

4,1-Benzoxazepin derivatives and their use

FIELD OF THE INVENTION

This invention relates to 4,1-benzoxazepin-2-one derivatives or salts which are useful for inhibiting squalene synthetase and fungal growth, and their use.

BACKGROUND OF THE INVENTION

Hypercholesteremia, high blood pressure and smoking are known as three major dangerous factors of causing ischemic diseases. Adequate control of cholesterol concentration in blood is remarkably important for the prophylaxis or therapy of, besides ischemic diseases, coronary sclerosis.

As pharmaceutical compositions for lowering cholesterol in blood, attention has been drawn to those for controlling the biosynthesis of cholesterol, besides those of inhibiting its absorption by binding bile acid including, among others, cholestyramine, colestipol (disclosed in, for example, USP 4027009), and those of suppressing the intestinal absorption of cholesterol by inhibiting acyl coenzyme A cholesterol acyl transferase (ACAT) including melinamide (disclosed in French Patent No.1476569). As pharmaceutical preparations for controlling the biosynthesis of cholesterol, lovastatin (disclosed in USP 4231938), simvastatin (disclosed in USP 4444784), pravastatin (USP 4346227), etc., which are capable of inhibiting especially 3-hydroxy-3-methyl glutaryl coenzyme (HMG-CoA) reductase, are provided for medicinal use. However, when HMG-CoA reductase is inhibited, not only the biosynthesis of cholesterol but the biosynthesis of some other components such ubiquinone, dolichol and heme A, which are necessary for the living body, is also inhibited, so that occurrences of undesirable side effects to be caused thereby are feared.

Squalene synthetase is the enzyme involved in the committed step of the de novo cholesterol biosynthetic pathway. This enzyme catalyzes the reductive dimerization of two molecules of farnesyl pyrophosphate to form squalene.

On the other hand, the compounds expected as inhibitors of cholesterol biosynthesis by inhibiting squalene synthetase are disclosed in JPA H1(1989)-213288, JPA H2(1990)-101088, JPA H2(1990)-235820, JPA H2(1990)-235821, JPA H3(1991)-20226, JPA H3(1991)-68591, JPA H3(1991)-48288, USP 5,019,390, Journal of Medicinal Chemistry, 51 (10), p.1869-1871 (1988), USP 5,135,935 and WO 9215579.

Also, the compounds expected as inhibitors of fungal growth by inhibiting squalene synthetase are disclosed in JPA H4 (1992)-279589, EP 475706-A, EP 494622-A and EP 503520-A.

Among 4,1-benzoxazepine derivatives, in 4,1-benzoxazepin-2-one derivatives in which 2-position is substituted with ketone group, those in which one of the hydrogen atoms at 3-position is replaced with a different substituent, are disclosed in JPA S57(1982)-345765 and Chem. Pharm. Bull., 34, 140 (1986).

Ubiquinone, dolichol and heme A have been known as being synthesized from farnesyl pyrophosphate along the cholesterol biosynthesis pathway. Therefore, for avoiding occurrence of side effects due to loss of these substances, it is desirable to inhibit enzymes subsequent to farnesyl pyrophosphate, especially squalene synthetase, in the cholesterol biosynthetic pathway.

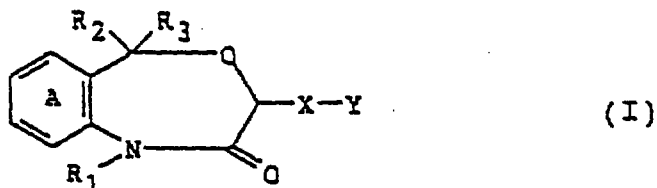
SUMMARY OF THE INVENTION

Through intensive investigations from the above viewpoint, the present inventors found that 4,1-benzoxazepin-2-one derivatives exhibit excellent squalene synthetase inhibitory action and antifungal

action, and developed the present invention.

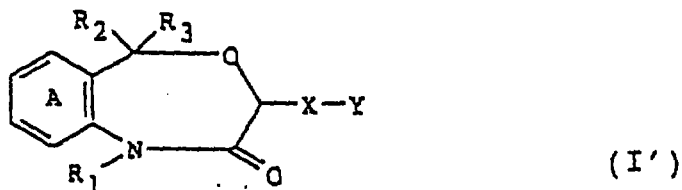
Accordingly, the present invention provides:

(1) 4,1-Benzoxazepin-2-one derivatives represented by the formula (I):



, wherein R_1 stands for hydrogen atom or an optionally substituted hydrocarbon group; R_2 and R_3 independently stand for hydrogen atom, an optionally substituted lower alkyl group, an optionally substituted phenyl group or an optionally substituted aromatic heterocyclic group; X stands for a bond or a spacer having the chain length of 1 to 7 atoms; Y stands for an optionally esterified or thioesterified carboxyl group, an optionally substituted hydroxyl group, an optionally substituted amino group, an optionally substituted phenyl group, an optionally substituted carbamoyl group or a N-containing heterocyclic residue having hydrogen atom capable of being deprotonated; provided that, when X is methylene and R_1 is not an alkyl group having carbon atoms of more than 4, Y is neither carboxyl group nor alkoxy carbonyl group; and the ring A may optionally be substituted, or salts thereof,

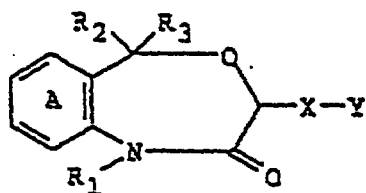
(2) 4,1-Benzoxazepin-2-one derivatives represented by the formula (I'):



, wherein R^1 stands for hydrogen atom or an optionally

substituted hydrocarbon group; R_1 and R_2 independently stand for hydrogen atom, an optionally substituted lower alkyl group, an optionally substituted phenyl group or an optionally substituted aromatic heterocyclic group; X stands for a bond or a spacer having the chain length of 1 to 7 atoms; Y stands for an optionally esterified or thioesterified carboxyl group, an optionally substituted hydroxyl group, an optionally substituted amino group, an optionally substituted phenyl group, an optionally substituted carbamoyl group or a N-containing heterocyclic residue having hydrogen atom capable of being deprotonated; provided that, when X is methylene, Y is neither carboxyl group nor alkoxycarbonyl group; and the ring A may optionally be substituted, or salts thereof,

(3) a squalene synthetase inhibitor comprising as an active ingredient a 4,1-Benzoxazepin-2-one derivative represented by the formula (I''):

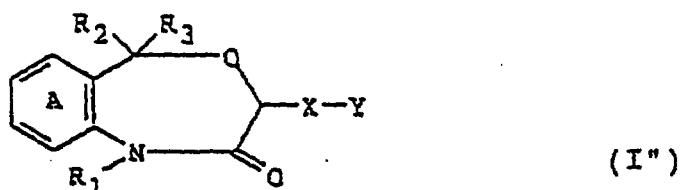


(I'')

, wherein R^1 stands for hydrogen atom or an optionally substituted hydrocarbon group; R_2 and R_3 independently stand for hydrogen atom, an optionally substituted lower alkyl group, an optionally substituted phenyl group or an optionally substituted aromatic heterocyclic group; X stands for a bond or a spacer having the chain length of 1 to 7 atoms; Y stands for an optionally esterified or thioesterified carboxyl group, an optionally substituted hydroxyl group, an optionally substituted amino group, an optionally substituted phenyl group, an optionally substituted carbamoyl group or a N-containing heterocyclic residue

having hydrogen atom capable of being deprotonated; and the ring A may optionally be substituted, or a salt thereof, and

(4) a fungal growth inhibitor comprising as an active ingredient a 4,1-Benzoxazepin-2-one derivative represented by the formula (I''):



, wherein R¹ stands for hydrogen atom or an optionally substituted hydrocarbon group; R₂ and R₃ independently stand for hydrogen atom, an optionally substituted lower alkyl group, an optionally substituted phenyl group or an optionally substituted aromatic heterocyclic group; X stands for a bond or a spacer having the chain length of 1 to 7 atoms; Y stands for an optionally esterified or thioesterified carboxyl group, an optionally substituted hydroxyl group, an optionally substituted amino group, an optionally substituted phenyl group, an optionally substituted carbamoyl group or a N-containing heterocyclic residue having hydrogen atom capable of being deprotonated; and the ring A may optionally be substituted, or a salt thereof.

Further, the present invention is to provide a method of producing the novel compounds represented by the formula (I) and (I') or salts thereof.

In the above-mentioned formulae (I), (I') and (I''), as the hydrocarbon group of "optionally substituted hydrocarbon group" shown by R₁, mention is made of aliphatic chain hydrocarbon groups, alicyclic hydrocarbon group and aryl group, among others, with preference given to aliphatic chain hydrocarbon groups.

As the aliphatic chain hydrocarbon group of said hydrocarbon group, mention is made of straight-chain or branched aliphatic hydrocarbon groups, for example, alkyl group, alkenyl group and alkynyl group, with preference given to lower alkyl group, lower alkenyl group and lower alkynyl group. As the lower alkyl group, C_{1-7} lower alkyl groups are preferable, which are exemplified by methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, isopentyl, neopentyl, tert-pentyl, 1-ethylpropyl, hexyl, isohexyl, 1,1-dimethylbutyl, 2,2-dimethylbutyl, 3,3-dimethylpropyl, 3,3-dimethylbutyl, 2-ethylbutyl and 1-ethylpropyl, with preference given to C_{2-3} alkyl groups, more preferably C_{4-5} alkyl groups. As the lower alkenyl group, C_{2-6} lower alkenyl groups are preferable, which are exemplified by vinyl, allyl, 2-methylallyl, isopropenyl, 1-propenyl, 2-methyl-1-propenyl, 2-methyl-2-propenyl, 1-butenyl, 2-butenyl, 3-butenyl, 2-ethyl-1-butenyl, 2-methyl-2-butenyl, 3-methyl-2-butenyl, 1-pentenyl, 2-pentenyl, 3-pentenyl, 4-pentenyl, 4-methyl-3-pentenyl, 1-hexenyl, 2-hexenyl, 3-hexenyl, 4-hexenyl and 5-hexenyl. Among them, vinyl, allyl, isopropenyl, 2-methylallyl, 2-methyl-1-propenyl, 2-methyl-2-propenyl, and 3-methyl-2-butenyl are especially preferable. As the lower alkynyl group, C_{2-6} lower alkynyl groups are preferable, which are exemplified by ethynyl, 1-propynyl, 2-propynyl, 1-butyne, 2-butyne, 3-butyne, 1-pentyne, 2-pentyne, 3-pentyne, 4-pentyne, 1-hexynyl, 2-hexynyl, 3-hexynyl, 4-hexynyl and 5-hexynyl. Among them, ethynyl, 1-propynyl and 2-propynyl are especially preferable.

As the alicyclic hydrocarbon group of the said hydrocarbon group, mention is made of saturated or unsaturated alicyclic hydrocarbon groups, which are exemplified by cycloalkyl group, cycloalkenyl group or cycloalkadienyl group. As the cycloalkyl group, C_{3-9}

cycloalkyl groups are preferable, which are exemplified by cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl and cyclononyl. Among them, C₃₋₆ cycloalkyl groups such as cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl are especially preferable. Examples of the cycloalkenyl group include 2-cyclopenten-1-yl, 3-cyclopenten-1-yl, 2-cyclohexen-1-yl, 3-cyclohexen-1-yl, 1-cyclobuten-1-yl and 1-cyclopenten-1-yl. Examples of the cycloalkadienyl group include 2,4-cyclopentadien-1-yl, 2,4-cyclohexadien-1-yl, and 2,5-cyclohexadien-1-yl.

As the aryl group of said hydrocarbon group, mention is made of monocyclic or condensed polycyclic aromatic hydrocarbon groups, which are exemplified by phenyl, naphthyl, anthryl, phenanthryl and acenaphthylenyl. Among them, phenyl, 1-naphthyl and 2-naphthyl are especially preferable.

As the substituent of "optionally substituted hydrocarbon group" shown by R₁, mention is made of optionally substituted aryl groups, optionally substituted cycloalkyl groups or cycloalkenyl groups, optionally substituted heterocyclic groups, optionally substituted amino groups, optionally substituted hydroxyl groups, optionally substituted thiol groups and halogen atoms (e.g. fluorine, chlorine, bromine and iodine). Number of these optional substituents ranges from 1 to 5 (preferably 1 to 3). As the aryl group of said optionally substituted aryl group, mention is made of phenyl, naphthyl, anthryl, phenanthryl and acenaphthylenyl. Among them, phenyl, 1-naphthyl and 2-naphthyl are preferable. As the substituent on said optionally substituted aryl group, mention is made of C₁₋₃ alkoxy groups (e.g. methoxy, ethoxy and propoxy), halogen atoms (e.g. fluorine, chlorine, bromine and iodine) and C₁₋₃ alkyl groups (e.g. methyl, ethyl and propyl). Number of these optional substituents ranges

from 1 to 2. As the cycloalkyl group of said optionally substituted cycloalkyl group, mention is made of C₃₋₇ cycloalkyl groups such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl. Kinds and number of the substituents on said optionally substituted cycloalkyl group are the same as those mentioned for the substituents in the above-mentioned optionally substituted aryl groups. As the cycloalkenyl group of said optionally substituted cycloalkenyl group, mention is made of C₃₋₆ cycloalkenyl groups including cyclopropanyl, cyclobutenyl, cyclopentenyl and cyclohexenyl. Kinds and number of the substituents on said optionally substituted cycloalkenyl group are the same as those mentioned for the substituents in the above-mentioned optionally substituted aryl groups. As the heterocyclic group of said optionally substituted heterocyclic group, mention is made of an aromatic heterocyclic group and a saturated or unsaturated non-aromatic heterocyclic group (aliphatic heterocyclic group) having at least one hetero atom selected from oxygen, sulfur and nitrogen, with preference given to an aromatic heterocyclic group. As said aromatic heterocyclic group, mention is made of aromatic monocyclic heterocyclic groups (e.g. furyl, thienyl, pyrrolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, imidazolyl, pyrazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl, furazanyl, 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,3,4-thiadiazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, tetrazolyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, triazinyl, etc.) and aromatic condensed heterocyclic groups (e.g. benzofuranyl, isobenzofuranyl, benzo[h] thienyl, indolyl, isoindolyl, 1H-indazolyl, benzimidazolyl, benzoxazolyl, 1,2-benzoisoxazolyl, benzothiazolyl, 1,2-benzisothiazolyl, 1H-benzotriazolyl, quinolyl, isoquinolyl, cinnolinyl, quinazolinyl, quinoxalinyl,

phthalazinyl, naphthylidiny, purinyl, pteridinyl, carbazolyl, α -carbolinyl, β -carbolinyl, γ -carbolinyl, acrydinyl, phenoxazinyl, phenothiazinyl, phenazinyl, phenoxthiny, thianthrenyl, phenanthridinyl, phenanthrolinyl, indolidinyl, pyrrolo[1,2-b]pyridazinyl, pyrazolo[1,5-a]pyridyl, imidazo[1,2-a]pyridyl, imidazo[1,5-a]pyridyl, imidazo[1,2-b]pyridazinyl, imidazo[1,2-a]pyrimidinyl, 1,2,4-triazolo[4,3-a]pyridyl, 1,2,4-triazolo[4,3-b]pyridazinyl, etc.), with preference given to furyl, thienyl, pyridyl, pyrimidinyl, pyrazinyl, indolyl and isoindolyl. As said non-aromatic heterocyclic group, mention is made of, for example, oxiranyl, azetidiny, oxetanyl, thiethanyl, pyrrolidinyl, tetrahydrofuryl, thioranyl, piperidyl, tetrahydropyranyl, morpholinyl, thiomorpholinyl, piperazinyl, etc. As the substituent of said optionally substituted heterocyclic group, mention is made of C_{1-3} alkyl groups (e.g. methyl, ethyl and propyl). As the substituent of said optionally substituted amino group, optionally substituted hydroxyl group or optionally substituted thiol group, mention is made of C_{1-3} alkyl groups (e.g. methyl, ethyl and propyl). In the case where the hydrocarbon group in the optionally substituted hydrocarbon group shown by R_1 is an alicyclic hydrocarbon group or aryl group, it may further have a C_{1-3} alkyl group (e.g. methyl, ethyl and propyl).

In the above-mentioned formulae (I), (I') and (I''), as the optionally substituted lower alkyl groups shown by R_2 and R_3 , mention is made of C_{1-6} lower alkyl groups (e.g. methyl, ethyl, n-propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, isopentyl, neopentyl, hexyl and isohexyl), preferably C_{1-4} alkyl groups such as methyl, ethyl, propyl, isopropyl, butyl and t-butyl. As the substituent of said optionally substituted lower alkyl group, mention is made of

halogen atoms (e.g. fluorine, chlorine, bromine and iodine), C_{1-4} lower alkoxy groups (e.g. methoxy, ethoxy, propoxy, isopropoxy, butoxy and t-butoxy), among others.

Substituents of "optionally substituted phenyl group" shown by R_2 and R_3 are independently exemplified by halogen atom (e.g. fluorine, chlorine, bromine or iodine), optionally substituted C_{1-4} lower alkyl groups (e.g. methyl, ethyl, propyl, isopropyl, butyl and t-butyl), optionally substituted C_{1-4} lower alkoxy groups (e.g. methoxy, ethoxy, propoxy, isopropoxy, butoxy and t-butoxy), optionally substituted hydroxyl group, nitro group and cyano group, and "optionally substituted phenyl group" may have 1 to 3 of these substituents. As the substituent of said optionally substituted lower (C_{1-4}) alkyl group or optionally substituted (C_{1-4}) alkoxy group, mention is made of, among others, halogen atoms (e.g. fluorine, chlorine, bromine, iodine), and 1 to 3 of them may be substituted on optional positions. As the substituent of optionally substituted hydroxyl group, mention is made of, among others, lower (C_{1-4}) alkyl groups (e.g. methyl, ethyl, propyl, isopropyl, butyl and t-butyl), C_{3-6} cycloalkyl groups (e.g. cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl), aryl groups (e.g. phenyl, 1-naphthyl and 2-naphthyl) and aralkyl groups (e.g. benzyl, phenethyl). Further, two adjoining substituents on the phenyl group may cooperate therewith to form a ring. Examples of such rings are the following formulae:

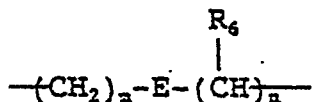


As the aromatic heterocyclic group of "optionally substituted aromatic heterocyclic group" shown by R_2 and R_3 , mention is made of the same aromatic heterocyclic

groups as those specified for R_1 . Among them furyl, thienyl, imidazolyl, pyridyl, pyrimidinyl, pyrazinyl, indolyl and isoindolyl are preferred. As the substituent of said aromatic heterocyclic group, mention is made of lower C_{1-3} alkyl groups (e.g. methyl, ethyl and propyl), among others.

As the spacer having a chain length of 1 to 7 atoms shown by X, any one can be exemplified, so long as it is a divalent chain in which the number of atoms constituting the straight chain is 1 to 7, and it may have a side chain.

For example, said spacer includes one represented by the following formula:



wherein m and n denote independently 0, 1, 2 or 3; E stands for a bond or oxygen atom, sulfur atom, sulfoxide, sulfone,



---NHCO--- , ---CON--- or ---NHCONH--- . Herein, R_6 and R_7 independently stand for hydrogen atom, an optionally substituted lower alkyl group, an optionally substituted aralkyl group or an optionally substituted phenyl group. And, R_5 stands for hydrogen atom, a lower alkyl group, aralkyl group or acyl group.

As the alkyl groups of "optionally substituted lower alkyl groups" shown by R_6 and R_7 , mention is made of C_{1-6} straight-chain or branched lower alkyl groups (e.g. methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, t-butyl, n-pentyl, isopentyl, neopentyl, etc.). As the substituent of said optionally substituted lower alkyl group, mention is made of

aromatic heterocyclic groups (e.g. furyl, thienyl, pyridyl, pyrimidinyl, pyrazinyl, indolyl, imidazolyl and isoindolyl), optionally substituted amino groups, optionally substituted hydroxyl groups, optionally substituted thiol groups, optionally esterified carboxyl groups and halogen atoms (e.g. fluorine, chlorine, bromine and iodine). As the substituent of optionally substituted amino group, optionally substituted hydroxyl group or optionally substituted thiol group, mention is made of lower (C_{1-3}) alkyl groups (e.g. methyl, ethyl and propyl). As the optionally esterified carboxyl group, mention is made of methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, phenoxycarbonyl, 1-naphthoxycarbonyl, 2-naphthoxycarbonyl, with preference given to methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl.

As the aralkyl groups of "optionally substituted aralkyl groups shown by R_6 and R_7 , mention is made of benzyl, naphthylmethyl, phenylethyl, phenylpropyl, phenylbutyl, etc. As the substituent of said "optionally substituted aralkyl groups", mention is made of halogen atoms (e.g. fluorine, chlorine, bromine, iodine), C_{1-3} alkoxy groups (e.g. methoxy, ethoxy, propoxy, etc.), hydroxyl group, amino group, carboxyl group, sulfhydryl, etc.

As the substituent of the optionally substituted phenyl group shown by R_6 and R_7 , mention is made of halogen atoms (e.g. fluorine, chlorine, bromine and iodine), C_{1-3} alkoxy groups (e.g. methoxy, ethoxy, propoxy, etc.) and C_{1-3} alkyl groups (e.g. methyl, ethyl, propyl, etc.).

R_6 may be different depending on the corresponding methylene chains.

And, examples of "lower alkyl group" and "aralkyl group" shown by R_3 include a C_{1-4} lower alkyl group (e.g. methyl, ethyl, propyl, butyl, t-butyl, etc.), a

C₇₋₁₅ aralkyl group (e.g. benzyl, phenethyl, phenylpropyl, phenylbutyl, naphthylmethyl, etc.).

As the acyl group shown by R₃, mention is made of lower alkanoyl groups (formyl, acetyl, propionyl, butyryl, isobutyryl, valeryl, isoveleryl, pivaloyl and hexanoyl), lower alkenoyl groups (acryloyl, methacryloyl, crotonoyl and isocrotonoyl), cycloalkanecarbonyl (cyclopropanecarbonyl, cyclobutanecarbonyl, cyclopentanecarbonyl and cyclohexanecarbonyl), lower alkanesulfonyl groups (mesyl, ethanesulfonyl and propanesulfonyl), aroyl groups (benzoyl, p-toluoyl, 1-naphthoyl and 2-naphthoyl), aryl lower alkanoyl groups (phenylacetyl, phenylpropionyl, hydroatropoyl and phenylbutyryl), aryl lower alkenoyl groups (cinnamoyl and atropoyl) and arenesulfonyl groups (benzenesulfonyl and p-toluenesulfonyl), among others.

Examples of optionally esterified carboxyl group shown by Y include lower alkoxycarbonyl groups (methoxycarbonyl, ethoxycarboxyl, propoxycarbonyl, isopropoxycarbonyl, butoxycarbonyl, tert-butoxycarbonyl, sec-butoxycarbonyl, pentyloxycarbonyl, isopentyloxycarbonyl, neopentyloxycarbonyl and tert-pentyloxycarbonyl) and aryloxycarbonyl groups (phenoxycarbonyl, 1-naphtoxycarbonyl and benzyloxycarbonyl).

Said lower alkoxycarbonyl groups may have 1 or more substituents at any possible positions. Examples of such substituents include optionally substituted hydroxyl groups, optionally esterified carboxyl groups, optionally substituted carbamoyl groups, optionally substituted phenyl groups, optionally substituted C₃₋₆ cycloalkyl groups (e.g. cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl), lower C₁₋₃ alkenyl groups (e.g. vinyl, allyl, etc.) and 5-membered heterocyclic residue containing one to three of oxygen atom. As the

substituent of said optionally substituted hydroxyl group, mention is made of lower alkanoyl groups (e.g. pivaloyl, etc.) and optionally esterified carboxyl groups (e.g. methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, isopropoxycarbonyl and cyclohexyloxycarbonyl). As the substituent of said optionally esterified carboxyl group, mention is made of lower C_{1-4} alkoxy carbonyl groups (e.g. methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, isopropoxycarbonyl, butoxycarbonyl tert-butoxycarbonyl and sec-butoxycarbonyl). As the substituent of said optionally carbamoyl group, mention is made of lower C_{1-3} alkyl groups (e.g. methyl, ethyl and propyl), C_{3-6} cycloalkyl groups (e.g. cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl), phenyl group, benzyl group and optionally esterified carboxyl groups (e.g. methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl). As the substituents of said optionally substituted phenyl group or optionally substituted C_{3-6} cycloalkyl group, mention is made of lower C_{1-3} alkyl groups (e.g. methyl, ethyl and propyl) and lower C_{1-3} alkoxy groups (e.g. methoxy, ethoxy and propoxy). Said 5-membered heterocyclic residue may have 1 or more substituents at any possible positions. Examples of such substituents include lower C_{1-3} alkyl groups (e.g. methyl, ethyl and propyl) and oxo. Further, said heterocyclic group may cooperate with a benzen ring to form a fused ring.

Said aryloxycarbonyl group may have 1 or more substituents at any possible positions. Examples of such substituents include lower C_{1-3} alkyl groups (e.g. methyl, ethyl and propyl), lower C_{1-3} alkoxy groups (e.g. methoxy, ethoxy and propoxy) and optionally esterified carboxyl groups (e.g. methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl).

Also, the optionally esterified carboxyl group

shown by Y may be thioesterified.

Example substituents of optionally substituted hydroxyl group shown by Y include lower C_{1-4} alkyl groups (e.g. methyl, ethyl, propyl, isopropyl, butyl and t-butyl), C_{3-6} cycloalkyl groups (cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl), aryl groups (e.g. phenyl, 1-naphthyl and 2-naphthyl) and aralkyl groups (e.g. benzyl and phenethyl).

Example substituents of optionally substituted amino group shown by Y include lower C_{1-4} alkyl groups (e.g. methyl, ethyl, propyl, isopropyl, butyl and t-butyl), C_{3-6} cycloalkyl groups (cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl), aryl groups (e.g. phenyl, 1-naphthyl and 2-naphthyl) and aralkyl groups (e.g. benzyl and phenethyl). Also, two substituents on a nitrogen atom may cooperate therewith to form a cyclic amino group. Examples of such cyclic amino groups include 1-azetidiny, 1-pyrrolidinyl, piperidino, morpholino, 1-piperazinyl, and 1-piperazinyl having a lower C_{1-3} alkyl group (e.g. methyl, ethyl, propyl, etc.), an aralkyl group (e.g. benzyl, phenethyl, etc.), an aryl group (e.g. phenyl, etc.) or the like at the 4-position.

Example substituents of optionally substituted phenyl group shown by Y include optionally substituted lower C_{1-4} alkyl groups (e.g. methyl, ethyl, propyl, isopropyl, butyl and t-butyl), lower C_{1-4} alkoxy groups (e.g. methoxy, ethoxy, propoxy, isopropoxy, butoxy, t-butoxy), optionally esterified carboxyl groups (e.g. methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, isopropoxycarbonyl, butoxycarbonyl, tert-butoxycarbonyl and sec-butoxycarbonyl), optionally substituted phenyl groups, optionally substituted amino groups and a N-containing heterocyclic residue having hydrogen atom capable of being deprotonated.

As the substituent of said optionally lower C_{1-4} alkyl

group or said optionally substituted phenyl group, mention is made of optionally esterified carboxyl groups (e.g. methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, isopropoxycarbonyl, butoxycarbonyl, tert-butoxycarbonyl and sec-butoxycarbonyl). As the substituent of said optionally substituted amino group, mention is made of lower C₁₋₃ alkyl groups (e.g. methyl, ethyl and propyl). Said N-containing heterocyclic residue includes tetrazol-5-yl, 2,5-dihydro-5-oxo-1,2,4-oxadiazol-3-yl, 2,5-dihydro-5-oxo-1,2,4-thiadiazol-3-yl.

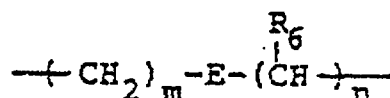
Example substituents of optionally substituted carbamoy group shown by Y include lower C₁₋₄ alkyl groups (e.g. methyl, ethyl, propyl, isopropyl, butyl and t-butyl), C₃₋₆ cycloalkyl groups (cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl), aryl groups (e.g. phenyl, 1-naphthyl and 2-naphthyl) and aralkyl groups (e.g. benzyl and phenethyl). Also, two substituents on a nitrogen atom may cooperate therewith to form a cyclic amino group. Examples of such cyclic amino groups include 1-azetidiny, 1-pyrrolidinyl, piperidino, morpholino, 1-piperazinyl, and 1-piperazinyl having a lower C₁₋₃ alkyl group (e.g. methyl, ethyl, propyl, etc.), an aralkyl group (e.g. benzyl, phenethyl, etc.), an aryl group (e.g. phenyl, etc.) optionally substituted with halogen (e.g. fluorine, chlorine, bromine, iodine) or the like at the 4-position. Further, said piperidino may cooperate with a benzene ring to form a fused ring.

Examples of N-containing heterocyclic residue having hydrogen atom capable of being protonated shown by Y include tetrazol-5-yl, 2,5-dihydro-5-oxo-1,2,4-oxadiazol-3-yl, 2,5-dihydro-5-oxo-1,2,4-thiadiazol-3-yl.

As the substituent of ring A, mention is made of halogen atoms (e.g. fluorine, chlorine, bromine,

iodine), C_{1-4} optionally substituted lower alkyl groups (e.g. methyl, ethyl, propyl, butyl and tert-butyl), C_{1-4} optionally substituted lower alkoxy groups (e.g. methoxy, ethoxy, propoxy, isopropoxy, butoxy and tert-butoxy), nitro group and cyano group. The ring A may have 1 to 3, preferably one or two, of these substituents. And, these substituents may form a ring with each of the adjacent substituents. As the substituent of said optionally substituted lower alkyl group or optionally substituted lower alkoxy group, mention is made of halogen atoms (e.g. fluorine, chlorine, bromine, iodine), and 1 to 3 of these halogen atoms may be substituted on an optional position.

And, when X is shown by the formula



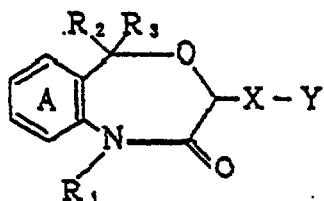
, wherein symbols are of the same meaning as defined above, E is preferably a bond or -CONH-. When E is -CONH-, preferably $m=1$, $n=1$ or $m=2$, $n=1$, especially $m=1$, $n=1$. In this case, R_6 is preferably hydrogen atom benzyl and 3-indolyl methyl, especially hydrogen atom and 3-indolyl methyl. When E is -CONH-, Y is preferably carboxyl group and esterified carboxyl group, especially carboxyl group.

Further, preferable examples of substituents of the ring A include no substituent, lower alkoxy or a halogen atom, and methoxy or chlorine atom is especially preferable.

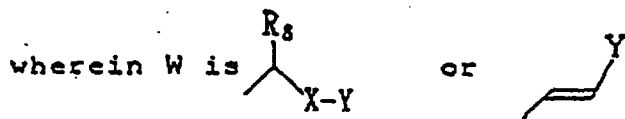
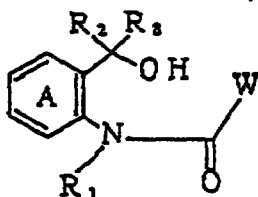
As salts of the compound (I), (I') or (I''), mention is made of pharmacologically acceptable salts including inorganic salts such as hydrochloride, hydrobromide, sulfate, nitrate, phosphate, etc., organic acid salts such as acetate, tartrate, citrate, fumarate, maleate, toluensulfonate, methanesulfonate, etc., metal salts such as sodium salt, potassium salt,

calcium salt, aluminium salt, etc. and basic salts such as triethylamine salt, guanidine salt, ammonium salt, hydrazine salt, quinine salt, cinchonine salt, etc.

Further, the present invention provides a method of producing a compound represented by the formula (I) or the formula (I').:



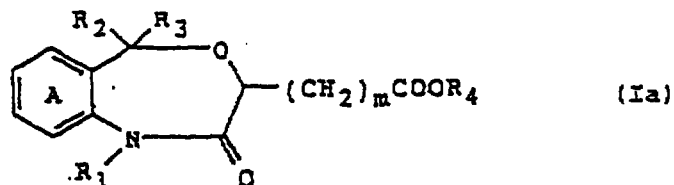
wherein each of the symbols is of the same meaning as defined above or a pharmaceutically acceptable salt thereof, by subjecting a compound represented by the following formula:



wherein R₈ is halogen (e.g. fluorine, chlorine, bromine and iodine) or -OSO₂CH₃ or other symbols are of the same meaning as defined above, to a cyclization reaction.

Methods of producing compounds of this invention are described below:

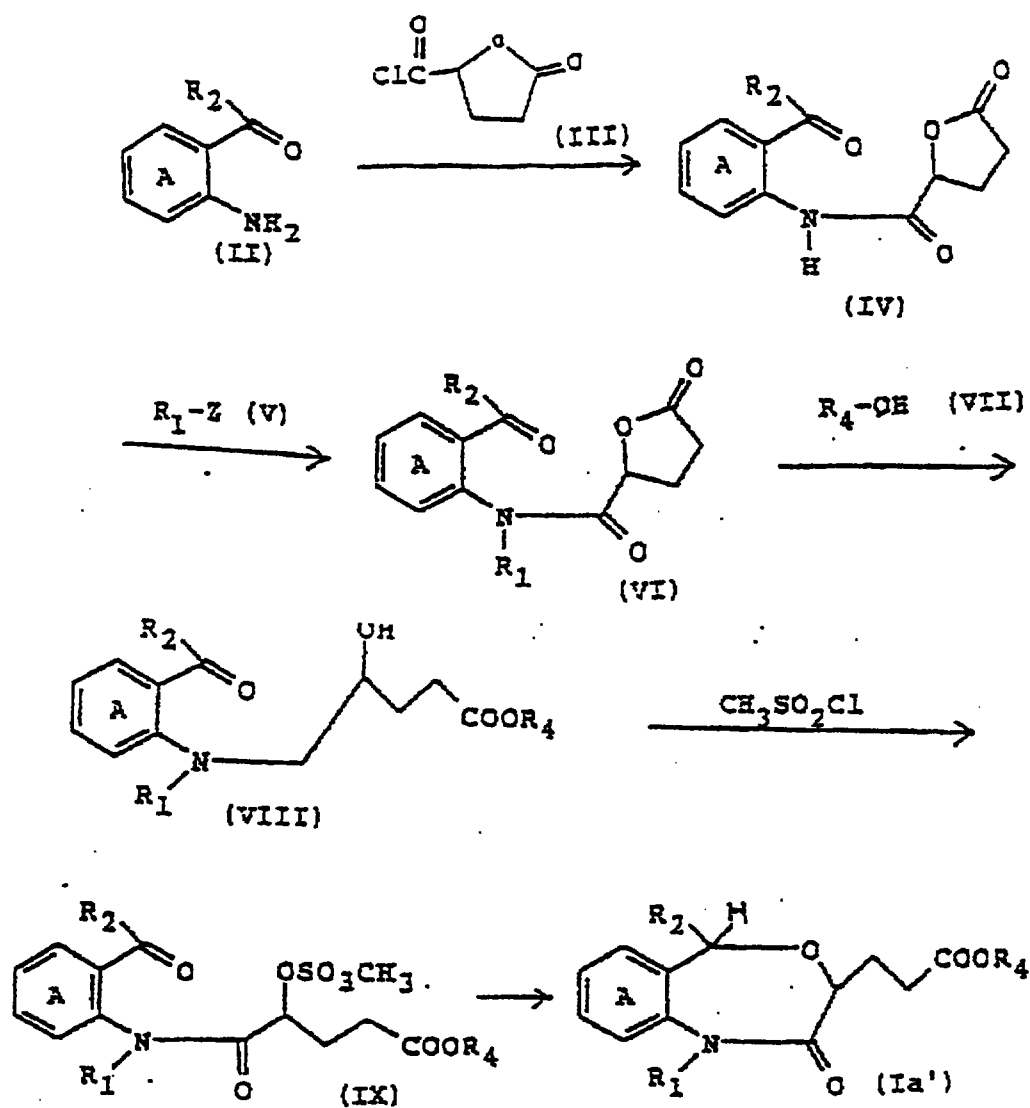
Among the compounds of formula (I) and (I'), compounds represented by the formula (Ia)



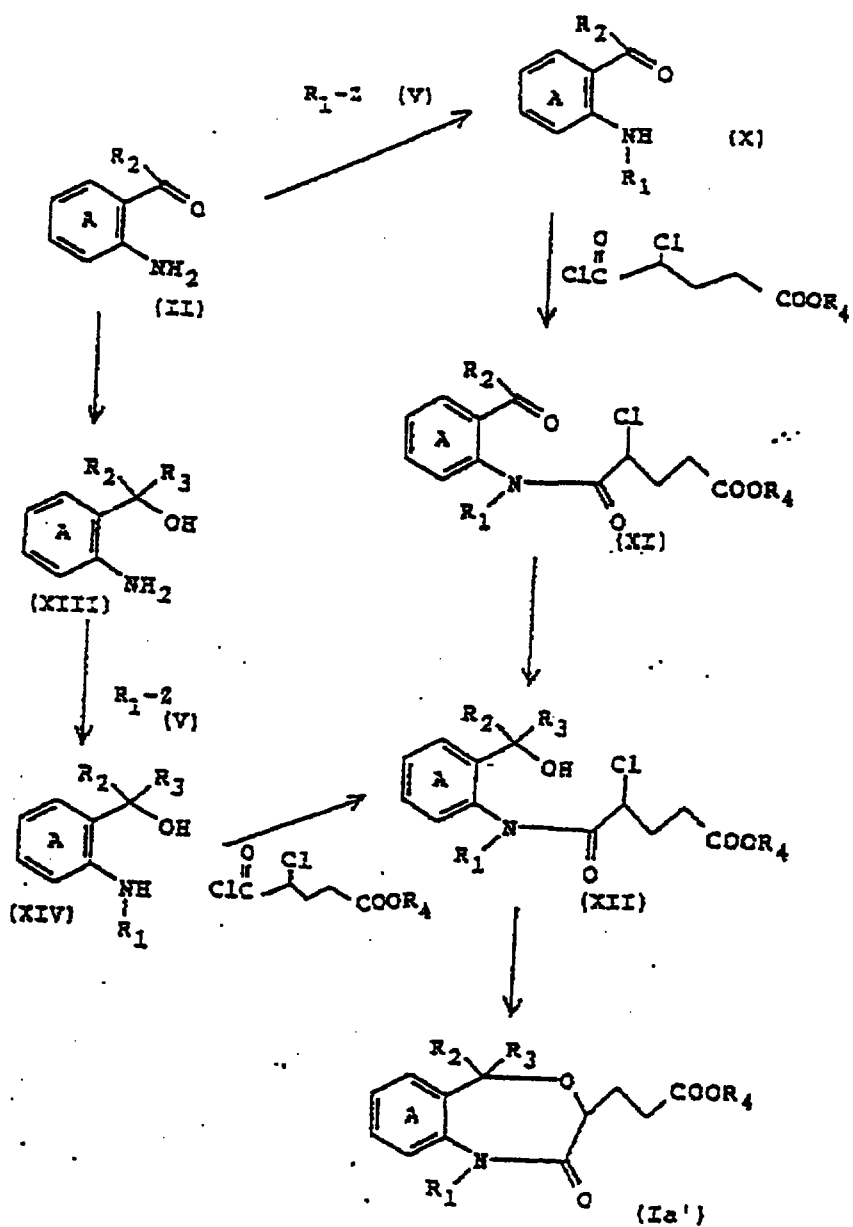
, wherein R_4 stands for a C_{1-8} alkyl group or aralkyl group, and other symbols are of the same meaning as defined above, can be produced by the following methods.

2-aminobenzophenones as the starting material can be synthesized by, or in accordance with, the method described in D.A. Walsh, Synthesis, 677 (1980) or the method cited in said reference.

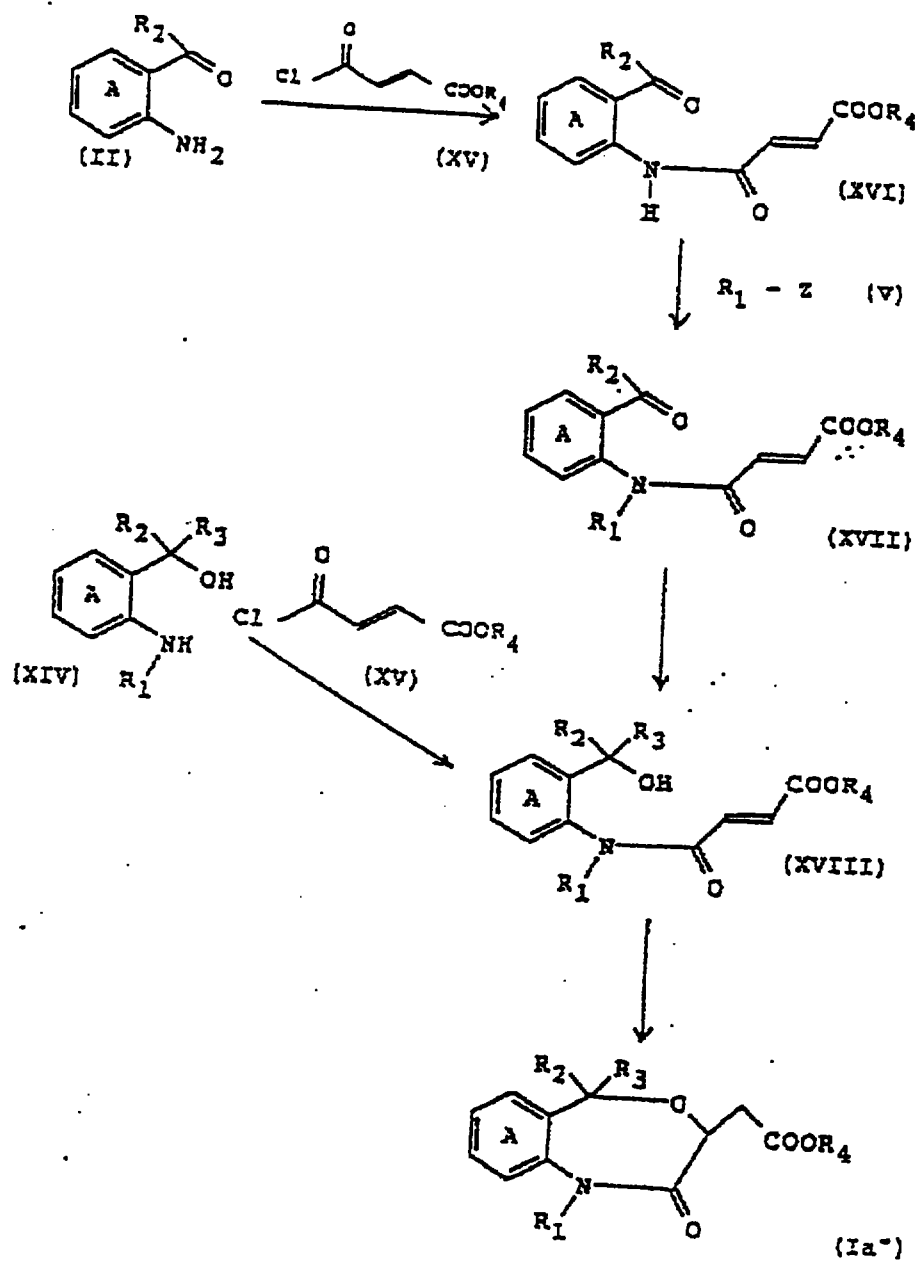
[Method A]



[Method B]



[Method C]



, wherein Z stands for a halogen atom, and other symbols are of the same meaning as defined above.

The reactions from the formula (II) to the formula (IV) and from the formula (VIII) to the formula (IX) in the above-mentioned [Method A] or those from the formula (X) to the formula (XI) and from the formula (XIV) to the formula (XII) in the above-mentioned [Method B] can be carried out by utilizing a per se known acylation reaction. For example, the acylation reaction of this invention can be conducted in a solvent exemplified by an ether-type solvent such as diethyl ether, tetrahydrofuran, dioxane, etc., a halogen-type solvent such as dichloromethane, dichloroethane, chloroform, carbon tetrachloride, etc., a hydrocarbon-type solvent such as benzene, toluene, hexane, heptane, etc., dimethylformamide, dimethyl sulfoxide, etc., and, depending on necessity, in the presence of water and a base (e.g. an organic base such as 4-dimethylaminopyridine, triethylamine, triethylenediamine, tetramethylethylenediamine, etc. an inorganic base such as sodium hydrogencarbonate, potassium hydrogencarbonate, sodium carbonate, potassium carbonate, sodium hydroxide, potassium hydroxide, etc, sodium hydride, potassium hydride), among others. Relative to one mole of a compound represented by the formulae (II), (VIII), (X) and (XIV), acid chloride and methanesulfonyl chloride by the formula (III) and ester of 4-chloroformyl butyric acid are usually employed in an amount of 1 to 10 mol., preferably 1 to 3 mol. And, the reaction time usually ranges from about 1 to 48 hours, preferably from about 5 to 10 hours. The reaction temperature ranges from - 50 to 100°C, preferably from about 0 to 50°C.

And, the reaction from the formula (IV) to the formula (VI) in [Method A] and the reactions from the formula (II) to the formula (X) and from the formula

(XIII) to the formula (XIV) in [Method B] can be carried out in an ether type solvent such as diethyl ether, tetrahydrofuran, dioxane etc., a hydrocarbon type solvent such as benzene, toluene, hexane, heptane etc., an alcohol type solvent such as methanol, ethanol, propanol, butanol etc., acetone or dimethylformamide, and, depending on necessity, in the presence of a base (e.g. sodium hydrogencarbonate, potassium hydrogencarbonate, sodium carbonate, potassium carbonate, sodium hydride, potassium hydride or the like). Relative to one mole of a compound represented by the formula (II), the formula (IV) or the formula (XIII), a compound represented by the formula (V) is employed usually in an amount ranging from 1 to 10 mol., preferably about 1 to 2 mol. The reaction temperature ranges from 0 to 100°C, preferably from about 20 to 50°C. The reaction time ranges usually from 1 to 24 hours, preferably about 3 to 10 hours.

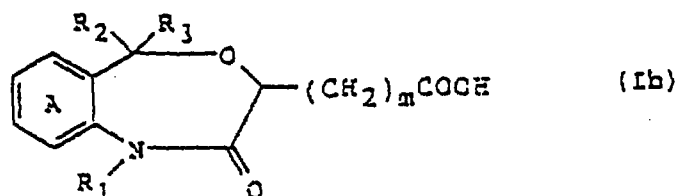
And, the reduction reaction of carbonyl group from the formula (IX) to the formula (Ia') in [Method A], from the formula (II) to the formula (XIII) and from the formula (XI) to the formula (XII) in [Method B] can be conducted in a protonic solvent (e.g. methanol, ethanol, propanol, butanol, etc.) or a non-protonic solvent (e.g. ethyl ether, tetrahydrofuran, dioxane, etc.) in the presence of a metal hydrogen complex (e.g. lithium aluminum hydride, sodium aluminum hydride, sodium triethoxyaluminum hydride, sodium borohydride, etc.). Relative to one each mol. of compounds shown by the formula (IX), the formula (II) and the formula (XI), such a metal hydrogen complex as mentioned above is employed in an amount, usually ranging from 0.3 to 5 mol. equivalents, preferable from 0.5 to 2 mol. equivalents. The reaction temperature ranges from -20 to 100°C, preferably from 20 to 50°C.

The cyclization reaction to the formula (Ia') from the formula (XII) in [Method B] can be carried out in a solvent, for example, an ether type solvent such as diethyl ether, tetrahydrofuran, dioxane, etc., a hydrocarbon type solvent such as benzene, toluene, hexane, heptane, etc., an alcohol type solvent such as methanol, ethanol, propanol, butanol, etc., acetone, dimethylformamide or the like, in the presence of, depending on necessity, a base (e.g. sodium hydrogencarbonate, potassium hydrogencarbonate, sodium carbonate, potassium carbonate, sodium hydride, potassium hydride, etc.). Relative to one mol. of a compound shown by the formula (XII), a base as exemplified above is employed in an amount usually ranging from 1 to 5 mol., preferable from about 1 to 2 mol. The reaction temperature ranges usually from -20 to 200°C, preferably from 20 to 100°C. The reaction time ranges usually from 1 to 20 hours, preferably from 2 to 5 hours.

The reaction from the formula (VI) to (VIII) in [Method A] can be conducted in an alcohol shown by the formula (VII), and, depending on necessity, in the presence of an inorganic acid such as nitric acid, hydrochloric acid, hydrobromic acid or sulfuric acid, or an organic acid such as toluenesulfonic acid or methanesulfonic acid, at temperatures ranging from -20 to 100°C, preferably from 20 to 50°C. The reaction time ranges from 10 to 100 hours, preferably from 10 to 48 hours.

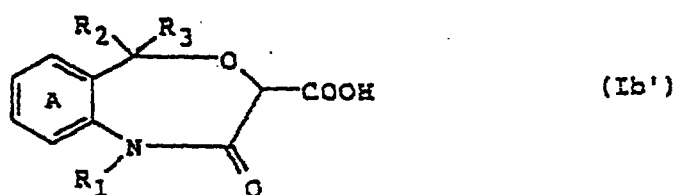
The compound shown by the formula (Ia'') can be produced in accordance with a conventional method.

Among the compounds shown by the formula (I) and (I'), a compound represented by the formula (Ib)

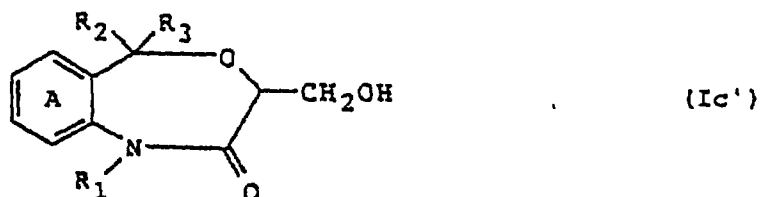


, wherein symbols are of the same meaning as defined above, can be produced by subjecting a compound shown by the formula (Ia) to hydrolysis, for example, by processing a compound shown by the formula (Ia) with an acid or a base. More specifically, a compound shown by the formula (Ia) is processed in an aqueous solution of a mineral acid (e.g. nitric acid, hydrochloric acid, hydrobromic acid, iodic acid, sulfuric acid or the like) or an alkali metal hydroxide (sodium hydroxide, potassium hydroxide, barium hydroxide, lithium hydroxide) at temperatures ranging from 0 to 150°C, preferably from 20 to 50°C. The strength of the acid or the base ranges usually from 1 to 10 N, preferably from 4 to 10N. The reaction time varies with the reaction temperature, but usually ranges from 1 to 24 hours, preferably from about 2 to 10 hours.

A compound shown by the formula (Ib')

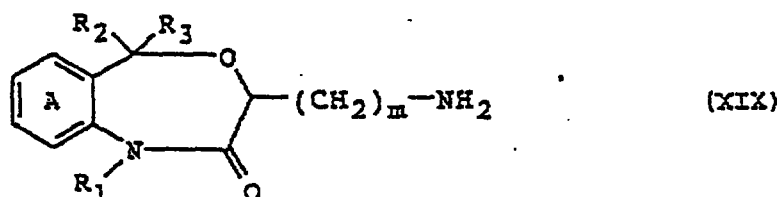


, wherein symbols are of the same meaning as defined above, can be produced by subjecting a compound shown by the formula (Ic')



, wherein symbols are of the same meaning as defined above, to oxidation. The solvent then to be used may be any one so long as it does not hamper the reaction, which is exemplified by acetone, dioxane, tetrahydrofuran, dichloromethane, dichloroethane or chloroform. As the oxidizing agent, permanganate, chromic acid or nickel peroxide can be used, for example. In this case, the oxidizing agent is used in an amount ranging from 0.5 to 20 mol. equivalents, preferably from 1 to 3 mol. equivalents, relative to one mol. of the compound shown by the formula (Ic'), the reaction temperature ranges from 0 to 100°C, preferably from 15 to 50°C and the reaction time ranges from 0.5 to 5 hours, preferably from about 1 to 2 hours.

Among the compounds to be used as intermediates for synthesizing a compound of formula (I) or (I'), a compound shown by the formula (XIX)

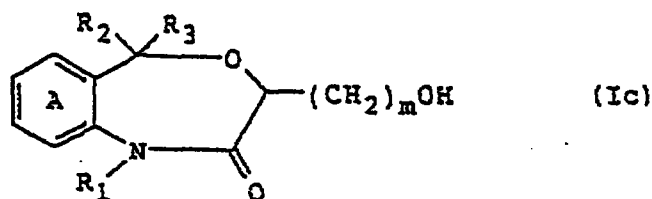


, wherein symbols are of the same meaning as defined above, can be produced by allowing a compound shown by the formula (Ib) to react with diphenylphosphoryl azide in a solvent in the presence of a base, then by processing the resultant with an acid in a solvent. The solvent to be used in the reaction between a compound shown by the formula (Ib) and diphenylphosphoryl azide may be any one, so long as it does not hamper the reaction, which is exemplified by dimethylformamide, a halogen-type solvent such as dichloromethane, chloroform or dichloroethane and an ether-type solvent such as ether, tetrahydrofuran or

dioxane. Typical examples of the base to be employed include triethylamine, 4-dimethylaminopyridine, triethylenediamine and tetramethylethylenediamine. Relative to 1 mol. of a compound shown by the formula (Ib), 1 to 10 mol. equivalents, preferably about 1.5 to 3 mol. equivalents, of diphenylphosphoryl azide is employed. The reaction temperature ranges from -20 to 50°C, preferably from 0 to 20°C, and the reaction time ranges from 0.5 to 5 hours, preferably from about 1 to 2 hours.

In the case of processing the product obtained by the above-described reactions, the solvent to be used is exemplified by water, dioxane, dimethylformamide etc., and, as the acid to be employed, a mineral acid such as sulfuric acid, hydrochloric acid, nitric acid or hydrobromic acid can be exemplified. The reaction temperature ranges from 20 to 200°C, preferably from about 50 to 100°C, and the reaction time ranges from 0.5 to 5 hours, preferably from about 1 to 2 hours.

Among the compounds represented by the formula (I) and (I'), a compound shown by the formula (Ic)



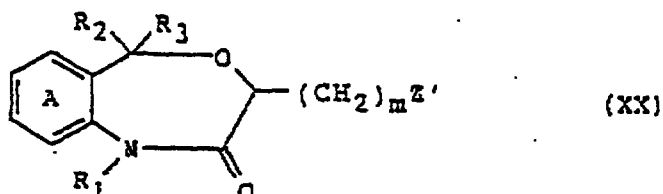
, wherein symbols are of the same meaning as defined above, can be produced by subjecting a compound shown by the formula (Ia) to reduction. More specifically, the compound shown by the formula (Ic) can be produced by processing the compound shown by the formula (Ia) with a metal hydride complex (e.g. lithium aluminum hydride, sodium aluminum hydride, sodium borohydride) in a protonic solvent (e.g. methanol, ethanol propanol, butanol etc.) or a non-protonic solvent (e.g. ethyl ether, tetrahydrofuran, dioxane etc.) Relative to one

mol. of the compound shown by the formula (Ia), such a metal hydride complex compound is used in an amount ranging usually from 0.3 to 5 mol. equivalents, preferably from 0.5 to 2 mol. equivalents. The reaction temperature ranges from -20°C to 100°C , preferably from 0 to 20°C . The reaction time ranges from 0.5 to 10 hours, preferably from about 1 to 3 hours.

And, a compound shown by the formula (Ic) can be produced also by converting the amine portion of a compound shown by the formula (XIX) into hydroxyl group. For example, a compound of the formula (Ic) can be produced by adding sodium nitrite to a compound of the formula (XIX) in a solvent in the presence of an acid then by processing the resultant azide compound in a solvent in the presence of a base. In the method of azidation, for example, 0.5 to 3, preferably 1 to 1.5, mol. equivalents of sodium nitrite, is employed relative to 1 mol. of a compound of (XIX). As the acid, any one can be employed so long as it does not hamper the reaction, typically exemplified by acetic acid and sulfuric acid. The reaction temperature ranges from -20 to 20°C , preferably 0 to 5°C , and the reaction time ranges from 5 to 60 minutes, preferably about 10 to 30 minutes. The method of converting the azide of thus-obtained azide compound into hydroxyl group comprises, for example, use of, as the base, for example, sodium hydrogencarbonate, potassium hydrogencarbonate, sodium carbonate, potassium carbonate, sodium hydroxide, potassium hydroxide or the like in water or an aqueous organic solvent (e.g. an alcohol-type solvent such as methanol, ethanol, propanol, butanol or the like, an ether-type solvent such as tetrahydrofuran, dioxane or the like, dimethylformamide, etc.). The reaction temperature ranges from 20 to 200°C , preferably from 50 to 100°C ,

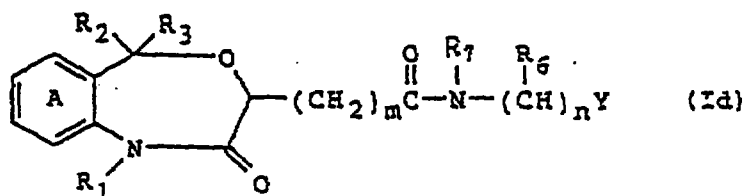
and the reaction time ranges from 5 minutes to 2 hours, preferably from about 15 to 30 minutes.

The compound shown by the formula (XX)



, wherein Z' stands for halogen (chlorine, bromine, iodine) and other symbols are of the same meaning as defined above, which is an intermediate for synthesizing the compound of the formula (I), can be produced by, like the method employed in the case of producing the compound (Ic) from the compound (XIX), subjecting a compound shown by the formula (XIX) to diazotization with sodium nitrite in hydrochloric acid, hydrobromic acid or hydroiodic acid, then by heating thus diazotized compound. The reaction temperature ranges from 20 to 200°C, preferably from 50 to 100°C, and the reaction time ranges from 5 minutes to 2 hours, preferably from about 15 to 30 minutes.

Among the compounds represented by the formula (I) and (I'), a compound shown by the formula (Id)

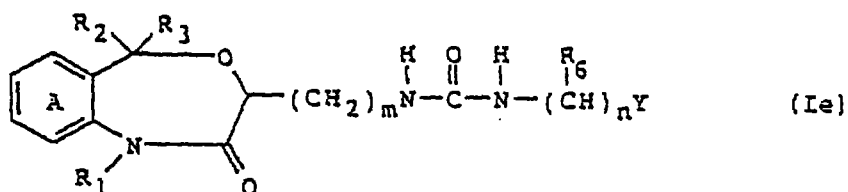


, wherein Y' stands for, among the definitions given to Y as above, esterified carboxyl group and hydroxyl group, and other symbols are of the same meaning as defined above, can be produced by subjecting a compound shown by the formula (Ib) to condensation with a compound represented by the formula (XXI)



, wherein symbols are of the same meaning as defined above, more specifically, the compound (Ib) and the compound (XXI) are subjected to condensation in a solvent by using a condensing agent, and, upon necessity, in the presence of a base. The solvents to be employed are exemplified by hydrocarbon-type solvents such as benzene, toluene, hexane, heptane etc., halogen-type solvents such as dichloromethane, dichloroethane, chloroform carbon tetrachloride etc., ether-type solvents such as ethyl ether, tetrahydrofuran, dioxane, etc., acetonitrile, dimethylformamide, etc. As the base, use is made of, among others, triethylamine, 4-dimethyl aminopyridine, triethylenediamine and tetramethyl ethylenediamine. As condensing agents, mention is made of those to be employed for peptide synthesis, which are exemplified by, among others, cyclohexyl carbodiimide, diethyl cyanophosphate and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide. Relative to one mol. of the compound shown by the formula (Ib), a compound represented by the formula (XXI) is used in an amount ranging from 0.5 to 2 mol. equivalents, preferably from 1 to 1.2 mol. equivalent, and a condensing agent is used in an amount ranging from 0.5 to 5 mol. equivalents, preferably 1 to 2 mol. equivalents. The reaction temperature ranges from 0 to 100°C, preferably from 20 to 50°C, and the reaction time ranges from 0.5 to 24 hours, preferably from about 1 to 5 hours.

Among the compounds represented by the formula (I) and (I'), a compound shown by the formula (Ie)

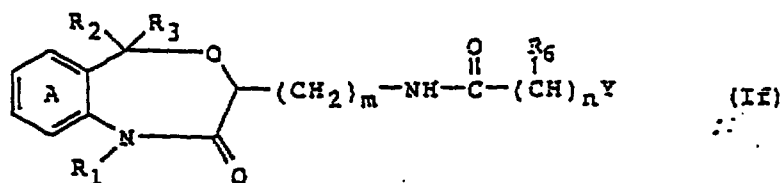


, wherein symbols are of the same meaning as defined above, can be produced by allowing a compound (Ib) to react with diphenyl phosphoryl azide in a solvent in the presence of a base, then by allowing the resultant compound to react with a compound (XXI). As the solvent to be employed in the reaction between the compound (Ib) and diphenyl phosphoryl azide, any one can be used so long as it does not hamper the reaction, which is exemplified by dimethylformamide or a halogen-type solvent such as dichloromethane, chloroform, dichloroethane etc., and an ether-type solvent such as ether, tetrahydrofuran, dioxane etc. The base to be employed is typically exemplified by triethylamine, 4-dimethyl aminopyridine, triethylene diamine or tetramethyl ethylenediamine. Relative to one mol. of the compound shown by the formula (Ib), 1-10, preferably about 1.5 to 3 mol. equivalents of diphenyl phosphoryl azide is employed. The reaction temperature ranges from -20 to 50°C, preferably from 0 to 20°C, and the reaction time ranges from 0.5 to 5 hours, preferably from about 1 to 2 hours.

The solvent to be employed in the reaction between the compound obtained thus above and a compound shown by the formula (XXI) is exemplified by a halogen-type solvent such as dichloromethane, dichloroethane, chloroform etc., an ether-type solvent such as ether, tetrahydrofuran, dioxane etc., acetonitrile, dimethylformamide, among others. And, depending on necessity, a base is employed. As the base, mentioned is made of an organic base including triethylamine, 4-dimethyl aminopyridine, triethylenediamine and

tetramethyl ethylenediamine. Relative to one mol. of the compound (Ib), 0.5 to 3, preferably 1 to 1.5, mol. equivalents of the compound (XXI). The reaction temperature ranges from 0 to 150°C, preferably from 30 to 100°C, and the reaction time ranges from 0.5 to 24, preferably about 1 to 3, hours.

Among the compounds represented by the formula (I) and (I'), a compound shown by the formula (If)

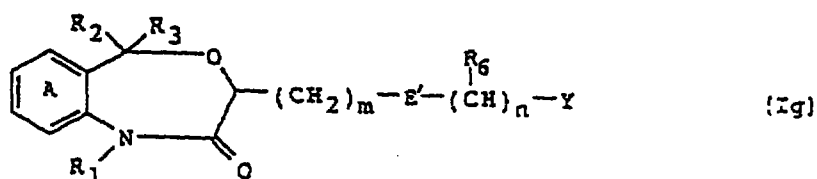


, wherein symbols are of the same meaning as defined above, can be produced by subjecting a compound of (XIX) to condensation with a compound represented by the formula (XXII)



, wherein symbols are of the same meaning as defined above. This reaction can be conducted in completely the same manner as in the production of the compound (Id).

Among the compounds represented by the formula (I) and (I'), a compound shown by the formula (Ig)



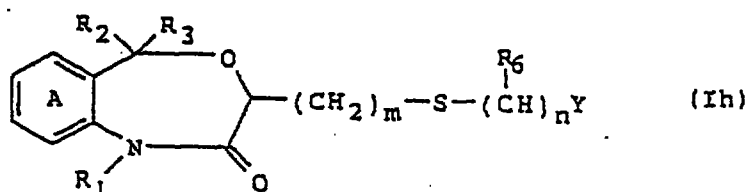
, wherein E' stands for, among the definitions given above, oxygen atom or -NH-, and other symbols are of the same meaning as defined above, can be produced by allowing a compound shown by the formula (Ic) or a compound shown by the formula (XIX) to react with a

compound represented by the formula (XXIII)



, wherein symbols are of the same meaning as defined above. More specifically, the compound (Ic) or the compound (XIX) is allowed to react with the compound (XXIII) in an alcohol-type solvent such as methanol, ethanol, propanol, butanol etc., an ether-type solvent such as diethyl ether, tetrahydrofuran, dioxane etc. or dimethylformamide, among others, in the presence of a base including an inorganic base such as sodium hydrogencarbonate, potassium hydrogencarbonate, sodium carbonate, potassium carbonate etc., an organic base such as triethylamine, 4-dimethyl aminopyridine, triethylenediamine, tetramethyl ethylenediamine etc. or sodium hydride. Relative to one mol. of the compound (Ic) or (XIX), 0.5 to 1.5 mol. equivalent of the compound (XXIII) is used, and, relative to one mol. of the compound (Ic) or (XIX), 1 to 5, preferably 1 to 2, mol. equivalents of the base is used. The reaction temperature ranges from 0 to 200°C, preferably from 20 to 100°C, and the reaction time ranges from 0.5 to 24 hours, preferably from about 1 to 3 hours.

Among the compounds represented by the formula (I) and (I'), a compound shown by the formula (Ih)

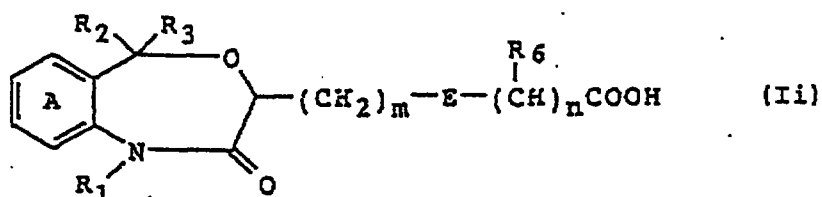


, wherein symbols are of the same meaning as defined above, can be produced by allowing a compound (XX) to react with a compound represented by the formula (XXV)

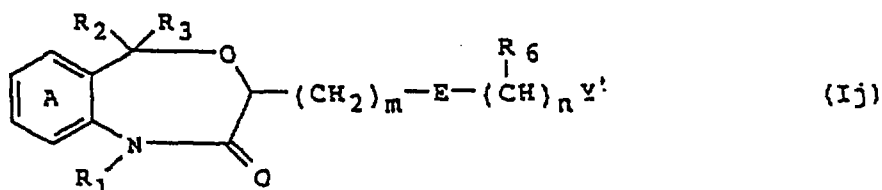


, wherein symbols are of the same meaning as defined above. The solvent to be employed is a non-protonic solvent exemplified by ethyl ether, tetrahydrofuran, dioxane, acetonitrile, dimethylformamide or the like. Depending on necessity, an inorganic base such as sodium hydrogencarbonate, potassium hydrogencarbonate, sodium carbonate or potassium carbonate, an organic base such as triethylamine, 4-dimethyl aminopyridine, triethylenediamine or tetramethyl ethylenediamine, sodium hydride, cesium fluoride or the like may be used. Relative to one mol. of the compound (XX), 0.5 to 5, preferably 1 to 2, mol. equivalents of the compound (XXV) is employed. The reaction temperature ranges from 0 to 200°C, preferably 20 to 100°C, and the reaction time ranges from 10 minutes to 5 hours, preferably from about 30 minutes to 2 hours.

Among the compounds represented by the formula (I) and (I'), a compound shown by the formula (Ii)



, wherein symbols are of the same meaning as defined above, can be produced by subjecting a compound represented by the formula (Ij)



, wherein Y' stands for, among the groups defined by Y as above, esterified carboxyl group, and other symbols

are of the same meaning as defined above, to hydrolysis. More specifically, the hydrolysis is conducted in a solvent such as water, methanol, ethanol, propanol or butanol in the presence of an alkali metal hydroxide (e.g. sodium hydroxide, potassium hydroxide, barium hydroxide or lithium hydroxide), sodium hydrogencarbonate, potassium hydrogencarbonate, sodium carbonate or potassium carbonate, or, in the presence of a mineral acid (e.g. nitric acid, hydrochloric acid, hydrobromic acid, iodic acid or sulfuric acid) or trifluoroacetic acid, at temperatures ranging from 10 to 150°C, preferably from 10 to 50°C. While the reaction time varies with the reaction temperature, it ranges usually from 1 to 24 hours, preferably from about 2 to 10 hours.

While the compound represented by the formula (I") of this invention has a squalene synthetase inhibiting action and an antifungal action, among the compounds used in the present invention, there are compounds capable of inhibiting other enzymes in the pathway of cholesterol biosynthesis. Be the matter as it may, the compound represented by the formula (I") of this invention inhibits biosynthesis of cholesterol, which is useful for the prophylaxis or therapy of hypercholesteremia or coronary sclerosis of mammals (e.g. mouse, rat, rabbit, dog, cat, cow, pig and human being) and, further, for the prophylaxis or therapy of fungus infections.

Said compound (I") can be administered to man orally or non-orally. The orally administrable compositions may be in a solid or liquid form, more specifically tablets (including sugar-coated tablets and film-coated tablets), syrups, emulsions, suspensions or the like. These compositions can be prepared by a per se known method and contain carriers or excipients conventionally used in the field of

pharmaceutical preparation, for example, carriers or excipients such as lactose, starch, sucrose or magnesium stearate for preparing tablets.

The non-orally administrable compositions are exemplified by injections and suppositories, and the injections include hypodermic injections, intradermal injections and intramuscular injections. These injections can be prepared by a per se known method, more specifically, by suspending or emulsifying the compound of this invention in a sterile water or oil conventionally used for preparing injectable compositions. The aqueous liquid to be used for preparation of injections include physiological saline solution and isotonic solution, and, depending on necessity, a suitable suspending agent such as sodium carboxymethyl cellulose, a non-ionic surfactant or the like may be jointly used. As the oil, mention is made of sesame oil, soybean oil, etc., and benzyl benzoate, benzyl alcohol etc. as a solubilizer may be jointly used. Injections thus prepared are, in general, filled in appropriate ampoules.

The compound represented by the formula (I") or a salt thereof can be used safely with low toxicity. Although the daily dose varies depending on the condition and weight of the patient, kind of the compound, route of administration and other factors, for example, in the case of administering the compound of the present invention for the therapy of hypercholesteremia, a daily oral dosage per adult human is about 1 to 500 mg, preferably about 10 to 200 mg. Within this range, no toxicity is observed at all.

The compound of the formula (I") for squalene synthetase inhibition is effectively administered to a mammal, e.g. human, in a therapeutically effective amount which is generally provided with an oral daily dosage per adult of from about 1 to about 500mg, preferably about 10 to about 200mg. In terms of a non-oral daily dosage range such as for an injection or suppository, a therapeutically effective amount is generally in the range of from about 0.1 to about 100mg, preferably about 1 to about 20mg.

The present invention compounds also demonstrate broad spectrum antifungal activity as determined by broth or agar dilution methods.

In case of administering the compound of the present invention for the therapy of fungus infections, generally from 2 to 5 mg/kg should be employed as a unit dosage in an antifungal treatment.

The compound of the formula (I") for fungus treatment is effectively administered to a mammal, e.g. human, in a therapeutically effective amount which is generally provided with an oral daily dosage per adult of from about 0.1 to about 100mg, preferably about 1 to about 50mg. In terms of a non-oral daily dosage range such as for an injection or suppository, a therapeutically effective amount is generally in the range of from about 0.1 to about 100mg, preferably about 1 to about 50mg.

Abbreviations for amino acids, and other used in the present specification are based on abbreviations specified by the IUPAC-IUB Commission on Biochemical Nomenclature or abbreviations in common use in relevant fields. Some examples are given below. When an optical isomer may be present in amino acid, it is of the L-configuration, unless otherwise stated.

Trp or Y : Tryptophan
Ser or S : Serine
Asp or D : Aspartic acid
Glu or E : Glutamic acid
Me : Methyl
Et : Ethyl
Ph : Phenyl

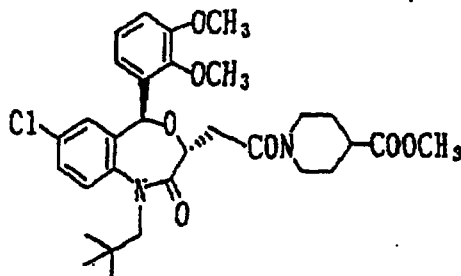
Best Mode of Carrying out the Invention

The following Working Examples, formulation examples and experimental examples are intended to illustrate the present invention in further detail and should by no means be construed as limiting the invention.

[Examples]

Reference Example 1

Methyl ester of N-[(3R,5S)-7-chloro-5-(2,3-dimethoxyphenyl)-1-neopentyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-acetyl]piperidine-4-carboxylic acid



To a solution of (3R,5S)-7-chloro-5-(2,3-dimethoxyphenyl)-1-neopentyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-acetic acid (0.5 g) and 0.25 g of piperidine-4-carboxylic acid methyl ester hydrochloride in dimethylformamide (10 ml) were added, at room temperature, diethylcyanophosphonate (0.28 g) and triethylamine (0.38 ml), and the mixture was stirred for one hour. To the mixture were added water (100 ml) and ethyl acetate (100 ml). The organic layer was washed with 1N HCl and a saturated aqueous solution of

sodium hydrogencarbonate, followed by drying over anhydrous magnesium sulfate. The solvent was distilled off, and the residue was purified by silica gel column chromatography (eluents: hexane : ethyl acetate = 1:1 (v/v) to afford 0.62 g of a colorless crystalline product, m.p. 124-126°C.

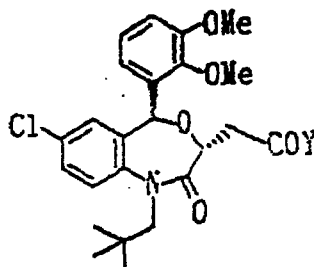
Elemental analysis for $C_{31}H_{39}ClN_2O_7 \cdot 0.3H_2O$:

Calcd. : C, 62.84; H, 6.74; N, 4.73

Found : C, 62.78; H, 6.69; N, 4.72

Reference Example 1'

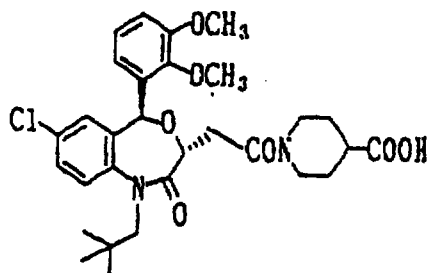
By substantially the same procedure as in Example 1, the following compound was obtained.



Compound No	Y	m.p. (°C)
2-38		150-151

Reference Example 2

N-[(3R,5S)-7-chloro-5-(2,3-dimethoxyphenyl)-1-neopentyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-acetyl]piperidine-4-carboxylic acid



The compound (0.5 g) obtained in Reference Example 1 was dissolved in a mixture of 1N aqueous solution of sodium hydroxide (4 ml), methanol (10 ml) and tetrahydrofuran (5 ml). The solution was stirred for one hour at room temperature, to which were added 1N HCl (50 ml) and ethyl acetate (100 ml). The organic layer was washed with water and dried over anhydrous magnesium sulfate. The solvent was removed, and the residue was recrystallized from hexane-diethyl ether to afford 0.47 g of colorless crystals, m.p. 145-147°C.

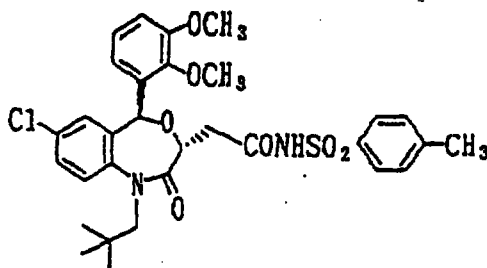
Elemental analysis for $C_{30}H_{37}ClN_2O_7 \cdot 0.3H_2O$:

Calcd. : C, 62.29; H, 6.55; N, 4.84

Found : C, 62.20; H, 6.65; N, 4.83

Reference Example 3

N-Toluenesulfonyl-(3R,5S)-7-chloro-5-(2,3-dimethoxyphenyl)-1-neopentyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-acetylamide



To a solution of (3R,5S)-7-chloro-5-(2,3-dimethoxyphenyl)-1-neopentyl-2-oxo-1,2,3,5-tetrahydro-

4,1-benzoxazepine-3-acetic acid (0.5 g) and p-toluenesulfonamide (0.22 g) in dichloromethane were added 1-ethyl-3-(3'-dimethylaminopropyl)carbodiimide (0.27 g) and dimethylaminopyridine (20 mg). The mixture was stirred for 3 hours at room temperature, which was concentrated under reduced pressure. The concentrate was dissolved in ethyl acetate (100 ml). The solution was washed with water and dried, then the solvent was distilled off. The residue was purified by silica gel column chromatography (eluent: dichloromethane:methanol:water=200:10:1 (v/v)) to give 0.6 g of colorless crystals, m.p. 110-113°C.

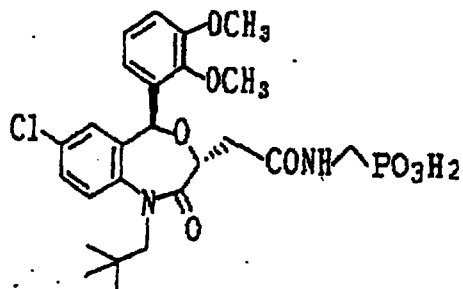
Elemental analysis for $C_{31}H_{35}ClN_2O_7S \cdot H_2O$:

Calcd. : C, 58.81; H, 5.89; N, 4.42

Found : C, 58.73; H, 5.73; N, 4.62

Reference Example 4

(3R,5S)-N-phosphonomethyl-7-chloro-5-(2,3-dimethoxyphenyl)-1-neopentyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-acetamide



To a solution of the compound (1.0 g) produced in Reference Example 1' in dichloromethane (5 ml) was added trimethylsilyl bromide (0.38 g). The mixture was stirred overnight at room temperature, to which was added ethyl acetate. The mixture was washed with a 0.5N aqueous solution of sodium hydroxide, a saturated aqueous solution of ammonium chloride and water, followed by drying over anhydrous sodium sulfate. The solvent was distilled off, and the residue was

recrystallized from a mixture of ethanol and diethyl ether (1:10) to afford 0.41 g of colorless crystals, m.p. 152-155°C

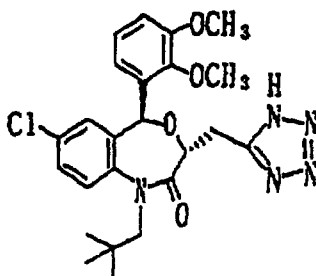
Elemental analysis for $C_{25}H_{32}ClN_2O_8P \cdot 1.7H_2O$:

Calcd. : C, 51.28; H, 6.09; N, 4.78

Found : C, 51.20; H, 6.11; N, 4.77

Reference Example 5

(3R,5S)-7-Chloro-5-(2,3-dimethoxyphenyl)-1-neopentyl-1,2,3,5-tetrahydro-3-(1H(or 3H)-tetrazol-5-yl)methyl-4,1-benzoxazepin-2-one



(1) A dimethylformamide solution of (3R,5S)-7-chloro-5-(2,3-dimethoxyphenyl)-1-neopentyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-acetic acid (2.0 g), ammonium chloride (1.2 g) and triethylamine (1.0 ml) was cooled in ice bath. To the solution were added diethylcyanophosphonate (0.85 g) and triethylamine (0.5 ml). The mixture was stirred for further 20 minutes, to which was added ice-water, followed by extraction with ethyl acetate. The organic layer was washed with water, which was dried over anhydrous magnesium sulfate. The solvent was distilled off, and the residue was recrystallized from diethyl ether to give 1.0 g of (3R,5S)-7-chloro-5-(2,3-dimethoxyphenyl)-1-neopentyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-acetamide as colorless crystals, m.p. 170-172°C.

(2) The compound (3.2 g) obtained in (1) and thionyl chloride (1.8 ml) were suspended in toluene (40 ml). The suspension was stirred for one hour at temperatures

ranging from 110 to 120°C. The solvent was removed. To the residue were added ethyl acetate (100 ml) and a saturated aqueous solution of sodium hydrogencarbonate (50 ml). The organic layer was dried over anhydrous sodium sulfate, then the solvent was distilled off. The residue was purified by silica gel column chromatography (eluents: hexane : ethyl acetate = 3:1 (v/v)) to give 1.7 g of (3R,5S)-7-chloro-5-(2,3-dimethoxyphenyl)-1-neopentyl-1,2,3,5-tetrahydro-3-cyanomethyl-4,1-benzoxazepin-2-one as colorless crystals, m.p. 193-194°C.

(3) To a solution of the compound (1.7 g) obtained in (2) in toluene (20 ml) were added trimethyl silyl azide (0.45 g) and dibutyltin (IV) oxide (30 mg). The mixture was stirred for 24 hours at temperatures ranging from 110 to 120°C. The reaction mixture was concentrated, to which was added diethyl ether (20 ml), followed by washing with an aqueous solution of sodium hydroxide. The aqueous layer was acidified with 1N HCl, which was then subjected to extraction with ethyl acetate. The organic layer was washed with water, which was then dried over anhydrous sodium sulfate. The solvent was distilled off, and the residue was recrystallized from dichloromethane-hexane to give colorless crystals, m.p. 148-150°C.

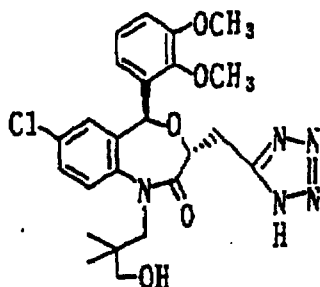
Elemental analysis for $C_{24}H_{23}ClN_5O_4 \cdot 0.5H_2O$:

Calcd. : C, 58.24; H, 5.91; N, 14.15

Found : C, 58.43; H, 6.18; N, 13.76

Working Example 1

(3R,5S)-7-Chloro-5-(2,3-dimethoxyphenyl)-1-(3-hydroxy-2,2-dimethylpropyl)-1,2,3,5-tetrahydro-3-[1H (or 3H)-tetrazol-5-yl]methyl-4,1-benzoxazepin-2-one



(1) To a solution of (S)-4-chloro-2-[α-hydroxy-(2,3-dimethoxyphenyl)methyl]aniline (2.0 g) and sodium hydrogencarbonate (0.86 g) in ethyl acetate (20 ml) was added dropwise a solution of monoethyl ester of dimethyl malonic acid chloride (1.3 g) in ethyl acetate (20 ml). The mixture was stirred for 3 hours under ice-cooling. To the solution was added water (30 ml), and the organic layer was dried over anhydrous sodium sulfate. The solvent was distilled off, and the residue was purified by silica gel column chromatography to give (S)-2-[N-[2-(2,3-dimethoxy-α-hydroxybenzyl)-4-chlorophenyl]carbamoyl]-2,2-dimethylacetic acid ethyl ester (2.92 g) as a colorless oily compound.

¹H-NMR(CDCl₃) δ: 1.22(3H,t,J=7.4Hz), 1.37(3H,s), 1.42(3H,s), 3.84(3H,s), 3.89(3H,s), 4.05-4.19(3H,m), 6.01(1H,s), 6.61(1H,dd,J=1.8,7.4Hz), 6.90-7.05(3H,m), 7.28(1H,dd,J=3.0,8.8Hz), 8.07(1H,d,J=8.4Hz), 9.49(1H,br)

(2) To a solution of the compound (2.83 g) obtained in (1) in tetrahydrofuran (30 ml) was added, under ice-cooling, lithium aluminum hydride (0.5 g). The mixture was stirred for 3 hours at room temperature. To the reaction mixture were added a 1N aqueous solution of sodium hydroxide (13 ml) and water (50 ml), then insolubles were filtered off. The filtrate was extracted with ethyl acetate. The extract was washed with water and dried, then the solvent was distilled

off. The residue was purified by silica gel column chromatography (eluents: hexane:ethyl acetate = 1:1 (v/v)) to give (S)-[5-chloro-2-(2,2-dimethyl-3-hydroxypropyl)aminophenyl](2,3-dimethoxyphenyl)methanol (0.88 g) as a colorless oily compound.

¹H-NMR(CDCl₃) δ: 0.91(3H,s), 0.93(3H,s), 2.95(2H,s), 3.37(2H,s), 3.83(3H,s), 3.88(3H,s), 5.99(1H,s), 6.63(1H,d,J=8.8Hz), 6.77(1H,dd,J=1.6,7.6Hz), 6.90(1H,dd,J=1.6,7.6Hz), 7.03(1H,d,J=2.6Hz), 7.03(1H,t,J=7.6Hz), 7.13(1H,dd,J=2.6,8.8Hz)

(3) To a solution of the compound (0.88 g) obtained in (2) in ethyl acetate (10 ml) was added sodium hydrogencarbonate (0.39 g). To the mixture was added a solution of monoethyl ester of fumaric acid chloride (0.45 g) in ethyl acetate (10 ml), which was stirred for 30 minutes at room temperature. The reaction mixture was washed with water and dried, then the solvent was distilled off. The residue was dissolved in ethanol (10 ml), to which was added potassium carbonate (0.70 g). The mixture was stirred overnight at room temperature. To the reaction mixture was added ethyl acetate (50 ml), which was washed with water and dried. The solvent was distilled off, and the residue was recrystallized from ethyl acetate - hexane to give (3R,5S)-7-chloro-5-(2,3-dimethoxyphenyl)-1-(2,2-dimethyl-3-hydroxypropyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-acetic acid ethyl ester (0.57 g) as colorless crystals, m.p. 188-190°C.

(4) The compound (0.5 g) obtained in (3) was dissolved in a mixture of tetrahydrofuran (5 ml) and ethanol (3 ml). To the solution was added a 1N aqueous solution of sodium hydroxide (1 ml), which was stirred for 20 minutes at 60°C. To the reaction mixture was added water (50 ml), which was extracted with ethyl acetate. The extract was dried, and the solvent was distilled off. The residue was recrystallized from ethyl acetate

- hexane to give (3R,5S)-7-chloro-5-(2,3-dimethoxyphenyl)-1-(3-hydroxy-2,2-dimethylpropyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-acetic acid (0.33 g) as colorless crystals, m.p. 199-202°C.

(5) To a solution of the compound (2 g) obtained in (4) and 3-aminopropionitrile (0.29 g) in dimethylformamide (20 ml) were added, at room temperature, diethyl cyanophosphonate (0.75 g) and triethylamine (0.51 g). The mixture was stirred for 30 minutes, to which was added ethyl acetate ester (100 ml). The mixture was washed with water and dried. The solvent was then distilled off, and the residue was recrystallized from hexane to give 3-[[[(3R,5S)-7-chloro-5-(2,3-dimethoxyphenyl)-1-(3-hydroxy-2,2-dimethylpropyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-acetyl]amino]propionitrile (2.25 g) as colorless crystals, m.p. 118-121°C.

(6) The compound (2 g) obtained in (5) and acetic anhydride (0.39 g) were dissolved in pyridine (20 ml). To the solution was added dimethylaminopyridine (0.1 g), and the mixture was stirred for 30 minutes at room temperature. The solvent was distilled off, and the residue was dissolved in ethyl acetate (100 ml). The solution was washed with 1N HCl and water, followed by drying over anhydrous magnesium sulfate. The solvent was distilled off to leave 3-[(3R,5S)-1-(3-acetyloxy-2,2-dimethylpropyl)-7-chloro-5-(2,3-dimethoxyphenyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-acetyl]aminopropionitrile (2.2 g) as a colorless amorphous solid product.

¹H-NMR(CDCl₃) δ: 0.95(3H,s), 1.01(3H,s), 2.03(3H,s), 2.55-2.71(2H,m), 2.92(1H,dd,J=8.0,14.4Hz), 3.41-3.59(3H,m), 3.62(3H,s), 3.72(1H,d,J=11.2Hz), 3.86(1H,d,J=11.2Hz), 3.90(3H,s), 4.33(1H,dd,J=5.0,8.0Hz), 4.56(1H,d,J=14.2Hz), 6.26(1H,s), 6.50-6.60(1H,br), 6.64(1H,s), 6.97-

7.38(5H,m)

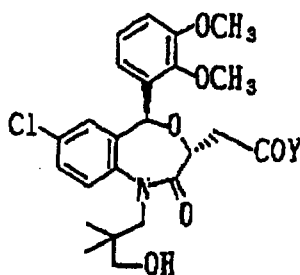
(7) A solution of the compound (2.2 g) obtained in (6), triphenylphosphine (2.0 g), diethyl azodicarboxylate (0.87 g) and triethylsilyl azide (1.3 g) in tetrahydrofuran (10 ml) was stirred for 2 hours at 60°C. The reaction mixture was concentrated under reduced pressure. The concentrate was purified by silica gel column chromatography (eluents: hexane : ethyl acetate = 1:1 (v/v)) to give (3R,5S)-7-chloro-3-[1-(2-cyanoethyl)-1H-tetrazol-5-yl]methyl-5-(2,3-dimethoxyphenyl)-1-(2,2-dimethyl-3-hydroxypropyl)-1,2,3,5-tetrahydro-4,1-benzoxazepin-2-one as a colorless oily compound. This compound was dissolved in a mixture of methanol (10 ml) and tetrahydrofuran (10 ml), to which was added a 1N aqueous solution of sodium hydroxide (8 ml). The mixture was stirred for one hour at 60°C. To the reaction mixture was added water (50 ml), which was acidified with 1N HCl, followed by extraction with ethyl acetate. The extract was dried, and the solvent was distilled off. The residue was recrystallized from ethyl acetate - hexane to give 0.96 g of colorless crystals, m.p. 158-160°C. Elemental analysis for $C_{24}H_{28}ClN_5O_5$:

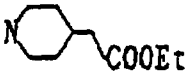
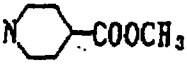
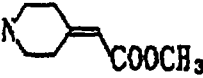
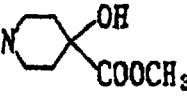
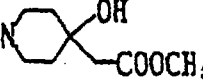
Calcd. : C, 57.43; H, 5.62; N, 13.95

Found : C, 57.55; H, 5.58; N, 13.75

Working Example 2

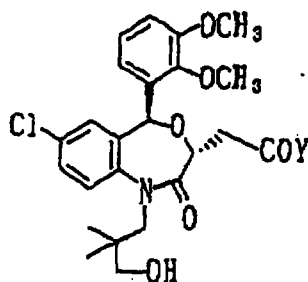
The compound obtained in Example 1 -(4) was subjected to substantially the same procedure as in Reference Example 1 to afford compounds shown in [Table 1]

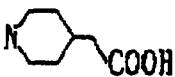
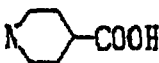
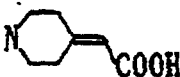
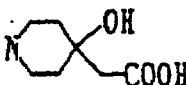


Compound No.	Y	m.p. (°C)
2-1		115-116
2-2		121-124
2-3		133-135
2-4		134-137
2-5		160-161
2-6		116-119

Working Example 3

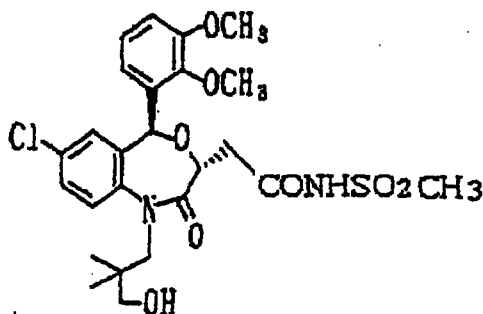
The compound obtained in Example 2 was subjected to substantially the same procedure as in Reference Example 2 to afford compounds shown in [Table 2]
[Table 2]



Compound No.	Y	m.p. (°C)
3-1		135-140
3-2		162-165
3-3		228-230
3-4		161-165
3-5		155-158

Working Example 4

(3R,5S)-N-methylsulfonyl-7-chloro-5-(2,3-dimethoxyphenyl)-1-(3-hydroxy-2,2-dimethylpropyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-acetamide



Using the compound produced in Working Example 1-(4) (0.4 g) and methanesulfonamide (0.1 g), substantially the same procedure as in Working Example 14 was followed to give 0.075 g of a colorless crystalline product, m.p. 221-223°C.

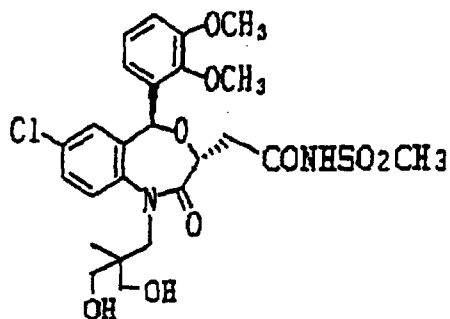
Elemental analysis for $C_{25}H_{31}ClN_2O_8S$:

Calcd. : C, 54.10; H, 5.63; N, 5.05

Found : C, 54.30; H, 5.69; N, 4.87

Working Example 5

(3R,5S)-N-methylsulfonyl-7-chloro-5-(2,3-dimethoxyphenyl)-1-(3-hydroxy-2-hydroxymethyl-2-methylpropyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-acetamide



(1) To a solution of oxalyl chloride (2.2 ml) in dichloromethane (120 ml) was added dropwise, at -78°C , a solution of dimethyl sulfoxide (2.4 ml) in dichloromethane (20 ml). The mixture was stirred at -78°C for 10 minutes, to which was then added a solution of 5-(hydroxymethyl)-2,2,5-trimethyl-1,3-dioxane (2 g) in dichloromethane (40 ml). The mixture was stirred at -78°C for further 15 minutes. To this solution was added triethylamine (13.2 ml). The mixture was warmed up to 0°C , to which was added a saturated aqueous solution of ammonium chloride (40 ml). The organic layer was washed with water and dried over anhydrous sodium sulfate, followed by distilling off the solvent. The residue was purified by silica gel column chromatography [eluents: hexane-ethyl acetate (3:1)] to give 2 g of aldehyde of a colorless oily compound. To a methanol solution of this aldehyde (2 g) were added (S)-4-chloro-2-[α -hydroxy-(2,3-dimethoxyphenyl)methyl]aniline (3.3 g) and acetic acid (0.75 g). The mixture was stirred at room temperature for 10 minutes, to which was then added sodium cyanoborohydride (0.8 g).

The mixture was stirred at 60°C overnight, to which was added water, followed by extraction with ethyl acetate. The extract was sequentially washed with 1N aqueous solution of sodium hydroxide and water, which was dried over anhydrous sodium sulfate. The solvent was distilled off, and the residue was purified by silica gel column chromatography [eluents: hexane-ethyl acetate (2:1)] to give 3.7 g of (S)-[2-(2,2,5-trimethyl-1,3-dioxan-5-ylmethyl)amino-5-chlorophenyl](2,3-dimethoxyphenyl)methanol as a colorless oily compound.

¹H-NMR(CDCl₃) δ: 0.81(3H,s), 1.38-1.45(6H,m), 3.22(2H,s), 3.30-3.40(1H,br), 3.60(4H,s), 3.83(3H,s), 3.89(3H,s), 4.90-5.00(4H,br), 5.97(1H,s), 6.71-7.27(6H,m)

(2) To a solution of the compound produced in (1) (3.7 g) in ethyl acetate (40 ml) was added sodium hydrogencarbonate (1.78 g). To the mixture was added, at 0°C, monoethyl ester of fumaric acid chloride (1.41 g). The mixture was stirred at room temperature for 30 minutes. To the solution was added water. The organic layer was washed with water, which was then dried over anhydrous sodium sulfate, followed by distilling off the solvent. The residue (5.2 g) was dissolved in ethanol (100 ml), to which was added potassium carbonate (1.1 g). The mixture was stirred overnight at room temperature. To the reaction mixture was added water, which was extracted with ethyl acetate. The extract was dried over anhydrous sodium sulfate, then the solvent was distilled off. The residue was purified by silica gel column chromatography [eluents: hexane-ethyl acetate (2:1) to ethyl acetate] to afford 2.65 g of (3R,5S)-7-chloro-1-(2,2,5-trimethyl-1,3-dioxan-5-ylmethyl)-5-(2,3-dimethoxyphenyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-acetic acid

ethyl ester (A) and 1.12 g of (3R,5S)-7-chloro-1-(3-hydroxy-2-hydroxymethyl-2-methylpropyl)-5-(2,3-dimethoxyphenyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-acetic acid ethyl ester (B), both as colorless amorphous solid products.

A: $^1\text{H-NMR}(\text{CDCl}_3)$ δ : 0.95(3H,s), 1.24(3H,t,J=7.0Hz), 1.36&1.39(each 3H,s), 2.77(1H,dd,J=5.8,16.4Hz), 3.04(1H,dd,J=7.8,16.4Hz), 3.29(1H,d,J=12.2Hz), 3.40(1H,d,J=12.2Hz), 3.58(3H,s), 3.68(2H,s), 3.89(3H,s), 4.07-4.19(3H,m), 4.40(1H,dd,J=5.8,7.8Hz), 4.48(1H,d,J=14.2Hz), 6.16(1H,s), 6.63(1H,d,J=1.8Hz), 6.95-7.45(6H,m)

B: $^1\text{H-NMR}(\text{CDCl}_3)$ δ : 0.62(3H,s), 1.25(3H,t,J=7.0Hz), 2.78(1H,dd,J=5.2,16.6Hz), 3.07(1H,dd,J=8.2,16.6Hz), 3.39-3.80(4H,m), 3.60(3H,s), 3.89(3H,s), 4.13(2H,dq,J=1.8,7.0Hz), 4.20-4.28(1H,m), 4.41(1H,dd,J=5.2,18.2Hz), 4.85(1H,d,J=14.6Hz), 6.12(1H,s), 6.63(1H,s), 6.89-7.39(6H,m)

(3) To an ethanol solution of the compound (A) produced in (2) (2.25 g) was added a 1N aqueous solution of sodium hydroxide (4.0 ml). The mixture was stirred at 60°C for one hour, to which was added water, followed by neutralization with 1N HCl. The reaction mixture was extracted with ethyl acetate. The extract was dried over anhydrous sodium sulfate, then the solvent was distilled off to leave 2.3 g of (3R,5S)-7-chloro-1-(2,2,5-trimethyl-1,3-dioxan-5-ylmethyl)-5-(2,3-dimethoxyphenyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-acetic acid as a colorless amorphous solid product.

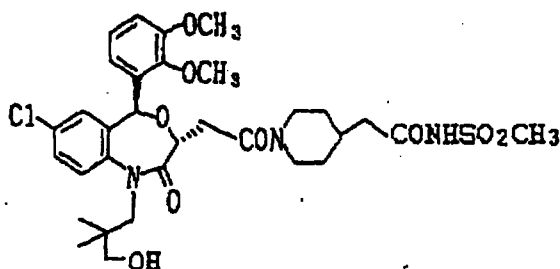
$^1\text{H-NMR}(\text{CDCl}_3)$ δ : 0.95(3H,s), 1.35&1.39(each 3H,s), 2.84(1H,dd,J=5.4,16.4Hz), 3.08(1H,dd,J=7.8,16.4Hz), 3.28(1H,d,J=12.2Hz), 3.41(1H,d,J=12.2Hz), 3.58(3H,s), 3.69(2H,s), 3.89(3H,s), 4.16(1H,d,J=13.8Hz), 4.35(1H,dd,J=5.4,7.8Hz), 4.89(1H,d,J=13.8Hz), 6.16(1H,s), 6.65(1H,d,J=2.0Hz), 6.96-7.47(5H,m)

(4) To a solution of the compound produced in (3) (0.15 g) in dimethylformamide (2 ml) were added methanesulfonamide (29 mg), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide·hydrochloride (65 mg) and dimethylaminopyridine (10 mg). The mixture was stirred overnight at room temperature, to which was added ethyl acetate (50 ml). The mixture was washed with water, followed by drying over anhydrous sodium sulfate. The solvent was distilled off, and the residue was dissolved in acetone (2 ml). To the solution was added p-toluenesulfonic acid monohydrate (0.1 g). The mixture was stirred overnight at room temperature, to which was added ethyl acetate (50 ml). The mixture was washed with water, which was dried over anhydrous sodium sulfate, followed by distilling off the solvent. The residue was washed with a mixture of ethyl ether and hexane (1:1), which was filtrated to afford 40 mg of a colorless amorphous solid product.

¹H-NMR(CDCl₃) δ: 0.63(3H,s), 2.85-2.92(2H,m), 3.28(3H,s), 3.25-3.70(5H,m), 3.59(3H,s), 3.89(3H,s), 4.43(1H,t,J=6.1Hz), 4.78(1H,d,J=14.2Hz), 8.16(1H,s), 6.67(1H,s), 6.95-7.40(6H,m)

Working Example 6

N-methylsulfonyl-[N-[(3R,5S)-7-chloro-5-(2,3-dimethoxyphenyl)-1-(3-hydroxy-2,2-dimethylpropyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-acetyl]piperidine]-4-acetamide



Using the compound (0.5 g) produced in Working Example 3 -1 and methanesulfonamide (0.1 g), substantially the same procedure as in Reference Example 3 was followed to give 90 mg of colorless crystals, m.p.175-180°C.

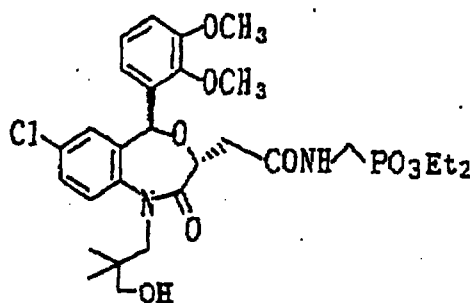
Elemental analysis for $C_{12}H_{12}ClN_2O_3S$:

Calcd. : C, 56.50; H, 6.22; N, 6.18

Found : C, 56.70; H, 6.50; N, 5.90

Working Example 7

(3R,5S)-N-bis(ethoxy)phosphinylmethyl-7-chloro-5-(2,3-dimethoxyphenyl)-1-(3-hydroxy-2,2-dimethylpropyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-acetamide



Using the compound produced in Working Example 1-(4) (1.0 g) and diethyl aminomethylphosphonate (0.38 g), substantially the same procedure as in Reference Example 1 was followed to afford 1.24 g of colorless crystals, m.p.138-140°C.

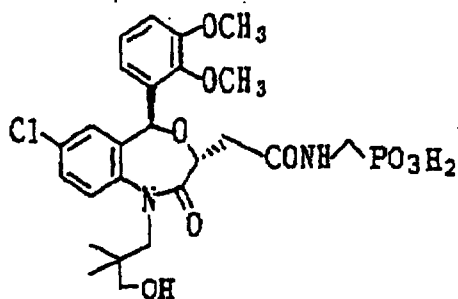
Elemental analysis for $C_{29}H_{40}ClN_2O_9P$:

Calcd. : C, 55.55; H, 6.43; N, 4.47

Found : C, 55.25; H, 6.47; N, 4.44

Working Example 8

(3R,5S)-N-phosphonomethyl-7-chloro-5-(2,3-dimethoxyphenyl)-1-(3-hydroxy-2,2-dimethylpropyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-acetamide

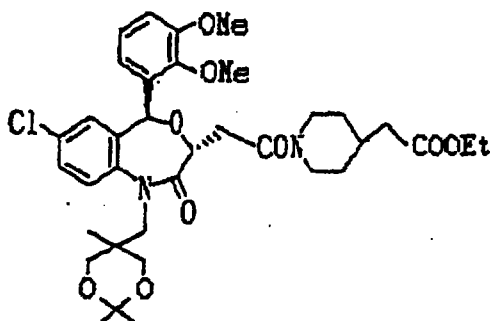


The compound produced in Working Example 7 (0.3 g) was subjected to substantially the same procedure as in Reference Example 4 to afford 0.26 g of an amorphous solid compound.

$^1\text{H-NMR}(\text{CD}_3\text{OD})$ δ : 0.84(3H,s), 0.93(3H,s), 2.75-2.82(2H,m), 3.20(1H,d,J=11.4Hz), 3.40-3.70(3H,m), 3.58(3H,s), 3.89(3H,s), 4.35-4.46(2H,m), 6.18(1H,s), 6.53(1H,d,J=2.2Hz), 7.08-7.61(5H,m)

Working Example 9

N-[(3R,5S)-7-chloro-1-(2,2,5-trimethyl-1,3-dioxan-5-ylmethyl)-5-(2,3-dimethoxyphenyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-acetyl]piperidine-4-acetic acid ethyl ester



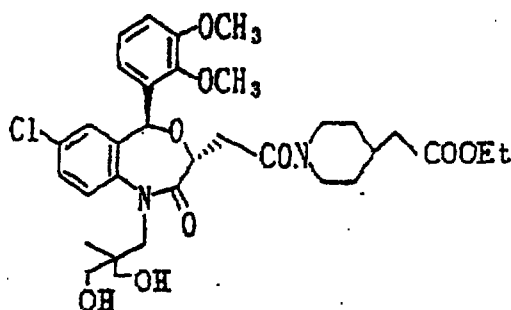
Using the compound produced in Working Example 5-(3) (2 g) and piperidine-4-acetic acid ethyl ester hydrochloride (0.7 g), substantially the same procedure as in Reference Example 1 was followed to afford 2.4 g of a colorless amorphous solid product.

$^1\text{H-NMR}(\text{CDCl}_3)$ δ : 0.96(3H,s), 1.25(3H,t,J=7.2Hz), 1.36&1.39(each 3H,s), 1.65-1.82(4H,m), 1.95-2.08(1H,m),

2.18-2.26(2H,m), 2.49-2.63(1H,m),
2.73(1H,dd,J=4.8,15.8Hz), 2.92-3.06(1H,m),
3.12(1H,dd,J=8.2,15.8Hz), 3.31(1H,d,J=12.0Hz),
3.10(1H,d,J=12.0Hz), 3.58(3H,s), 3.65(1H,d,J=11.8Hz),
3.73(1H,d,J=11.8Hz), 3.89(3H,s), 3.94-3.99(1H,m), 4.04-
4.18(3H,m), 4.46-4.56(3H,m), 6.16(1H,s), 6.60-
6.62(1H,m), 6.95-7.46(5H,m)

Working Example 10

N-[(3R,5S)-7-chloro-1-(3-hydroxy-2-hydroxymethyl-2-methylpropyl)-5-(2,3-dimethoxyphenyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-acetyl]piperidine-4-acetic acid ethyl ester



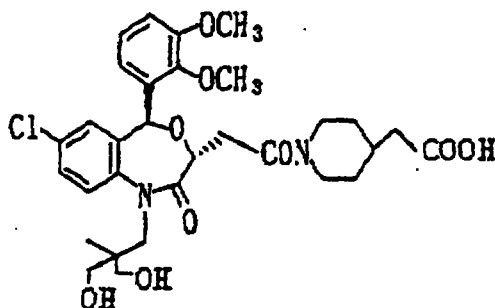
To a solution of the compound produced in Working Example 9 (2.0 g) in acetone (20 ml) were added p-toluenesulfonic acid monohydrate (35 mg) and water (2 ml). The mixture was stirred at 50°C for 6 hours. To the reaction mixture was added ethyl acetate (50 ml). The mixture was washed with a 1N aqueous solution of sodium hydroxide and water, followed by drying over anhydrous sodium sulfate. The solvent was distilled off to leave 1.62 g of a colorless amorphous solid product.

¹H-NMR(CDCl₃) δ: 0.62(3H,s), 1.00-1.34(2H,m),
1.26(3H,t,J=7.4Hz), 1.70-1.81(2H,m), 1.95-2.08(1H,m),
2.19-2.28(2H,m), 2.51-2.78(2H,m), 3.01-3.08(1H,m),
3.17(1H,dd,J=9.0,15.2Hz), 3.40-3.74(5H,m), 3.60(3H,s),
3.89(3H,s), 3.89-3.94(1H,m), 4.13(2H,q,J=7.4Hz), 4.48-

4.54(2H,m), 4.83(1H,d,J=14.6Hz), 6.13(1H,s),
6.61(1H,d,J=1.8Hz), 6.97-7.44(5H,m)

Working Example 11

N-[(3R,5S)-7-chloro-1-(3-hydroxy-2-hydroxymethyl-2-methylpropyl)-5-(2,3-dimethoxyphenyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-acetyl]piperidine-4-acetic acid

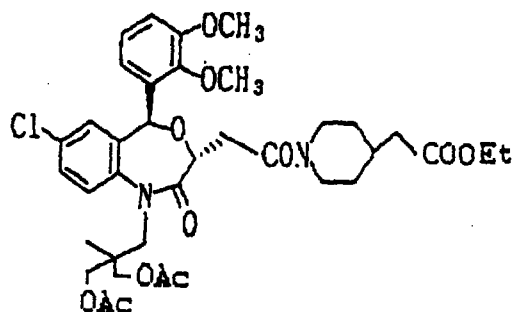


To an ethanol solution of the compound produced in Working Example 10 was added a 1N aqueous solution of sodium hydroxide. The mixture was stirred at 60°C for 2 hours. To the reaction mixture were added water (100 ml) and ethyl acetate (50 ml), which was acidified with 1N HCl. The organic layer was washed with water and dried over anhydrous sodium sulfate. The solvent was distilled off to leave 0.94 g of a colorless amorphous solid product.

¹H-NMR(CDCl₃) δ: 0.63(3H,s), 1.05-1.36(2H,m), 1.70-1.85(2H,m), 1.92-2.05(1H,m), 2.23-2.32(2H,m), 2.51-2.80(2H,m), 2.96-3.23(2H,m), 3.44-3.70(5H,m), 3.60(3H,s), 3.89(3H,s), 3.91-4.00(1H,m), 4.48-4.54(2H,m), 4.78(1H,d,J=15.2Hz), 6.12(1H,s), 6.61(1H,s), 6.97-7.39(5H,m)

Working Example 12

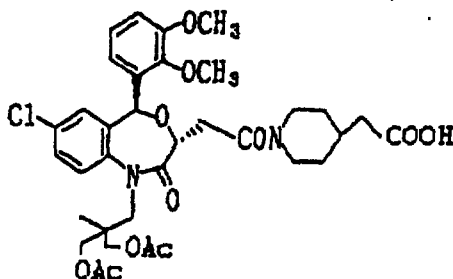
N-[(3R,5S)-1-(3-acetoxy-2-acetoxymethyl-2-methylpropyl)-7-chloro-5-(2,3-dimethoxyphenyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-acetyl]piperidine-4-acetic acid ethyl ester



To a solution of the compound produced in Working-
Example 10 (0.5 g) in pyridine (5 ml) were added acetic
anhydride (0.20 g) and dimethylaminopyridine (10 mg).
The mixture was stirred at room temperature for 30
minutes. To the reaction mixture was added ethyl
acetate (50 ml). The mixture was washed with 1N HCl
and water, which was then dried, followed by distilling
off the solvent. The residue was purified by silica
gel column chromatography (eluents: ethyl acetate) to
afford 0.50 g of a colorless amorphous solid product.
¹H-NMR(CDCl₃) δ: 1.02(3H,s), 1.00-1.40(2H,m),
1.25&1.26(total 3H, each t, J=7.2Hz), 1.60-1.80(2H,m),
1.92-2.05(1H,m), 2.00(3H,s), 2.03(3H,s), 2.16-
2.26(2H,m), 2.46-2.65(1H,m), 2.67-2.77(1H,m), 2.99-
3.19(2H,m), 3.60(3H,s), 3.64-4.19(6H,m), 3.89(3H,s),
4.44-4.54(2H,m), 4.67(1H,d,J=14.6Hz), 6.23(1H,s),
6.65(1H,s), 6.96-7.34(5H,m)

Working Example-13.

N-[(3R,5S)-1-(3-acetoxy-2-acetoxymethyl-2-
methylpropyl)-7-chloro-5-(2,3-dimethoxyphenyl)-2-oxo-
1,2,3,5-tetrahydro-4,1-benzoxazepine-3-
acetyl]piperidine-4-acetic acid

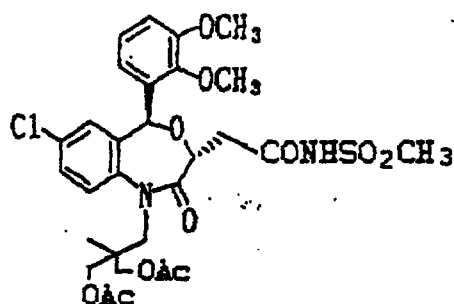


Using the compound produced in Working Example 11 substantially the same procedure as in Working Example 12 was followed to afford 0.28 g of a colorless amorphous solid product.

¹H-NMR(CDCl₃) δ: 0.95-1.36(2H,m), 1.03(3H,s), 1.71-1.83(2H,m), 1.93-2.07(1H,m), 2.00(3H,s), 2.05(3H,s), 2.23-2.33(2H,m), 2.48-2.63(1H,m), 2.65-2.78(1H,m), 3.00-3.18(2H,m), 3.60(3H,s), 3.65-4.14(6H,m), 3.89(3H,s), 4.46-4.56(2H,m), 4.66(1H,d,J=14.8Hz), 6.24(1H,s), 6.64(1H,s), 6.96-7.34(5H,m)

Working Example 14

(3R,5S)-N-methylsulfonyl-1-(3-acetoxy-2-acetoxymethyl-2-methylpropyl)-7-chloro-5-(2,3-dimethoxyphenyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-acetamide

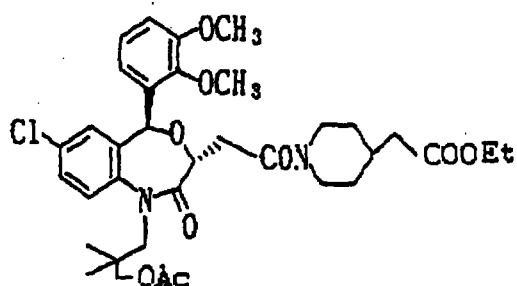


Using the compound produced in Working Example 5 (0.1 g), acetic anhydride (39 mg) and dimethylaminopyridine (5 mg), substantially the same procedure as in Working Example 12 was followed to afford 70 mg of a colorless amorphous solid product.

¹H-NMR(CDCl₃) δ: 1.00(3H,s), 2.00&2.02(each 3H,s), 2.85(1H,dd,J=5.4,15.4Hz), 2.98(1H,dd,J=7.2,15.4Hz), 3.26(3H,s), 3.61(3H,s), 3.70(1H,d,J=14.2Hz), 3.84(1H,d,J=11.4Hz), 3.89(3H,s), 3.94-3.99(2H,m), 4.11(1H,d,J=11.4Hz), 4.40(1H,d,J=6.2Hz), 4.46(1H,d,J=14.2Hz), 6.28(1H,s), 6.69(1H,d,J=1.6Hz), 6.97-7.43(5H,m)

Working Example 15

N-[(3R,5S)-1-(3-acetoxy-2,2-dimethylpropyl)-7-chloro-5-(2,3-dimethoxyphenyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-acetyl]piperidine-4-acetic acid ethyl ester

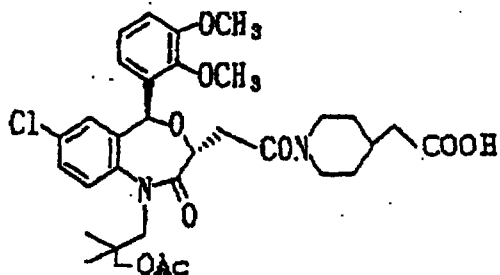


Using the compound produced in Working Example 2-1 (0.5 g), substantially the same procedure as in Working Example 12 was followed to afford 0.35 g of a colorless amorphous solid product.

$^1\text{H-NMR}(\text{CDCl}_3)$ δ : 0.93(3H,s), 1.02(3H,s), 1.26(3H,t), 2.02(3H,s), 3.61(3H,s), 3.89(3H,s), 4.14(2H,q), 4.5(3H,m), 6.26(1H,s), 6.62(1H,s), 6.9-7.4(5H,m)

Working Example 16

N-[(3R,5S)-1-(3-acetoxy-2,2-dimethylpropyl)-7-chloro-5-(2,3-dimethoxyphenyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-acetyl]piperidine-4-acetic acid



Using the compound produced in Working Example 3-1 (0.37 g), substantially the same procedure as in Working Example 12 was followed to afford 0.35 g of a colorless crystalline product, m.p.194-196°C.

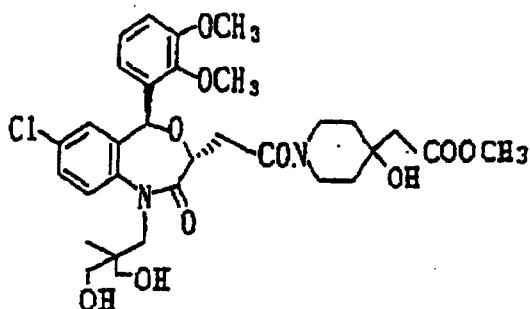
Elemental analysis for $C_{33}H_{41}ClN_2O_9$:

Calcd. : C, 61.44; H, 6.41; N, 4.34

Found : C, 61.23; H, 6.18; N, 4.39

Working Example 17

N-[(3R,5S)-7-chloro-1-(3-hydroxy-2-hydroxymethyl-2-methylpropyl)-5-(2,3-dimethoxyphenyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-acetyl]-4-hydroxypiperidine-4-acetic acid methyl ester



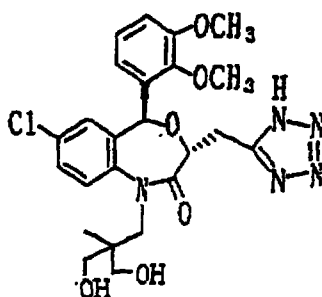
(1) To a solution of (3R,5S)-7-chloro-1-(3-hydroxy-2-hydroxymethyl-2-methylpropyl)-5-(2,3-dimethoxyphenyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-acetic acid ethyl ester (1.0 g) in ethanol (10 ml) was added a 1N aqueous solution of sodium hydroxide. The mixture was stirred at 60°C for one hour. To the reaction mixture was added water, which was neutralized with 1N HCl, followed by subjecting to extraction with ethyl acetate. The extract solution was dried over anhydrous sodium sulfate. The solvent was distilled off, and the residue was recrystallized from a mixture of ethyl acetate and hexane to afford 0.38 g of (3R,5S)-7-chloro-1-(3-hydroxy-2-hydroxymethyl-2-methylpropyl)-5-(2,3-dimethoxyphenyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-acetic acid, m.p. 208-210°C.

(2) Using the compound produced in (1) (0.25 g) and 4-hydroxypiperidine-4-acetic acid methyl ester hydrochloride (0.105 g), substantially the same procedure as in Reference Example 1 was followed to afford 0.125 g of a colorless amorphous solid product.

¹H-NMR(CDCl₃) δ: 1.35-1.84(6H,m), 2.47(2H,d), 2.65-2.85(1H,m), 2.95-3.28(2H,m), 3.35-3.78(7H,m), 3.62(3H,s), 3.73(3H,s), 3.90(3H,s), 4.22-4.40(2H,m), 4.52(1H,dd), 4.84(1H,dd), 6.13(1H,d), 6.62(1H,m), 6.95-7.43(5H,m)

Working Example 18

(3R,5S)-7-Chloro-1-(3-hydroxy-2-hydroxymethyl-2-methylpropyl)-1,2,3,5-tetrahydro-5-(2,3-dimethoxyphenyl)-3-(1H(or 3H)-tetrazol-5-yl)methyl-4,1-benzoxazepin-2-one



(1) To a solution of the compound produced in Working Example 5-(3) (0.5 g), ammonium chloride (0.25 g) and triethylamine (0.17 g) in dimethylformamide (5 ml) were added diethyl cyanophosphonate (0.21 g) and triethylamine (0.17 g). The mixture was stirred at room temperature for 30 minutes, to which was added ethyl acetate (50 ml). The mixture was washed with water, which was then dried over anhydrous sodium sulfate, followed by distilling off the solvent. The residue was purified by silica gel column chromatography (eluent: ethyl acetate) to give 0.52 g of an amide compound as amorphous solid.

(2) To a solution of dimethylformamide (41 mg) in acetonitrile (1.5 ml) was added oxalyl chloride (65 mg) at 0°C. The mixture was stirred for 10 minutes, to which were added a solution of the compound produced in (1) (0.25 g) in acetonitrile (1.5 ml) and pyridine (82 mg). The mixture was stirred at 0°C for 10 minutes.

To the reaction mixture was added ethyl acetate (50 ml). The mixture was washed with water and dried over anhydrous sodium sulfate, followed by distilling off the solvent. The residue was purified by silica gel column chromatography [eluents: hexane - ethyl acetate (2:1)] to give 0.31 g of a nitrile compound.

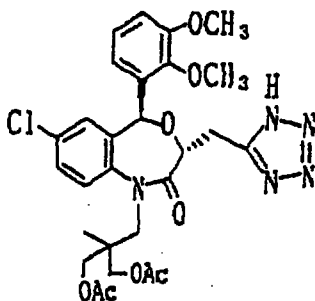
(3) A solution of the compound produced in (2) (1.0 g) in toluene (15 ml) was subjected to substantially the same procedure as in Reference Example 5-(3), using trimethylsilyl azide (0.43 g) and dibutyltin (IV) oxide (45 mg) to give (3R,5S)-7-chloro-1-(2,2,5-trimethyl-1,3-dioxan-5-ylmethyl)-5-(2,3-dimethoxyphenyl)-1,2,3,5-tetrahydro-3-(tetrazol-5-yl)methyl-4,1-benzoxazepin-2-one (1.03 g) as a colorless amorphous solid product.

(4) To a solution of the compound produced in (3) (1.0 g) in acetone (10 ml) were added p-toluenesulfonic acid monohydrate (50 mg) and water (1 ml). The mixture was stirred at 60°C overnight. To the reaction mixture was added water (50 ml), which was extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate. The solvent was distilled off, and the residue was purified by silica gel column chromatography [eluents: ethyl acetate - methanol (20:1)] to give 0.87 g of a colorless amorphous solid product.

¹H-NMR(CDCl₃) δ: 0.69(3H,s), 3.45(1H,dd,J=4.4, 14.4Hz), 3.56-3.75(5H,m), 3.62(3H,s), 3.90(3H,s), 4.29(1H,dd,J=4.4, 8.8Hz), 4.63(1H,d,J=15.2Hz), 6.18(1H,s), 6.67(1H,d,J=2.2Hz), 7.05-7.43(5H,m)

Working Example 19

(3R,5S)-1-(3-Acetoxy-2-acetoxymethyl-2-methylpropyl)-7-chloro-1,2,3,5-tetrahydro-5-(2,3-dimethoxyphenyl)-3-(1H (or 3H)-tetrazol-5-yl)-4,1-benzoxazepin-2-one

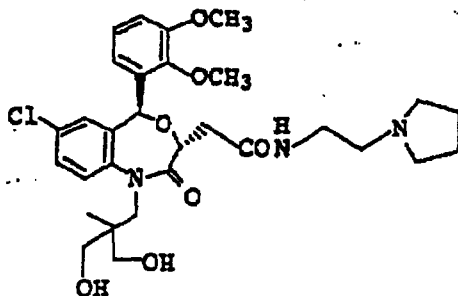


To a solution of the compound produced in Working Example 18 (0.77 g) in pyridine (7 ml) were added acetic anhydride (0.335 g) and dimethylaminopyridine (40 mg). The mixture was stirred at room temperature for 30 minutes, to which was added ethyl acetate (50 ml). The mixture was washed with 1N HCl and water, which was then dried over anhydrous sodium sulfate, followed by distilling off the solvent. The residue was washed with ethyl ether - hexane (1:1), which was filtrated to collect 0.80 g of a colorless amorphous solid product.

¹H-NMR(CDCl₃) δ: 0.98(3H,s), 2.03,2.04(each 3H,s), 3.40(1H,dd,J=5.1, 15.8Hz), 3.55-3.67(2H,m), 3.65(3H,s), 3.82-3.91(2H,m), 3.89(3H,s), 4.04(1H,d,J=11.6Hz), 4.18(1H,d,J=11.2Hz), 4.30(1H,dd,J=5.2,6.6Hz), 4.66(1H,d,J=14.6Hz), 6.27(1H,s), 6.69(1H,d,J=2.2Hz), 6.95-7.42(5H,m)

Working Example 20

(3R,5S)-N-[2-(Pyrrolidin-1-yl)ethyl]-7-chloro-1-(3-hydroxy-2-hydroxymethyl-3-methylpropyl)-5-(2,3-dimethoxyphenyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-acetamide



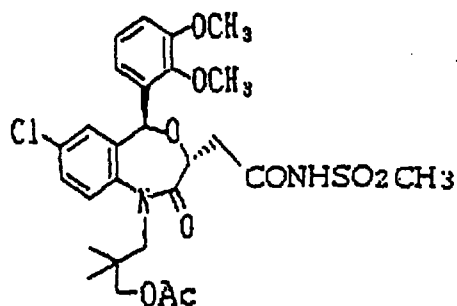
(1) To a solution of the compound produced in Working Example 5-(3) (0.5 g) and diethyl cyanophosphonate (54 mg) in dimethylformamide (1.5 ml) was added 1-(2-aminoethyl)pyrrolidine (0.16 g). The mixture was stirred at room temperature for 30 minutes, to which was added ethyl acetate (50 ml). The mixture was washed with water and dried, followed by distilling off the solvent. The residue was purified by silica gel column chromatography [eluents: ethyl acetate - methanol-triethylamine (10:1:0.1) to give (3R,5S)-N-(2-(pyridin-1-yl)ethyl)-7-chloro-1-(2,2,5-trimethyl-1,3-dioxan-5-ylmethyl)-5-(2,3-dimethoxyphenyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-acetamide (0.19 g) as a colorless amorphous solid product.

(2) To a solution of the compound produced in (1) (0.19 g) in tetrahydrofuran (2 ml) was added conc. HCl (1 ml). The mixture was stirred at 60°C for 30 minutes, to which was added water (50 ml), followed by neutralizing with 1N NaOH. The resultant was extracted with ethyl acetate, washed with water and dried, followed by distilling off the solvent. The residue was purified silica gel column chromatography (eluents: ethyl acetate - methanol-triethylamine (2:1:0.1) to give 97 mg of a colorless amorphous solid product.

¹H-NMR(CDCl₃) δ: 0.62(3H,s), 1.75-1.80(4H,m), 2.50-2.72(7H,m), 2.87(1H,dd,J=7.0,14.2Hz), 3.31-3.76(7H,m), 3.59(3H,s), 3.89(3H,s), 4.45(1H,t),J=6.4Hz), 4.82(1H,d,J=15.0Hz), 6.12(1H,s), 6.35-6.50(1H,br), 6.62(1H,s), 6.99-7.37(5H,m)

Working Example 21

(3R,5S)-N-Methylsulfonyl-1-(3-acetoxy-2,2-dimethylpropyl)-7-chloro-5-(2,3-dimethoxyphenyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-acetamide



The compound produced in Working Example 19 (1.2 g) was subjected to substantially the same procedure as in Working Example 19 to give 1.01 g of a colorless crystalline product, m.p. 108-112°C.

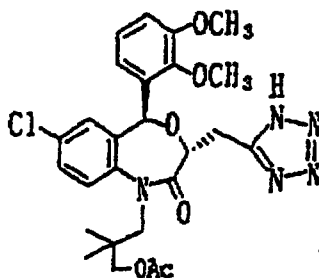
Elemental Analysis for $C_{27}H_{33}ClN_2O_9S \cdot 1.5H_2O$:

Calcd.: C, 51.96; H, 5.81; N, 4.49

Found : C, 52.01; H, 5.82; N, 4.30

Working Example 22

(3R,5S)-1-(3-Acetoxy-2,2-dimethylpropyl)-7-chloro-5-(2,3-dimethoxyphenyl)-1,2,3,5-tetrahydro-3-[1H(or 3H)tetrazol-5-yl]methyl-4,1-benzoxazepin-2-one



The compound produced in Working Example 1 (80 mg) was subjected to substantially the same procedure as in Working Example 19 to give 25 mg of a colorless amorphous solid product.

1H -NMR($CDCl_3$) δ : 0.97(3H,s), 0.99(3H,s), 2.05(3H,s), 3.3-3.8(4H,m), 3.65(3H,s), 3.89(3H,s), 4.05(1H,d), 4.28(1H,dd), 4.62(1H,d), 6.27(1H,s), 6.68(1H,d), 6.9-7.4(5H,m)

Formulation Examples

A therapeutic agent of hyperlipemia containing, as its effective component, the compound (1) or a salt thereof of this invention can be formulated in accordance with, for example, the following prescriptions.

1. Capsules

(1) Compound of Example 16	10 mg
(2) Lactose	90 mg
(3) Microcrystalline cellulose	70 mg
(4) Magnesium stearate	10 mg
1 capsule	180 mg

(1), (2) and (3) and one half of (4) were blended and the mixture was granulated, to which was added the balance of (4). The mixture was filled in a gelatin capsule.

2. Tablets

(1) Compound of Example 16	10 mg
(2) Lactose	35 mg
(3) Corn starch	150 mg
(4) Microcrystalline cellulose	30 mg
(5) Magnesium stearate	5 mg
One tablet	230 mg

(1), (2), (3), two third of (4) and one half of (5) were blended and the mixture was granulated, to which were added the balance of (4) and (5). The mixture was subjected to compression-molding to provide tablets.

3. Injections

(1) Compound Example 16	10 mg
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(2) Inositol	100 mg
(3) Benzyl alcohol	20 mg
One ampoule	130 mg

(1), (2) and (3) were dissolved in distilled water for injection to make the whole volume 2 ml, which was put in an ampoule, and the ampoule was sealed. All the processes were conducted under sterilized conditions.

Experimental Example 1

Squalene Synthetase Inhibitory Activity

Assay Method

The squalene synthetase inhibitory activity was assayed as follows with the enzyme solutions prepared in accordance with the method described below.

More specifically, an enzyme solution (protein content 0.8 μ g) prepared in accordance with the method described below was added to a solution (total volume 50 μ l)) containing 5 μ M [$1\text{-}^3\text{H}$] farnesyl pyrophosphate (specific activity 25 μ Ci/mole), 1 mM NADPH (nicotinamide adenine dinucleotide phosphate of reduced type), 5 mM MgCl_2 , 6 mM glutathione, a 100 mM buffer solution of potassium phosphate (pH 7.4) and a test drug (used as an aqueous solution or a DMSO solution), then the reaction was allowed to proceed at 37°C for 45 minutes. To the reaction mixture was added 150 μ l of a mixture of chloroform and methanol (1:2) to suspend the reaction, followed by adding 50 μ l of chloroform and 50 μ l of a 3N solution of sodium hydroxide. 50 μ l of the chloroform layer (lower layer) containing the reaction mixture having squalene as the principal component and 3 ml of toluene-based liquid scintillator were mixed, and its radioactivity was determined by means of a liquid scintillation counter.

The squalene synthetase inhibitory activity was expressed in terms of the concentration inhibiting by 50% the radioactivity taken into the chloroform layer

(IC₅₀, molar concentration (M)), as shown in Table 7.

Preparation of human-derived enzyme

Human hepatic carcinoma cells HepG2 (about 1×10^9 cells) obtained by incubation on a Dulbecco-modified Eagle's medium (37°C in the presence of 5% CO₂) containing 10% fetal bovine serum were suspended in 10 ml of an ice-cooled buffer solution [100 mM potassium phosphate buffer (pH 7.4), 30 mM nicotinamide and 2.5 mM MgCl₂]. The cells were crashed by means of ultrasonication (for 30 seconds, twice). The sonicate thus obtained was subjected to centrifugation for 20 minutes (4°C) with 10000 x g. The supernatant layer was subjected to further centrifugation for 90 minutes (4°C) with 105000 x g. The sediment was then suspended in an ice-cooled 100 mM potassium phosphate buffer (pH 7.4), which was again subjected to centrifugation for 90 minutes (4°C) with 105000 x g. This fraction was suspended in an ice-cooled 100 mM potassium phosphate buffer solution (pH 7.4) (about 4 mg/ml protein concentration). This suspension was used as the enzyme solution.

[Table 7]

Compound No.	Inhibitory Activity (IC ₅₀ , 10 ⁻⁵ M)
3-2	18
4	32
5	48
6	26
7	20

As is clear from the above results, the compounds of this invention have an excellent squalene synthetase inhibitory activity.

Experimental Example 2

Assay of cholesterogenesis in the liver:

Cholesterol biosynthesis in the liver of a rat was assayed as follows. Six-week old Wistar fatty rats were given orally a test compound [Compound 4-2 (suspended in a 0.5% methyl cellulose solution)], while the control group was orally given only a 0.5% methyl cellulose solution. One hour later, sodium acetate labelled with radioisotope ^{14}C (manufactured by Amasham) was given intravenously at the tail (10 $\mu\text{Ci}/0.3$ ml physiological saline/rat). One hour later, rats were sacrificed by decapitation, and 1.5 g of the first lobe of the liver was removed, which was saponified by immersing in 3.9 ml of an alkaline ethanol solution ($\text{KOH}:\text{EtOH}=1:2$) at 100°C for two hours, followed by extraction with 5 ml each portion of petroleum ether three times. The extract solution was dried, which was dissolved in 3 ml of ethanol:acetone (1:1). To the solution was added 2 ml of a 0.5% digitonin-ethanol solution. The mixture was left standing for one hour. Resulting precipitates were collected as total sterol, and the radioactivity was measured by means of a liquid scintillation counter. The results are shown below.

Amount given	Cholesterogenesis inhibitory rate (%)
0.6 mg/kg	80.1%
2.0 mg/kg	90.4%

As shown in the above results, the compound of this invention performs an excellent effect of inhibiting the cholesterogenesis by 80% or more.

Industrial Applicability

The compounds of this invention have a squalene

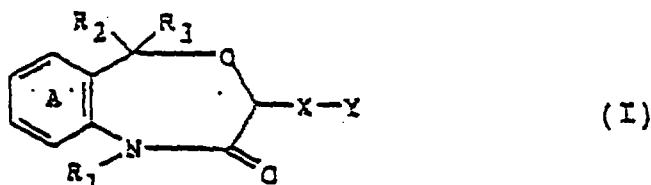
synthetase inhibitory activity, a cholesterol lowering activity and a triglyceride lowering activity, and are useful as a prophylactic and therapeutic agent of hyperlipemia as an agent of lowering lipids, and also useful for prophylaxis and therapy of, among other, arteriosclerosis.



CLAIMS

What is claimed is:

1. A 4,1-Benzoxazepin-2-one derivative represented by the formula (I):



wherein R_1 stands for a hydrocarbon group substituted with an optionally substituted hydroxy group; R_2 and R_3 independently stand for hydrogen atom, an optionally substituted lower alkyl group, an optionally substituted phenyl group or an optionally substituted aromatic heterocyclic group; X stands for a bond or a spacer having the chain length of 1 to 7 atoms; Y stands for an optionally esterified or thioesterified carboxyl group, an optionally substituted hydroxyl group, an optionally substituted amino group, an optionally substituted phenyl group, an optionally substituted carbamoyl group or a N-containing heterocyclic residue having hydrogen atom capable of being deprotonated; provided that, when X is methylene and R_1 is not an alkyl group having carbon atoms of more than 4, Y is neither carboxyl group nor alkoxycarbonyl group; and the ring A may optionally be substituted, or a salt thereof.

2. The 4,1-Benzoxazepin-2-one derivative according to claim 1, R_1 stands for an aliphatic chain hydrocarbon group substituted with an optionally substituted hydroxy group.
3. The 4,1-Benzoxazepin-2-one derivative according to claim 2, R_1 stands for an alkyl group substituted with an optionally substituted hydroxy group.
4. The 4,1-Benzoxazepin-2-one derivative according to claim 3, R_1 stands for a lower C_{1-7} alkyl group substituted with an optionally substituted hydroxy group.

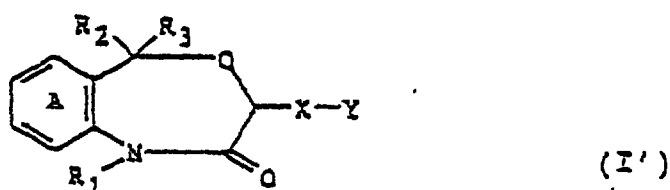


5. The 4,1-Benzoxazepin-2-one derivative according to claim 4, R_1 stands for a C_{1-7} alkyl group substituted with an optionally substituted hydroxy group.

6. The 4,1-Benzoxazepin-2-one derivative according to claim 1, R_2 or R_3 stands for an optionally substituted phenyl group.

7. The 4,1-Benzoxazepin-2-one derivative according to claim 1, Y stands for an optionally esterified carboxyl group or a N-containing heterocyclic residue having hydrogen atom capable of being deprotonated.

8. A 4,1-Benzoxazepin-2-one derivative represented by the formula (I'):

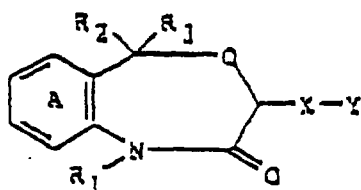


, wherein R_1 stands for hydrocarbon group substituted with an optionally substituted hydroxy group; R_2 and R_3 independently stand for hydrogen atom, an optionally substituted lower alkyl group, an optionally substituted phenyl group or an optionally substituted aromatic heterocyclic group; X stands for a bond or a spacer having the chain length of 1 to 7 atoms; Y stands for an optionally esterified or thioesterified carboxyl group, an optionally substituted hydroxyl group, an optionally substituted amino group, an optionally substituted phenyl group, an optionally substituted carbamoyl group or a N-containing heterocyclic residue having hydrogen atom capable of being deprotonated; provided that, when X is methylene, Y is neither carboxyl group nor alkoxycarbonyl group; and the ring A may optionally be substituted, or a salt thereof.

9. The 4,1-Benzoxazepin-2-one derivative according to claim 8, R_1 stands for an aliphatic chain hydrocarbon



- group substituted with an optionally substituted hydroxy group.
10. The 4,1-Benzoxazepin-2-one derivative according to claim 9, R_1 stands for an alkyl group substituted with an optionally substituted hydroxy group.
11. The 4,1-Benzoxazepin-2-one derivative according to claim 10, R_1 stands for a lower C_{1-7} alkyl group substituted with an optionally substituted hydroxy group.
12. The 4,1-Benzoxazepin-2-one derivative according to claim 8, R_2 or R_3 stands for an optionally substituted phenyl group.
13. The 4,1-Benzoxazepin-2-one derivative according to claim 8, Y is an optionally esterified carboxyl group or a N-containing heterocyclic residue having hydrogen atom capable of being deprotonated.
14. A pharmaceutical composition for inhibiting a squalene synthetase which comprises a therapeutically effective amount of a 4,1-Benzoxazepin-2-one derivative according to claim 1 or a salt thereof, and a pharmaceutical acceptable carrier.
15. A pharmaceutical composition for inhibiting a squalene synthetase which comprises a therapeutically effective amount of a 4,1-Benzoxazepin-2-one derivative according to claim 8 or a salt thereof, and a pharmaceutical acceptable carrier.
16. A pharmaceutical composition for inhibiting a fungal growth which comprises a therapeutically effective amount of a 4,1-Benzoxazepin-2-one derivative according to claim 1 or a salt thereof, and a pharmaceutical acceptable carrier.
17. A pharmaceutical composition for inhibiting a fungal growth which comprises a therapeutically effective amount of a 4,1-Benzoxazepin-2-one derivative according to claim 8 or a salt thereof, and a pharmaceutical acceptable carrier.
18. Use of a 4,1-Benzoxazepin-2-one derivative represented by the formula (I):



(I'')

wherein R^1 stands for hydrocarbon group substituted with an optionally substituted hydroxy group; R_2 and R_3 independently stand for hydrogen atom, an optionally substituted lower alkyl group, an optionally substituted phenyl group or an optionally substituted aromatic heterocyclic group; X stands for a bond or a spacer having the chain length of 1 to 7 atoms; Y stands for an optionally esterified or thioesterified carboxyl group, an optionally substituted hydroxyl group, an optionally substituted amino group, an optionally substituted phenyl group, an optionally substituted carbamoyl group or a N-containing heterocyclic residue having hydrogen atom capable of being deprotonated; and the ring A may optionally be substituted, or a salt thereof, for the manufacture of a medicament to be used as a squalene synthetase inhibitor.

19. The use according to claim 18, R_1 stands for an aliphatic chain hydrocarbon group substituted with an optionally substituted hydroxy group.

20. The use according to claim 19, R_1 stands for an alkyl group substituted with an optionally substituted hydroxy group.

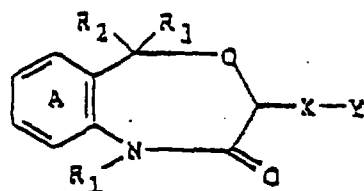
21. The use according to claim 20, R_1 stands for a lower C_{1-7} alkyl group substituted with an optionally substituted hydroxy group.

22. The use according to claim 18, R_2 or R_3 stands for an optionally substituted phenyl group.

23. The use according to claim 18, Y stands for an optionally esterified carboxyl group or a N-containing heterocyclic residue having hydrogen atom capable of being deprotonated.



24. Use of a 4,1-Benzoxazepin-2-one derivative represented by the formula (I''):

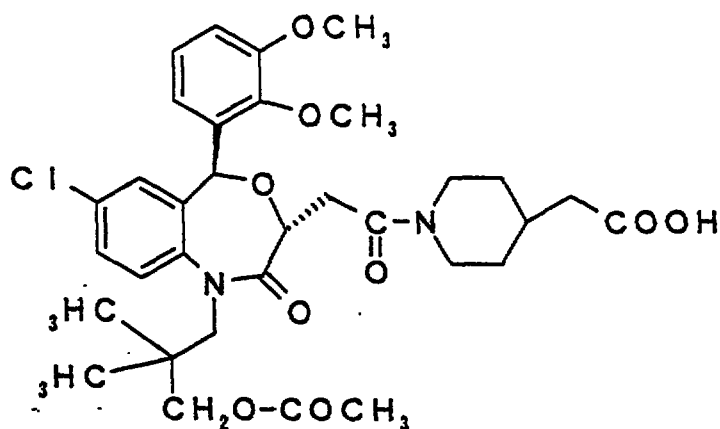


(I'')

wherein R¹ stands for hydrocarbon group substituted with an optionally substituted hydroxy group; R₂ and R₃ independently stand for hydrogen atom, an optionally substituted lower alkyl group, an optionally substituted phenyl group or an optionally substituted aromatic heterocyclic group; X stands for a bond or a spacer having the chain length of 1 to 7 atoms; Y stands for an optionally esterified or thioesterified carboxyl group, an optionally substituted hydroxyl group, an optionally substituted amino group, an optionally substituted phenyl group, an optionally substituted carbamoyl group or a N-containing heterocyclic residue having hydrogen atom capable of being deprotonated; and the ring A may optionally be substituted, or a salt thereof, for the manufacture of a medicament to be used as a fungal growth inhibitor.



25. A compound which is N-[(3R, 5S)-1-(3-acetoxy-2,2-dimethylpropyl)-7-chloro-5-(2,3-dimethoxyphenyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-acetyl]piperidine-4-acetic acid or its salt.



26. A compound which is N-[(3R, 5S)-1-(3-hydroxy-2,2-dimethylpropyl)-7-chloro-5-(2,3-dimethoxyphenyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-acetyl]piperidine-4-acetic acid or its salt.

