2H, m), 2.46 (4H, d, J=8Hz), 2.50 (2H, t, J=8Hz), 4.35-4.50 (2H, m), 5.63 (1H, s), 6.62 (2H, d, J=14Hz), 7.12 (4H, d, J=12Hz), 7.22 (4H, d, J=12Hz), 7.5-7.6 (1H, m), 7.70 (2H, d, J=14Hz), 7.80-7.96 (2H, m), 8.25 (1H, s), 8.46 (1H, d, J=8Hz)

Example 18

4-[3-[3-[Bis(4-isobutylphenyl)methylamino]benzoyl]-2,3-dihydro-2-oxo-1H-benzimidazol-1-yl]butyric acid

^{1}H-NMR ($CDCl_3$, δ) : 0.88 (12H, d, J=8Hz), 1.68-1.92 (2H, m), 2.0-2.18 (2H, m), 2.02-2.15 (2H, m), 2.43 (4H, d, J=8Hz), 2.46 (2H, t, J=8Hz), 3.86 (2H, t, J=8Hz), 5.44 (1H, s), 6.70 (1H, dd, J=1, 8Hz), 7.00-7.30 (14H, m), 7.82 (1H, dd, J=1, 8Hz)

Example 19

4-[3-[4-[Bis(4-isobutylphenyl)metoxy]benzoyl]-1H-indazo-1-yl]butyric acid

^{1}H-NMR (CDCl$_3$, δ) : 0.90 (12H, d, J=8Hz), 1.75-1.96 (2H, m), 2.26-2.45 (4H, m), 2.46 (4H, d, J=8Hz), 4.56 (2H, t, J=8Hz), 6.28 (1H, s), 7.06 (2H, d, J=9Hz), 7.12 (4H, d, J=8Hz), 7.20-7.50 (7H, m), 8.30 (2H, d, J=9Hz), 8.42 (1H, d, J=8Hz)

Example 20

4-[3-[3-[Bis(4-isobutylphenyl)methylamino]benzoyl]-1H-pyrrolo[2,3-b]pyridin-1-yl]butyric acid

^{1}H-NMR (CDCl$_3$, δ) : 0.87 (8H, d, J=8Hz), 1.72-1.95 (2H, m), 2.14-2.28 (2H, m), 2.38 (2H, t, J=8Hz), 2.42 (4H, d, J=8Hz), 4.36 (2H, t, J=8Hz), 5.51 (1H, s), 6.74 (1H, dd, J=2, 8Hz), 7.0-7.34 (12H, m), 7.60 (1H, s), 8.40 (1H, dd, J=1, 5Hz), 8.68 (1H, dd, J=1, 8Hz)

Example 21

Ethyl 4-[5-[3-[bis(4-isobutylphenyl)methylamino]-benzoyl]thien-2-yl]butyrate

^{1}H-NMR (CDCl$_3$, δ) : 0.89 (12H, d, J=7Hz), 1.26 (3H, t, J=7Hz), 1.84 (2H, m), 2.05 (2H, m), 2.38 (2H, t, J=7Hz), 2.45 (4H, d, J=7Hz), 2.90 (2H, t, J=7Hz), 4.15 (2H, q, J=7Hz), 5.48 (1H, s), 6.70 (1H, d, J=4Hz), 6.7-7.7 (13H, m)

Example 22

Ethyl 4-[5-[3-[bis(4-isobutylphenyl)methylamino]-benzoyl]-3-phenylthien-2-yl]butyrate

^{1}H-NMR (CDCl$_3$, δ) : 0.88 (12H, d, J=7Hz), 1.21 (3H, t, J=7Hz), 1.7-2.1 (4H, m), 2.32 (2H, t, J=7Hz), 2.43 (2H, d, J=7Hz), 2.94 (2H, t, J=7Hz), 4.08 (2H, q, J=7Hz), 5.50 (1H, m), 6.68 (1H, m), 7.0-7.5 (16H, m), 7.53 (1H, s)

Example 23

4-[3-[3-[Bis(4-isobutylphenyl)methylamino]benzoyl]-azulen-1-yl]butyric acid

^{1}H-NMR ($CDCl_3$, δ) : 0.85 (12H, d, J=7Hz), 1.82 (2H, m), 2.05 (2H, m), 2.40 (2H, t, J=7Hz), 2.42 (4H, d, J=7Hz), 3.06 (2H, t, J=7Hz), 5.51 (1H, s), 6.68 (1H, m), 7.08 (4H, d, J=8Hz), 7.0-7.3 (3H, m), 7.25 (4H, d, J=7Hz), 7.42 (1H, t, J=9Hz), 7.51 (1H, t, J=9Hz), 7.78 (1H, t, J=9Hz), 7.92 (1H, s), 8.41 (1H, d, J=9Hz), 9.59 (1H, d, J=9Hz)

Example 24

4-[1-[4-[Bis(4-isobutylphenyl)methoxy]benzoyl]-imidazo[1,5-a]pyridin-1-yl]butyric acid

^{1}H-NMR ($CDCl_3$, δ) : 0.88 (12H, d, J=7Hz), 1.83 (2H, m), 2.18 (2H, m), 2.43 (4H, d, J=7Hz), 2.56 (2H, t, J=7Hz), 3.11 (2H, t, J=7Hz), 6.28 (1H, s), 6.84 (1H, dt, J=1, 7Hz), 7.04 (2H, d, J=9Hz), 7.10 (4H, d, J=8Hz), 7.13 (1H, m), 7.30 (4H, d, J=8Hz), 7.98 (1H, d, J=7Hz), 8.33 (2H, d, J=9Hz), 8.46 (1H, d, J=9Hz)

The compounds of the following Examples 25 to 27 could be obtained by hydrolyzing the corresponding ethyl ester compound with an aqueous sodium hydroxide in accordance with a similar manner to that of Example 9.

Example 25

4-[5-[3-[Bis(4-isobutylphenyl)methylamino]benzoyl]-thien-2-yl]butyric acid

^{1}H-NMR ($CDCl_3$, δ) : 0.88 (12H, d, J=7Hz), 1.83 (2H, m), 2.03 (2H, m), 2.43 (2H, t, J=7Hz), 2.45 (4H, d, J=7Hz), 2.92 (2H, t, J=7Hz), 5.50 (1H, s), 6.70 (1H, d, J=4Hz), 6.74 (1H, m), 6.97 (1H, m), 7.05-7.3 (11H, m)

Example 26

4-[5-[3-[Bis(4-isobutylphenyl)methylamino]benzoyl]-3-phenylthien-2-yl]butyric acid

^{1}H-NMR ($CDCl_3$, δ) : 0.87 (12H, d, J=7Hz), 1.7-2.15 (4H, m), 2.38 (2H, t, J=7Hz), 2.42 (2H, d, J=7Hz), 2.97 (2H, t, J=7Hz), 5.49 (1H, s), 6.68 (1H, m), 7.0-7.45 (16H, m), 7.53 (1H, s)

Example 27

4-[1-[3-[Bis(4-isobutylphenyl)methylamino]benzoyl]-imidazo[1,5-a]pyridin-3-yl]butyric acid

^{1}H-NMR ($CDCl_3$, δ) : 0.84 (12H, d, J=7Hz), 1.81 (2H, m), 2.18 (2H, m), 2.52 (4H, d, J=7Hz), 2.54 (2H, t, J=7Hz), 3.10 (2H, t, J=7Hz), 5.52 (1H, s), 6.7-6.9 (2H, m), 7.0-7.85 (10H, m), 7.6-7.7 (2H, m), 7.98 (1H, d, J=7Hz), 8.40 (1H, d, J=8Hz)

Preparation 48

Methyl 4-[1-(4-hydroxybenzoyl)imidazo[1,5-a]pyridin-3-yl]butyrate could be obtained in accordance with a similar manner to that of Preparation 19.

^{1}H-NMR (DMSO-d_6, δ) : 2.08 (2H, m), 2.53 (2H, t, J=7Hz), 3.10 (2H, t, J=7Hz), 3.58 (3H, s), 6.88 (2H, d, J=9Hz), 7.05 (1H, t, J=7Hz), 7.33 (1H, m), 8.3-8.45 (3H, m), 8.48 (1H, d, J=7Hz)

Preparation 49

To a solution of 4-acetoxybenzoyl chloride (75 mg) and aluminum chloride (51 mg) in dichloromethane (3 ml) was added a solution of ethyl 4-(azulen-1-yl)butyrate (92 mg) in dichloromethane (2 ml). After stirring at room temperature for 1 hour, the mixture was washed with 7% hydrochloric acid and water, dried over magnesium sulfate and evaporated. The residue was chromatographed on silica gel eluting with a mixture of n-hexane and ethyl acetate (2:1) to give ethyl 4-[3-(4-acetoxybenzoyl)azulen-1-yl]butyrate (71 mg) as an oil.

^{1}H-NMR ($CDCl_3$, δ) : 9.65 (1H, d, J=9Hz), 8.49 (1H, d, J=9Hz), 7.93 (2H, d, J=10Hz), 7.75-7.9 (2H, m), 7.4-7.6 (2H, m), 7.25 (2H, d, J=10Hz), 7.2-7.3 (1H, m), 4.13 (2H, q, J=7Hz), 3.09 (2H, t, J=7Hz), 2.37 (2H, t, J=7Hz), 2.36 (3H, s), 2.0-2.2 (2H, m), 1.24 (3H, t, J=7Hz)

Preparation 50

To a solution of ethyl 4-[3-(4-acetoxybenzoyl)-azulen-1-yl]butyrate (40 mg) in ethanol (1 ml) was added sodium hydride 60% dispersion in mineral oil (5mg). After stirring at room temperature fro 10 minutes, the mixture was poured into 7% hydrochloric acid and extracted with ethyl acetate (10 ml). The organic layer was washed with water, dried over magnesium sulfate and evaporated to give ethyl 4-[3-(4-hydroxybenzoyl)aculen-1-yl]butyrate (39 mg) as an oil.

^{1}H-NMR ($CDCl_3$, δ) : 9.55 (1H, d, J=9Hz), 8.45 (1H, d, J=9Hz), 7.96 (1H, s), 7.80 (2H, d, J=9Hz), 7.7-7.9 (1H, m), 7.4-7.6 (2H, m), 6.93 (2H, d, J=9Hz), 6.50 (1H, brs), 4.13 (2H, q, J=7Hz), 4.13 (2H, q, J=7Hz), 3.10 (2H, t, J=7Hz), 2.40 (2H, t, J=7Hz), 2.0-2.2 (2H, m), 1.23 (3H, t, J=7Hz)

Example 28

To a mixture of methyl 4-[1-(4-hydroxybenzoyl)-imidazo[1,5-a]pyridin-3-yl]butyrate (267 mg), (R)-1-(4-isobutylphenyl)butanol (179 mg) and triphenylphosphine (228 mg) in a mixture of tetrahydrofuran (1 ml) and toluene (4 ml) was added diethyl azodicarboxylate (0.137 ml) at -20°C. After the mixture was stirred at -20°C for 3 hours, acetic acid (0.05 ml) was added and the mixture was warm up to room temperature. The solvent was evaporated under reduced pressure and the residue was chromatographed on silica gel (n-hexane/ethyl acetate, 3:2) to give methyl (S)-4-[1-[4-[1-(4-isobutylphenyl)butoxy]benzoyl]imidazo-[1,5-a]pyridin-3-yl]butyrate (119 mg) as an oil.

^{1}H-NMR ($CDCl_3$, δ) : 0.88 (6H, d, J=6.5Hz), 0.96 (3H, t, J=7.5Hz), 1.3-2.3 (7H, m), 2.44 (2H, d, J=6.5Hz), 2.53 (2H, t, J=7Hz), 3.09 (2H, t, J=7.5Hz), 3.69 (3H, s), 5.19 (1H, dd, J=5Hz, 8Hz), 6.8-7.0 (3H, m), 7.05-7.3 (5H, m), 8.03 (1H, d, J=7Hz), 8.35 (2H, d, J=9Hz), 8.48 (1H, d, J=9Hz)

Example 29

Ethyl (S)-4-[3-[4-[1-(4-isobutylphenyl)butoxy]benzoyl]-azulen-1-yl]butyrate could be obtained by reacting the corresponding starting compound with (R)-1-(4-isobutylphenyl)butanol in accordance with a similar manner to that of Example 28.

^{1}H-NMR ($CDCl_3$, δ) : 9.49 (1H, d, 9Hz), 8.43 (1H, d, 9Hz), 7.92 (1H, s), 7.75 (2H, d, 9Hz), 7.7-7.8 (1H, m), 7.3-7.6 (2H, m), 7.26 (2H, d, 9Hz), 7.11 (2H, d, 9Hz), 6.92 (2H, d, 9Hz), 5.19 (1H, m), 4.11 (2H, q, 7Hz), 3.07 (2H, t, 7Hz), 2.44 (2H, d, 7Hz), 2.38 (2H, t, 7Hz), 2.0-2.1 (3H, m), 1.7-2.0 (2H, m), 1.3-1.7 (2H, m), 1.23 (3H, t, 7Hz), 0.98 (3H, t, 7Hz), 0.89 (6H, d, 7Hz)

The compounds described in the following Examples 30 and 31 could be obtained by hydrolyzing the corresponding ethyl ester with aqueous sodium hydroxide in accordance with a similar manner to that of Example 9.

Example 30

(S)-4-[1-[4-[1-(4-Isobutylphenyl)butoxy]benzoyl]-imidazo[1,5-a]pyridyn-3-yl]butyric acid

^{1}H-NMR ($CDCl_3$, δ) : 0.88 (6H, d, J=6.5Hz), 0.96 (3H, t, J=7.5Hz), 1.3-2.3 (7H, m), 2.43 (2H, d, J=6.5Hz), 2.58 (2H, t, J=7Hz), 3.12 (2H, t, J=7.5Hz), 5.18 (1H, dd, J=5Hz, 8Hz), 6.8-7.0 (3H, m), 7.09 (2H, d, J=8.5Hz), 7.15-7.3 (3H, m), 7.98 (1H, d, J=7Hz), 8.30 (2H, d, J=9Hz), 8.47 (1H, d, J=9Hz)

Example 31

(S)-4-[3-[4-[1-(4-Isobutylphenyl)butoxy]benzoyl]-azulen-1-yl]butyric acid

^{1}H-NMR ($CDCl_3$, δ) : 9.49 (1H, d, J=9Hz), 8.42 (1H, d, J=9Hz), 7.92 (1H, s), 7.75 (2H, d, J=9Hz), 7.7-7.8 (1H, m), 7.3-7.6 (2H, m), 7.25 (2H, d, J=9Hz), 7.10 (2H, d, J=9Hz), 6.93 (2H, d, J=9Hz), 5.19 (1H, m), 3.10 (2H, t, J=7Hz), 2.4-2.5 (4H, m), 2.0-2.2 (3H, m), 1.7-2.0 (2H, m), 1.3-1.7 (2H, m), 0.97 (3H, t, J=7Hz), 0.89 (6H, d, J=7Hz)

CLAIMS

1. A compound of the formula :

$$R^1\text{-A-CO-X-Y-}R^2 \qquad \text{(I)}$$

in which R^1 is carboxy(lower)alkyl or protected carboxy(lower)alkyl,

R^2 is optionally substituted aralkyl,

X is optionally substituted arylene,

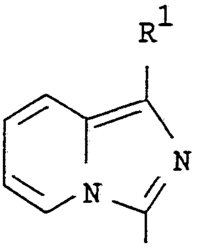
Y is -O- or $-\overset{R^6}{\overset{|}{N}}-$,

wherein R^6 is hydrogen, lower alkyl, optionally substituted aralkyl or amino-protective group, and

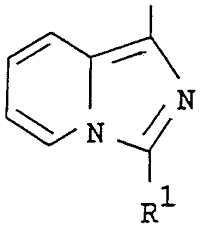
A is a bivalent radical derived from imidazopyridine, azulene, thiophene, pyrrolo[2,3-b]pyridine, quinolone, indazole or dihydrobenzimidazole, each of which may be substituted by one or more suitable substituent(s),

or a pharmaceutically acceptable salt thereof.

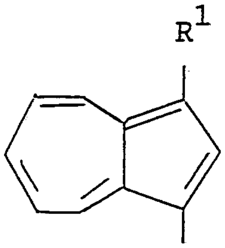
2. A compound of claim 1, in which R^1-A- can be represented by the formula :



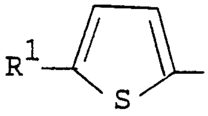
,



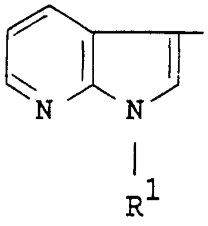
,



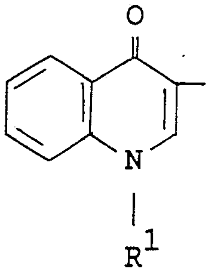
,



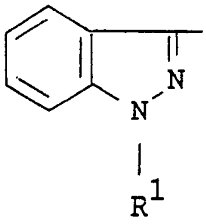
,



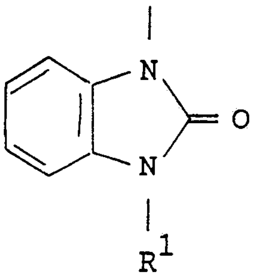
,



,



or



,

wherein R^1 is as defined above, and
X is phenylene.

3. A process for preparing a compound of the formula :

$$R^1\text{-A-CO-X-Y-}R^2 \qquad (I)$$

in which R^1, R^2, A, X and Y are each as defined above,
or a salt which comprises

(1) reacting a compound of the formula :

$$R^1\text{-A-CO-X-Y-H} \qquad (II)$$

in which R^1, A, X and Y are each as defined above, or a salt thereof with a compound of the formula :

$$\text{HO-}R^2 \qquad (III)$$

in which R^2 is as defined above,
or its reactive derivative at the hydroxy group,
or a salt thereof to give the compound (I), or

(2) removing the carboxy-protective group from a compound of the formula :

$$R_a^1\text{-A-CO-X-Y-}R^2 \qquad \text{(I-a)}$$

in which R_a^1 is protected carboxy(lower)alkyl, and
R^2, A, X and Y are each as defined above,
or a salt thereof to give a compound of the formula :

$$R_b^1\text{-A-CO-X-Y-}R^2 \qquad \text{(I-b)}$$

in which R_b^1 is carboxy(lower)alkyl, and
R^2, A, X and Y are each as defined above,
or a salt thereof.

4. A pharmaceutical composition comprising a compound of claim 1 or pharmaceutically acceptable salt thereof in association with a pharmaceutically acceptable, substantially non-toxic carrier or excipient.

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

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

7. Use of compound of claim 1 or pharmaceutically acceptable salt thereof as a testosteron 5α-reductase

inhibitor.

8. A process for preparing a pharmaceutical composition which comprises admixing a compound of claim 1 or pharmaceutically acceptable salt thereof with a pharmaceutically acceptable, substantially non-toxic carrier or excipient.

INTERNATIONAL SEARCH REPORT

International Application No PCT/JP 92/01674

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all)[6]

According to International Patent Classification (IPC) or to both National Classification and IPC

Int.Cl. 5 C07D471/04;	C07D333/24;	C07D215/22;	C07D231/56
C07D235/26;	C07C229/44;	C07C59/90;	A61K31/33

II. FIELDS SEARCHED

Minimum Documentation Searched[7]

Classification System	Classification Symbols
Int.Cl. 5	C07D ; C07C ; A61K

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched[8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT[9]

Category °	Citation of Document, [11] with indication, where appropriate, of the relevant passages [12]	Relevant to Claim No.[13]
A	EP,A,0 458 207 (FUJISAWA) 27 November 1991 see claims 1,10 ---	1,4
A	WO,A,9 113 060 (FUJISAWA) 5 September 1991 see claims 1,11 -----	1,4

° Special categories of cited documents : [10]

"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

"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

IV. CERTIFICATION

1

Date of the Actual Completion of the International Search 23 MARCH 1993	Date of Mailing of this International Search Report 14. 04. 93
International Searching Authority EUROPEAN PATENT OFFICE	Signature of Authorized Officer ALFARO FAUS I.

rnational application No.

PCT/JP 92/01674

INTERNATIONAL SEARCH REPORT

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:
Remark: Although claim 5 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

International Application No PCT/JP 92/01674

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) [6]

According to International Patent Classification (IPC) or to both National Classification and IPC

IPC⁵: A61K31/215 A61K31/19 // (C07D471/04, 235:00, 221:00) (C07D471/04, 221:00,209:00)

II. FIELDS SEARCHED

Minimum Documentation Searched [7]

Classification System	Classification Symbols
IPC⁵	

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched [8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT [9]

Category [•]	Citation of Document, [11] with Indication, where appropriate, of the relevant passages [12]	Relevant to Claim No. [13]

- • Special categories of cited documents: [10]
- "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
- "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

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report 14. 04. 93
International Searching Authority EUROPEAN PATENT OFFICE	Signature of Authorized Officer

Form PCT/ISA/210 (second sheet) (January 1985)

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO.

JP 9201674
SA 68138

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report.
The members are as contained in the European Patent Office EDP file on 23/03/93
The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
EP-A-0458207	27-11-91	AU-A-	7711691	21-11-91
		CN-A-	1056685	04-12-91
		JP-A-	4244061	01-09-92
WO-A-9113060	05-09-91	AU-A-	7257991	18-09-91
		CN-A-	1054250	04-09-91
		EP-A-	0516849	09-12-92

For more details about this annex : see Official Journal of the European Patent Office, No. 12/82