DESCRIPTION

Anti-itching Agent

Technical Field

The present invention relates to anantipruritic useful for the treatment of pruritus accompanying various diseases, comprising as an effective ingredient a morphinan derivative having a nitrogen-containing cyclic group or a pharmaceutically acceptable acid addition salt thereof.

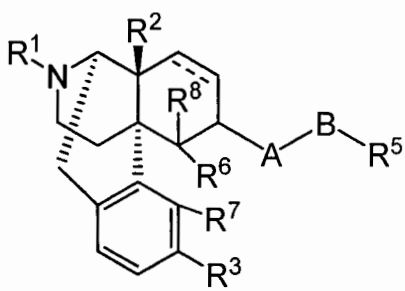
Background Art

Pruritus (itching) occurs in a variety of dermatoses with inflammation. It is known that pruritus is also sensed in internal diseases, pregnancy and vermination, and that pruritus is sometimes induced by drugs and by psychogenic reasons. Since quantitative and objective evaluation of pruritus is difficult, the study thereof has not been advanced, and the mechanism that induces pruritus has not yet been completely clarified. Reported substances which induce pruritus include histamine, substance P, bradykinin, proteinases, prostaglandins and opioid peptides.

For the treatment of pruritus, antihistamines and antiallergic drugs, which are oral drugs, have been mainly employed. External preparations such as antihistamines, adrenocortical steroid dermatologic preparations, nonsteroidal anti-inflammatory drugs, camphor, menthol, phenol, salicylic acid, tar, crotamiton, capsaicin, and humectants (urea, Hirudoid, and vaseline) have also been used. However, oral drugs have some problems, e.g. a long lag time before presenting effects, and adverse events such as suppressive effects on the central nervous system (drowsiness and malaise) and impairment of the gastrointestinal system. External preparations also have problems in that the antipruritic effect is insufficient, and especially, administration of steroid drugs for an extended period of time brings about systemic side effects such as decreased adrenal function as well as topical side effects such as rebound phenomenon, skin atrophy, steroid purpura, striae cutis

distensae and steroid acne.

As for the findings concerning the relationship between the compounds having morphinan skeleton and pruritus, it has been reported that pruritus was induced when morphine was epidurally or intrathecally administered, opposite to the cases where the compounds used in the present invention are administered (Non-patent Reference 1). On the other hand, it has been also reported that pruritus induced by intrathecally-administered morphine was suppressed by naloxone, an opioid antagonist (Non-patent Reference 2), and severe pruritus in cases of cholestasia with hepathopathy was suppressed by nalmefene, an opioid antagonist (Non-patent Reference 3). Further, morphinan compounds of which 6-position is substituted by a chain group, represented by the following general formula, which have antipruritic actions are also known (Patent Reference 1).



On the other hand, morphinan compounds having a nitrogen-containing cyclic group are known, which are described in Non-patent References 2 and 3. The disclosed uses of the compounds are analgesic and antitussive only (Non-patent References 2 and 3). In Non-patent References 4,5 and 6, only the compounds are described and no use thereof is disclosed (Non-patent References 4,5 and 6) (Use for the treatment of urinary frequency or urinary incontinence was disclosed after the priority date of the present application (Patent Reference 4)). However, there is no constant relationship between the structures of these compounds as well as the pharmacological activities through opioid receptors and the like and the antipruritic action according to the present invention, so that the references do not infer the

prominent and useful antipruritic action of the antipruritic according to the present invention characterized in that the morphinan structure has a nitrogen-containing cyclic group at its 6-position.

Non-patent Reference 1: J. H. Jaffe and W. R. Martin, Goodman and Gilman's Pharmacological Basis of Therapeutics, Macmillan, New York, 1985

Non-patent Reference 2: J. Bernstein et al., J. Invest. Dermatol., 78, 82-83, 1982

Non-patent Reference 3: J. R. Thornton and M. S. Losowsky, Br. Med. J., 297, 1501-1504, 1988

Non-patent Reference 4: C. Simon et al., Tetrahedron, 50, 9757-9768, 1994

Non-patent Reference 5: C. Simon et al., Synth. Commun., 22, 913-921, 1992

Non-patent Reference 6: L. M. Sayre et al., J. Med. Chem., 27, 1325-1335, 1984

Patent Reference 1: PCT International Publication WO98/23290

Patent Reference 2: Japanese Patent Publication No. 41-18824

Patent Reference 3: Japanese Patent Publication No. 41-18826

Patent Reference 4: PCT International Publication WO04/33457

Disclosure of the Invention

Object of the Invention to be attained

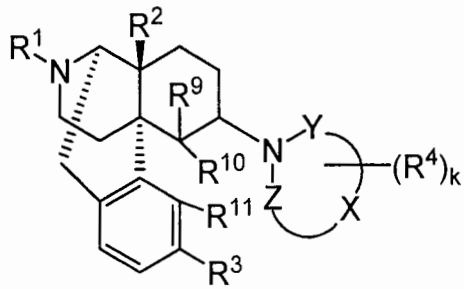
An object of the present invention is to provide novel antipruritic useful for the therapy of pruritus accompanying various diseases.

Means for attaining an object

To attain the above-mentioned object, the present inventors intensively studied to discover that compounds having a nitrogen-containing cyclic group on a specific position of morphinan structure have excellent therapeutic effects against pruritus, and that their side effects are small, thereby completing the present invention.

That is, the present invention providesantipruriticcomprisingas an effective ingredient a morphinan derivative having a nitrogen-containing cyclic group of the

Formula (I):



(I)

[wherein R^1 is hydrogen, C_1-C_5 alkyl, C_4-C_7 cycloalkylalkyl, C_6-C_8 cycloalkenylalkyl, C_6-C_{12} aryl, C_7-C_{13} aralkyl, C_3-C_7 alkenyl, furanylalkyl (wherein the number of carbon atoms in the alkyl moiety is 1 to 5), thienylalkyl (wherein the number of carbon atoms in the alkyl moiety is 1 to 5) or pyridylalkyl (wherein the number of carbon atoms in the alkyl moiety is 1 to 5);

R^2 and R^3 are independently hydrogen, hydroxy, C_1-C_5 alkoxy, C_3-C_7 alkenyloxy, C_7-C_{13} aralkyloxy or C_1-C_5 alkanoyloxy;

Y and Z independently represent valence bond or -C(=O)-;

-X- represents a C_2-C_7 carbon chain (one or more of the carbon atoms therein may be replaced by (a) nitrogen, oxygen or sulfur atom(s), and the carbon chain may contain (an) unsaturated bond(s)) constituting a part of the ring structure;

k is an integer of 0 to 8;

R^4 is(are) (a) substituent(s) in the number of k on the nitrogen-containing ring, which independently represent(s) fluorine, chlorine, bromine, iodine, nitro, hydroxy, C_1-C_5 alkyl, C_7-C_{13} cycloalkylalkyl, C_6-C_{12} aryl, C_7-C_{13} aralkyl, C_7-C_{13} aralkyloxy, C_1-C_5 alkoxy, trifluoromethyl, trifluoromethoxy, cyano, isothiocyanato, SR^6, SOR^6, SO_2R^6, $(CH_2)_pOR^6$, $(CH_2)_pCOR^6$, $(CH_2)_pCO_2R^6$, $SO_2NR^7R^8$, $CONR^7R^8$, $(CH_2)_pNR^7R^8$ or $(CH_2)_pN(R^7)COR^8$, or among the R^4s in the number of k, two R^4s bound to the same carbon atom or to the same sulfur atom cooperatively represent one oxygen atom to form carbonyl or sulfoxide, or two R^4s bound to the same carbon atom cooperatively

represent one sulfur atom to form thiocarbonyl, or four R^4s bound to the same sulfur atom cooperatively represent two oxygen atoms to form sulfone, or among the R^4s in the number of k, two R^4s bound to adjacent carbon atoms, respectively, cooperatively form benzene fused ring, pyridine fused ring, naphthalene fused ring, cyclopropane fused ring, cyclobutane fused ring, cyclopentane fused ring, cyclopentene fused ring, cyclohexane fused ring, cyclohexene fused ring, cycloheptane fused ring or cycloheptene fused ring, each of said fused rings is non-substituted or substituted by 1 or more R^5s, wherein R^5(s) independently represent(s) fluorine, chlorine, bromine, iodine, nitro, hydroxy, C_1-C_5 alkyl, C_1-C_5 alkoxy, trifluoromethyl, trifluoromethoxy, cyano, C_6-C_{12} aryl, isothiocyanato, SR^6, SOR^6, SO_2R^6, $(CH_2)_pOR^6$, $(CH_2)_pCOR^6$, $(CH_2)_pCO_2R^6$, $SO_2NR^7R^8$, $CONR^7R^8$, $(CH_2)_pNR^7R^8$ or $(CH_2)_pN(R^7)COR^8$;

R^9 is hydrogen, C_1-C_5 alkyl, C_1-C_5 alkenyl, C_7-C_{13} aralkyl, C_1-C_3 hydroxyalkyl, $(CH_2)_pOR^6$ or $(CH_2)_pCO_2R^6$;

R^{10} and R^{11} are bound to form -O-, -S- or -CH_2-, or R^{10} is hydrogen and R^{11} is hydrogen, hydroxy, C_1-C_5 alkoxy or C_1-C_5 alkanoyloxy;

p is an integer of 0 to 5;

R^6 is hydrogen, C_1-C_5 alkyl, C_3-C_7 alkenyl, C_6-C_{12} aryl or C_7-C_{13} aralkyl; and

R^7 and R^8 are independently hydrogen, C_1-C_5 alkyl or C_7-C_{13} aralkyl, and the Formula (I) includes (+), (-) and (±) isomers]

or a pharmaceutically acceptable acid addition salt thereof. The present invention also provides a use of the morphinan derivative having a nitrogen-containing cyclic group, represented by the above-described Formula (I) or a pharmaceutically acceptable acid addition salt thereof for the production of antipruritics. The present invention further provides a method for preventing pruritus comprising administering to a patient an effective amount of one or more of said morphinan derivative having a nitrogen-containing cyclic group, represented by the above-described Formula (I) or the pharmaceutically acceptable acid addition salt thereof.

Effect of the Invention

The antipruritic according to the present invention has an excellent antipruritic property and its side effects are small.

Best Mode for Carrying out the Invention

As mentioned above, the antipruritic according to the present invention comprises as an effective ingredient a morphinan derivative having a nitrogen-containing cyclic group of the Formula (I) or a pharmaceutically acceptable acid addition salt thereof. The antipruritic according to the present invention may comprise a single effective ingredient selected from the group consisting of the morphinan derivatives having a nitrogen-containing cyclic group of the Formula (I) and pharmaceutically acceptable acid addition salts thereof, or may comprise combination of two or more of the effective ingredients.

Among the compounds represented by Formula (I), those in which Y is -C(=O)- are preferred, and those in which both Y and Z are -C(=O)- are especially preferred.

R^1 is preferably hydrogen, C_4-C_7 cycloalkylalkyl, C_6-C_8 cycloalkenylalkyl, C_6-C_{12} aryl or C_3-C_7 alkenyl. Among these, hydrogen, cyclopropylmethyl, 2-cyclopropylethyl, 3-cyclopropylpropyl, 4-cyclopropylbutyl, cyclobutylmethyl, cyclopentylmethyl, cyclohexylmethyl, cyclobutenylmethyl, 2-cyclobutenylethyl, 3-cyclobutenylpropyl, phenyl, naphthyl, tolyl, allyl, 3-butynyl and prenyl are preferred. Among these, hydrogen, cyclopropylmethyl, cyclobutylmethyl, cyclopentylmethyl, cyclohexylmethyl, allyl and prenyl are preferred, and hydrogen, cyclopropylmethyl, cyclobutylmethyl and allyl are especially preferred.

R^2 and R^3 are hydrogen, hydroxy, C_1-C_5 alkoxy, C_3-C_7 alkenyloxy, C_7-C_{13} aralkyloxy or C_1-C_5 alkanoyloxy. Among these, hydrogen, hydroxy, methoxy, ethoxy, allyloxy, benzyloxy, acetoxy and propionoxy are preferred, and hydrogen, hydroxy, methoxy and acetoxy are especially preferred.

-X- is preferably a C_2-C_4 carbon chain (one carbon atom therein may be replaced by sulfur atom and the carbon chain contains (an) unsaturated bond(s)) constituting a part of the ring structure, and more preferably a carbon chain having two carbon atoms, constituting a part of the ring structure.

k is preferably an integer of 0 to 6.

R^4(s) is(are) preferably C_1-C_5 alkyl, C_7-C_{13} aralkyl or C_7-C_{13} aralkyloxy, or preferably, four R^4s bound to the same sulfur atom cooperatively represent two oxygen atoms to form sulfone, or preferably, two R^4s bound to adjacent carbon atoms, respectively, cooperatively form benzene fused ring, pyridine fused ring, naphthalene fused ring, cyclopropane fused ring, cyclobutane fused ring, cyclopentane fused ring, cyclopentene fused ring, cyclohexane fused ring, cyclohexene fused ring, cycloheptane fused ring or cycloheptene fused ring, each of said fused rings is non-substituted or substituted by 1 or more R^5s. Among these, methyl, ethyl, ethylidene, propyl, propylidene, butyl, butylidene, benzyl, benzylidene, methylbenzyl, methylbenzylidene, fluorobenzyl, fluorobenzylidene, trifluoromethoxybenzyl, trifluoromethoxybenzylidene, phenethyl, phenethylidene, cyclohexylmethyl, cyclohexylmethylidene, phenoxy and chlorophenoxy, as well as formation of sulfone group, or benzene fused ring and cyclohexene fused ring, are preferred. Especially preferred are the cases where two R^4s cooperatively form benzene fused ring or cyclohexene fused ring, each of which is non-substituted or substituted by 1 to 4 substituent R^5s. In these cases, the cases where additional four R^4s bound to the same sulfur atom cooperatively form a sulfone group are also preferred. Although formation of non-substituted benzene fused ring or non-substituted cyclohexene fused ring is preferred, the cases are also preferred where R^5(s) is(are) independently fluorine, chlorine, bromine, iodine, nitro, C_1-C_5 alkyl (especially, methyl, ethyl or propyl), C_7-C_{13} aralkyl (especially benzyl), hydroxy, C_1-C_5 alkoxy (especially methoxy or ethoxy), trifluoromethyl, trifluoromethoxy, cyano, phenyl, isothiocyanato,

SR^6, SOR^6, SO_2R^6, $(CH_2)_pOR^6$, $(CH_2)_pCOR^6$, $(CH_2)_pCO_2R^6$, $SO_2NR^7R^8$, $CONR^7R^8$, $(CH_2)_pNR^7R^8$, $(CH_2)_pN(R^7)COR^8$ (wherein p represents an integer of 0 to 5, R^6 represents hydrogen, C_1-C_5 alkyl (especially methyl, ethyl or propyl), C_3-C_7 alkenyl or C_6-C_{12} aryl (especially phenyl), and R^7 and R^8 independently represent hydrogen, C_1-C_5 alkyl (especially methyl, ethyl or propyl) or C_7-C_{13} aralkyl (especially benzyl)). Especially preferred are cases where the fused ring is non-substituted and the cases where R^5(s) is(are) fluorine, chlorine, bromine, iodine, nitro, methyl, ethyl, propyl, benzyl, hydroxy, methoxy, trifluoromethyl, trifluoromethoxy, cyano, phenyl, hydroxymethyl, hydroxyethyl, isothiocyanato, mercapto, methylthio, methylsulfinyl, methylsulfonyl, methoxymethyl, ethoxymethyl, methoxyethyl, acetoxy, phenyloxy, methoxycarbonyl, ethoxycarbonyl, methoxycarbonylmethyl, ethoxycarbonylmethyl, sulfamoyl, dimethylsulfamoyl, dimethylcarbamoyl, dimethylamino, dimethylaminomethyl, dimethylaminoethyl or amino.

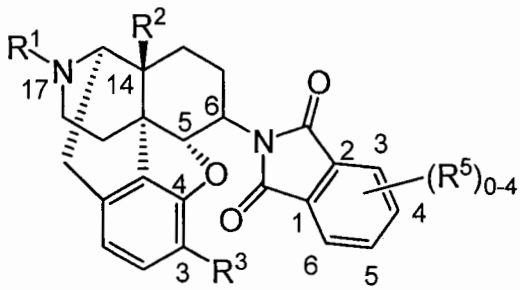
R^9 is preferably hydrogen, C_1-C_5 alkyl, allyl or benzyl, and more preferably hydrogen or methyl.

As for R^{10} and R^{11}, preferred are the cases where R^{10} and R^{11} are bound to form -O-, or R^{10} is hydrogen and R^{11} is hydrogen, hydroxy or methoxy, and the cases where R^{10} and R^{11} are bound to form -O- are especially preferred.

Preferred examples of the pharmaceutically acceptable acid addition salts include inorganic acid salts such as hydrochloric acid salt, sulfuric acid salt, nitric acid salt, hydrobromic acid salt, hydroiodic acid salt and phosphoric acid salt; organic carboxylic acid salts such as acetic acid salt, lactic acid salt, citric acid salt, oxalic acid salt, glutaric acid salt, malic acid salt, tartaric acid salt, fumaric acid salt, mandelic acid salt, maleic acid salt, benzoic acid salt and phthalic acid salt; and organic sulfonic acid salts such as methanesulfonic acid salt, ethanesulfonic acid salt, benzenesulfonic acid salt, p-toluenesulfonic acid salt and camphorsulfonic acid salt. Among these, hydrochloric acid salt, hydrobromic acid salt, phosphoric acid salt,

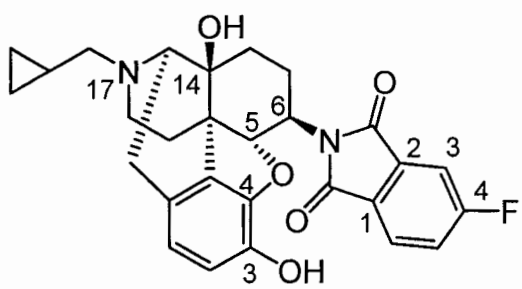
tartaric acid salt, methanesulfonic acid salt and the like are preferred, but the acid addition salt is not restricted thereto.

Among the compounds of the Formula (I) according to the present invention, specific examples of those wherein -X- is a carbon chain having two carbon atoms constituting a part of the ring structure; Y and Z are -C(=O)-; two R^4s form benzene fused ring which is not substituted or substituted by one or more R^5s; R^9 is hydrogen; R^{10} and R^{11} are bound to represent -O-, that is, those represented by the Formula (Ia) below are shown in Table 1. In the tables described below, CPM means cyclopropylmethyl, and the bond at 6-position is α or β.



(Ia)

Among the compounds represented by Formula (Ia), the compound wherein R^1 is cyclopropylmethyl, R^2 and R^3 are hydroxy, R^5 is 4-fluoro, and the configuration of the bond at the 6-position is β, that is, the compound of the following formula:



is named *N*-[17-(cyclopropylmethyl)-4,5α-epoxy-3,14-dihydroxymorphinan-6β-yl]-4-fluorophthalimide.

Table 1

R^1	R^2	R^3	R^5
CPM	OH	OH	(non-substituted)
CPM	OH	OH	3-F
CPM	OH	OH	4-F
CPM	OH	OH	3,6-F
CPM	OH	OH	4,5-F
CPM	OH	OH	3,4,5,6-F
CPM	OH	OH	3-Cl
CPM	OH	OH	4-Cl
CPM	OH	OH	3,6-Cl
CPM	OH	OH	4,5-Cl
CPM	OH	OH	3-Br
CPM	OH	OH	4-Br
CPM	OH	OH	3,6-Br
CPM	OH	OH	4,5-Br
CPM	OH	OH	3-Me
CPM	OH	OH	4-Me
CPM	OH	OH	3,6-Me
CPM	OH	OH	4,5-Me
CPM	OH	OH	3-OMe
CPM	OH	OH	4-OMe
CPM	OH	OH	3,6-OMe
CPM	OH	OH	4,5-OMe
CPM	OH	OH	3-OH
CPM	OH	OH	4-OH
CPM	OH	OH	3,6-OH
CPM	OH	OH	4,5-OH
CPM	OH	OH	3-NO_2
CPM	OH	OH	4-NO_2
CPM	OH	OH	3,6-NO_2
CPM	OH	OH	4,5-NO_2
CPM	OH	OH	3-NH_2
CPM	OH	OH	4-NH_2
CPM	OH	OH	3,6-NH_2
CPM	OH	OH	4,5-NH_2
allyl	OH	OH	(non-substituted)
allyl	OH	OH	3-F
allyl	OH	OH	4-F
allyl	OH	OH	3,6-F
allyl	OH	OH	4,5-F
allyl	OH	OH	3,4,5,6-F
allyl	OH	OH	3-Cl
allyl	OH	OH	4-Cl
allyl	OH	OH	3,6-Cl
allyl	OH	OH	4,5-Cl
allyl	OH	OH	3-Br

Table 1 (continued)

R^1	R^2	R^3	R^5
allyl	OH	OH	4-Br
allyl	OH	OH	3,6-Br
allyl	OH	OH	4,5-Br
allyl	OH	OH	3-Me
allyl	OH	OH	4-Me
allyl	OH	OH	3,6-Me
allyl	OH	OH	4,5-Me
allyl	OH	OH	3-OMe
allyl	OH	OH	4-OMe
allyl	OH	OH	3,6-OMe
allyl	OH	OH	4,5-OMe
allyl	OH	OH	3-OH
allyl	OH	OH	4-OH
allyl	OH	OH	3,6-OH
allyl	OH	OH	4,5-OH
allyl	OH	OH	3-NO_2
allyl	OH	OH	4-NO_2
allyl	OH	OH	3,6-NO_2
allyl	OH	OH	4,5-NO_2
allyl	OH	OH	3-NH_2
allyl	OH	OH	4-NH_2
allyl	OH	OH	3,6-NH_2
allyl	OH	OH	4,5-NH_2
CPM	H	OH	(non-substituted)
CPM	H	OH	3-F
CPM	H	OH	4-F
CPM	H	OH	3,6-F
CPM	H	OH	4,5-F
CPM	H	OH	3,4,5,6-F
CPM	H	OH	3-Cl
CPM	H	OH	4-Cl
CPM	H	OH	3,6-Cl
CPM	H	OH	4,5-Cl
CPM	H	OH	3-Br
CPM	H	OH	4-Br
CPM	H	OH	3,6-Br
CPM	H	OH	4,5-Br
CPM	H	OH	3-Me
CPM	H	OH	4-Me
CPM	H	OH	3,6-Me
CPM	H	OH	4,5-Me
CPM	H	OH	3-OMe
CPM	H	OH	4-OMe
CPM	H	OH	3,6-OMe

Table 1 (continued)

R^1	R^2	R^3	R^5
CPM	H	OH	4,5-OMe
CPM	H	OH	3-OH
CPM	H	OH	4-OH
CPM	H	OH	3,6-OH
CPM	H	OH	4,5-OH
CPM	H	OH	3-NO_2
CPM	H	OH	4-NO_2
CPM	H	OH	3,6-NO_2
CPM	H	OH	4,5-NO_2
CPM	H	OH	3-NH_2
CPM	H	OH	4-NH_2
CPM	H	OH	3,6-NH_2
CPM	H	OH	4,5-NH_2
allyl	H	OH	(non-substituted)
allyl	H	OH	3-F
allyl	H	OH	4-F
allyl	H	OH	3,6-F
allyl	H	OH	4,5-F
allyl	H	OH	3,4,5,6-F
allyl	H	OH	3-Cl
allyl	H	OH	4-Cl
allyl	H	OH	3,6-Cl
allyl	H	OH	4,5-Cl
allyl	H	OH	3-Br
allyl	H	OH	4-Br
allyl	H	OH	3,6-Br
allyl	H	OH	4,5-Br
allyl	H	OH	3-Me
allyl	H	OH	4-Me
allyl	H	OH	3,6-Me
allyl	H	OH	4,5-Me
allyl	H	OH	3-OMe
allyl	H	OH	4-OMe
allyl	H	OH	3,6-OMe
allyl	H	OH	4,5-OMe
allyl	H	OH	3-OH
allyl	H	OH	4-OH
allyl	H	OH	3,6-OH
allyl	H	OH	4,5-OH
allyl	H	OH	3-NO_2
allyl	H	OH	4-NO_2
allyl	H	OH	3,6-NO_2
allyl	H	OH	4,5-NO_2
allyl	H	OH	3-NH_2

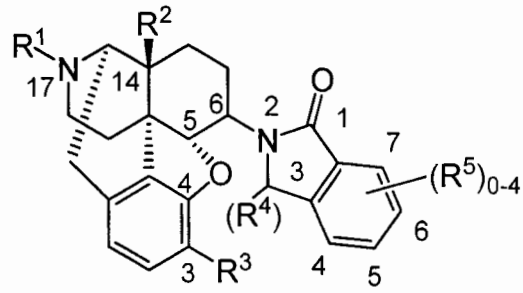
Table 1 (continued)

R^1	R^2	R^3	R^5
allyl	H	OH	4-NH_2
allyl	H	OH	3,6-NH_2
allyl	H	OH	4,5-NH_2
CPM	OAc	OH	(non-substituted)
CPM	OAc	OH	3-F
CPM	OAc	OH	4-F
CPM	OAc	OH	3,6-F
CPM	OAc	OH	4,5-F
CPM	OAc	OH	3,4,5,6-F
CPM	OAc	OH	3-Cl
CPM	OAc	OH	4-Cl
CPM	OAc	OH	3,6-Cl
CPM	OAc	OH	4,5-Cl
CPM	OAc	OH	3-Br
CPM	OAc	OH	4-Br
CPM	OAc	OH	3,6-Br
CPM	OAc	OH	4,5-Br
CPM	OAc	OH	3-Me
CPM	OAc	OH	4-Me
CPM	OAc	OH	3,6-Me
CPM	OAc	OH	4,5-Me
CPM	OAc	OH	3-OMe
CPM	OAc	OH	4-OMe
CPM	OAc	OH	3,6-OMe
CPM	OAc	OH	4,5-OMe
CPM	OAc	OH	3-OH
CPM	OAc	OH	4-OH
CPM	OAc	OH	3,6-OH
CPM	OAc	OH	4,5-OH
CPM	OAc	OH	3-NO_2
CPM	OAc	OH	4-NO_2
CPM	OAc	OH	3,6-NO_2
CPM	OAc	OH	4,5-NO_2
CPM	OAc	OH	3-NH_2
CPM	OAc	OH	4-NH_2
CPM	OAc	OH	3,6-NH_2
CPM	OAc	OH	4,5-NH_2
allyl	OAc	OH	(non-substituted)
allyl	OAc	OH	3-F
allyl	OAc	OH	4-F
allyl	OAc	OH	3,6-F
allyl	OAc	OH	4,5-F
allyl	OAc	OH	3,4,5,6-F
allyl	OAc	OH	3-Cl

Table 1 (continued)

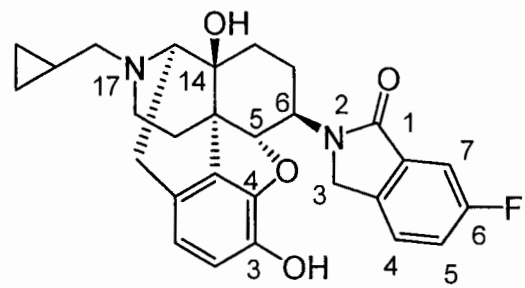
R^1	R^2	R^3	R^5
allyl	OAc	OH	4-Cl
allyl	OAc	OH	3,6-Cl
allyl	OAc	OH	4,5-Cl
allyl	OAc	OH	3-Br
allyl	OAc	OH	4-Br
allyl	OAc	OH	3,6-Br
allyl	OAc	OH	4,5-Br
allyl	OAc	OH	3-Me
allyl	OAc	OH	4-Me
allyl	OAc	OH	3,6-Me
allyl	OAc	OH	4,5-Me
allyl	OAc	OH	3-OMe
allyl	OAc	OH	4-OMe
allyl	OAc	OH	3,6-OMe
allyl	OAc	OH	4,5-OMe
allyl	OAc	OH	3-OH
allyl	OAc	OH	4-OH
allyl	OAc	OH	3,6-OH
allyl	OAc	OH	4,5-OH
allyl	OAc	OH	3-NO_2
allyl	OAc	OH	4-NO_2
allyl	OAc	OH	3,6-NO_2
allyl	OAc	OH	4,5-NO_2
allyl	OAc	OH	3-NH_2
allyl	OAc	OH	4-NH_2
allyl	OAc	OH	3,6-NH_2
allyl	OAc	OH	4,5-NH_2

Among the compounds of the Formula (I) used in the present invention, specific examples of those wherein -X- is a carbon chain having three carbon atoms constituting a part of the ring structure; Y is -C(=O)- and Z is valence bond; two R^4s form benzene fused ring which is not substituted or substituted by one or more R^5s; R^9 is hydrogen; R^{10} and R^{11} are bound to represent -O-, that is, those represented by the Formula (Ib) below are shown in Table 2.



(Ib)

Among the compounds represented by Formula (Ib), the compound wherein R^1 is cyclopropylmethyl, R^2 and R^3 are hydroxy, R^5 is 6-fluoro, and the configuration of the bond at the 6-position is β, that is, the compound of the following formula:



is named 2-[17-(cyclopropylmethyl)-4,5α-epoxy-3,14-dihydroxymorphinan-6β-yl]-6-fluoro-2,3-dihydro-isoindol-1-one.

Table 2

R^1	R^2	R^3	R^4	R^5
CPM	OH	OH	-	(non-substituted)
CPM	OH	OH	-	4-F
CPM	OH	OH	-	5-F
CPM	OH	OH	-	6-F
CPM	OH	OH	-	7-F
CPM	OH	OH	-	5,6-F
CPM	OH	OH	-	4,5,6,7-F
CPM	OH	OH	-	4-Cl
CPM	OH	OH	-	5-Cl
CPM	OH	OH	-	6-Cl
CPM	OH	OH	-	7-Cl
CPM	OH	OH	-	5,6-Cl
CPM	OH	OH	-	4-Me
CPM	OH	OH	-	5-Me
CPM	OH	OH	-	6-Me
CPM	OH	OH	-	7-Me
CPM	OH	OH	-	5,6-Me
CPM	OH	OH	-	4-OMe
CPM	OH	OH	-	5-OMe
CPM	OH	OH	-	6-OMe
CPM	OH	OH	-	7-OMe
CPM	OH	OH	-	5,6-OMe
allyl	OH	OH	-	(non-substituted)
allyl	OH	OH	-	4-F
allyl	OH	OH	-	5-F
allyl	OH	OH	-	6-F
allyl	OH	OH	-	7-F
allyl	OH	OH	-	5,6-F
allyl	OH	OH	-	4,5,6,7-F
allyl	OH	OH	-	4-Cl
allyl	OH	OH	-	5-Cl
allyl	OH	OH	-	6-Cl
allyl	OH	OH	-	7-Cl
allyl	OH	OH	-	5,6-Cl
allyl	OH	OH	-	4-Me
allyl	OH	OH	-	5-Me
allyl	OH	OH	-	6-Me
allyl	OH	OH	-	7-Me
allyl	OH	OH	-	5,6-Me
allyl	OH	OH	-	4-OMe
allyl	OH	OH	-	5-OMe
allyl	OH	OH	-	6-OMe
allyl	OH	OH	-	7-OMe
allyl	OH	OH	-	5,6-OMe

Table 2 (continued)

R^1	R^2	R^3	R^4	R^5
CPM	H	OH	-	(non-substituted)
CPM	H	OH	-	4-F
CPM	H	OH	-	5-F
CPM	H	OH	-	6-F
CPM	H	OH	-	7-F
CPM	H	OH	-	5,6-F
CPM	H	OH	-	4,5,6,7-F
CPM	H	OH	-	4-Cl
CPM	H	OH	-	5-Cl
CPM	H	OH	-	6-Cl
CPM	H	OH	-	7-Cl
CPM	H	OH	-	5,6-Cl
CPM	H	OH	-	4-Me
CPM	H	OH	-	5-Me
CPM	H	OH	-	6-Me
CPM	H	OH	-	7-Me
CPM	H	OH	-	5,6-Me
CPM	H	OH	-	4-OMe
CPM	H	OH	-	5-OMe
CPM	H	OH	-	6-OMe
CPM	H	OH	-	7-OMe
CPM	H	OH	-	5,6-OMe
allyl	H	OH	-	(non-substituted)
allyl	H	OH	-	4-F
allyl	H	OH	-	5-F
allyl	H	OH	-	6-F
allyl	H	OH	-	7-F
allyl	H	OH	-	5,6-F
allyl	H	OH	-	4,5,6,7-F
allyl	H	OH	-	4-Cl
allyl	H	OH	-	5-Cl
allyl	H	OH	-	6-Cl
allyl	H	OH	-	7-Cl
allyl	H	OH	-	5,6-Cl
allyl	H	OH	-	4-Me
allyl	H	OH	-	5-Me
allyl	H	OH	-	6-Me
allyl	H	OH	-	7-Me
allyl	H	OH	-	5,6-Me
allyl	H	OH	-	4-OMe
allyl	H	OH	-	5-OMe
allyl	H	OH	-	6-OMe
allyl	H	OH	-	7-OMe
allyl	H	OH	-	5,6-OMe

Table 2 (continued)

R^1	R^2	R^3	R^4	R^5
CPM	OH	OH	OH	(non-substituted)
CPM	OH	OH	OH	4-F
CPM	OH	OH	OH	5-F
CPM	OH	OH	OH	6-F
CPM	OH	OH	OH	7-F
CPM	OH	OH	OH	5,6-F
CPM	OH	OH	OH	4,5,6,7-F
CPM	OH	OH	OH	4-Cl
CPM	OH	OH	OH	5-Cl
CPM	OH	OH	OH	6-Cl
CPM	OH	OH	OH	7-Cl
CPM	OH	OH	OH	5,6-Cl
CPM	OH	OH	OH	4-Me
CPM	OH	OH	OH	5-Me
CPM	OH	OH	OH	6-Me
CPM	OH	OH	OH	7-Me
CPM	OH	OH	OH	5,6-Me
CPM	OH	OH	OH	4-OMe
CPM	OH	OH	OH	5-OMe
CPM	OH	OH	OH	6-OMe
CPM	OH	OH	OH	7-OMe
CPM	OH	OH	OH	5,6-OMe
allyl	OH	OH	OH	(non-substituted)
allyl	OH	OH	OH	4-F
allyl	OH	OH	OH	5-F
allyl	OH	OH	OH	6-F
allyl	OH	OH	OH	7-F
allyl	OH	OH	OH	5,6-F
allyl	OH	OH	OH	4,5,6,7-F
allyl	OH	OH	OH	4-Cl
allyl	OH	OH	OH	5-Cl
allyl	OH	OH	OH	6-Cl
allyl	OH	OH	OH	7-Cl
allyl	OH	OH	OH	5,6-Cl
allyl	OH	OH	OH	4-Me
allyl	OH	OH	OH	5-Me
allyl	OH	OH	OH	6-Me
allyl	OH	OH	OH	7-Me
allyl	OH	OH	OH	5,6-Me
allyl	OH	OH	OH	4-OMe
allyl	OH	OH	OH	5-OMe
allyl	OH	OH	OH	6-OMe
allyl	OH	OH	OH	7-OMe
allyl	OH	OH	OH	5,6-OMe

Table 2 (continued)

R^1	R^2	R^3	R^4	R^5
CPM	H	OH	OH	(non-substituted)
CPM	H	OH	OH	4-F
CPM	H	OH	OH	5-F
CPM	H	OH	OH	6-F
CPM	H	OH	OH	7-F
CPM	H	OH	OH	5,6-F
CPM	H	OH	OH	4,5,6,7-F
CPM	H	OH	OH	4-Cl
CPM	H	OH	OH	5-Cl
CPM	H	OH	OH	6-Cl
CPM	H	OH	OH	7-Cl
CPM	H	OH	OH	5,6-Cl
CPM	H	OH	OH	4-Me
CPM	H	OH	OH	5-Me
CPM	H	OH	OH	6-Me
CPM	H	OH	OH	7-Me
CPM	H	OH	OH	5,6-Me
CPM	H	OH	OH	4-OMe
CPM	H	OH	OH	5-OMe
CPM	H	OH	OH	6-OMe
CPM	H	OH	OH	7-OMe
CPM	H	OH	OH	5,6-OMe
allyl	H	OH	OH	(non-substituted)
allyl	H	OH	OH	4-F
allyl	H	OH	OH	5-F
allyl	H	OH	OH	6-F
allyl	H	OH	OH	7-F
allyl	H	OH	OH	5,6-F
allyl	H	OH	OH	4,5,6,7-F
allyl	H	OH	OH	4-Cl
allyl	H	OH	OH	5-Cl
allyl	H	OH	OH	6-Cl
allyl	H	OH	OH	7-Cl
allyl	H	OH	OH	5,6-Cl
allyl	H	OH	OH	4-Me
allyl	H	OH	OH	5-Me
allyl	H	OH	OH	6-Me
allyl	H	OH	OH	7-Me
allyl	H	OH	OH	5,6-Me
allyl	H	OH	OH	4-OMe
allyl	H	OH	OH	5-OMe
allyl	H	OH	OH	6-OMe
allyl	H	OH	OH	7-OMe
allyl	H	OH	OH	5,6-OMe

Table 2 (continued)

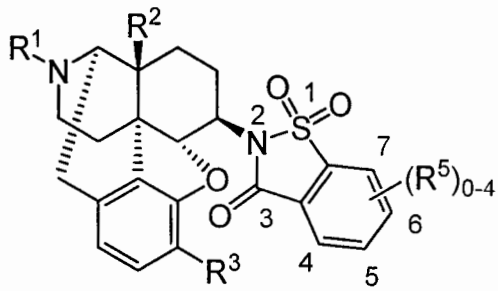
R^1	R^2	R^3	R^4	R^5
CPM	OH	OH	CH_2COOMe	(non-substituted)
CPM	OH	OH	CH_2COOMe	4-F
CPM	OH	OH	CH_2COOMe	5-F
CPM	OH	OH	CH_2COOMe	6-F
CPM	OH	OH	CH_2COOMe	7-F
CPM	OH	OH	CH_2COOMe	5,6-F
CPM	OH	OH	CH_2COOMe	4,5,6,7-F
CPM	OH	OH	CH_2COOMe	4-Cl
CPM	OH	OH	CH_2COOMe	5-Cl
CPM	OH	OH	CH_2COOMe	6-Cl
CPM	OH	OH	CH_2COOMe	7-Cl
CPM	OH	OH	CH_2COOMe	5,6-Cl
CPM	OH	OH	CH_2COOMe	4-Me
CPM	OH	OH	CH_2COOMe	5-Me
CPM	OH	OH	CH_2COOMe	6-Me
CPM	OH	OH	CH_2COOMe	7-Me
CPM	OH	OH	CH_2COOMe	5,6-Me
CPM	OH	OH	CH_2COOMe	4-OMe
CPM	OH	OH	CH_2COOMe	5-OMe
CPM	OH	OH	CH_2COOMe	6-OMe
CPM	OH	OH	CH_2COOMe	7-OMe
CPM	OH	OH	CH_2COOMe	5,6-OMe
allyl	OH	OH	CH_2COOMe	(non-substituted)
allyl	OH	OH	CH_2COOMe	4-F
allyl	OH	OH	CH_2COOMe	5-F
allyl	OH	OH	CH_2COOMe	6-F
allyl	OH	OH	CH_2COOMe	7-F
allyl	OH	OH	CH_2COOMe	5,6-F
allyl	OH	OH	CH_2COOMe	4,5,6,7-F
allyl	OH	OH	CH_2COOMe	4-Cl
allyl	OH	OH	CH_2COOMe	5-Cl
allyl	OH	OH	CH_2COOMe	6-Cl
allyl	OH	OH	CH_2COOMe	7-Cl
allyl	OH	OH	CH_2COOMe	5,6-Cl
allyl	OH	OH	CH_2COOMe	4-Me
allyl	OH	OH	CH_2COOMe	5-Me
allyl	OH	OH	CH_2COOMe	6-Me
allyl	OH	OH	CH_2COOMe	7-Me
allyl	OH	OH	CH_2COOMe	5,6-Me
allyl	OH	OH	CH_2COOMe	4-OMe
allyl	OH	OH	CH_2COOMe	5-OMe
allyl	OH	OH	CH_2COOMe	6-OMe
allyl	OH	OH	CH_2COOMe	7-OMe
allyl	OH	OH	CH_2COOMe	5,6-OMe

Table 2 (continued)

CPM	H	OH	CH_2COOMe	(non-substituted)
CPM	H	OH	CH_2COOMe	4-F
CPM	H	OH	CH_2COOMe	5-F
CPM	H	OH	CH_2COOMe	6-F
CPM	H	OH	CH_2COOMe	7-F
CPM	H	OH	CH_2COOMe	5,6-F
CPM	H	OH	CH_2COOMe	4,5,6,7-F
CPM	H	OH	CH_2COOMe	4-Cl
CPM	H	OH	CH_2COOMe	5-Cl
CPM	H	OH	CH_2COOMe	6-Cl
CPM	H	OH	CH_2COOMe	7-Cl
CPM	H	OH	CH_2COOMe	5,6-Cl
CPM	H	OH	CH_2COOMe	4-Me
CPM	H	OH	CH_2COOMe	5-Me
CPM	H	OH	CH_2COOMe	6-Me
CPM	H	OH	CH_2COOMe	7-Me
CPM	H	OH	CH_2COOMe	5,6-Me
CPM	H	OH	CH_2COOMe	4-OMe
CPM	H	OH	CH_2COOMe	5-OMe
CPM	H	OH	CH_2COOMe	6-OMe
CPM	H	OH	CH_2COOMe	7-OMe
CPM	H	OH	CH_2COOMe	5,6-OMe
allyl	H	OH	CH_2COOMe	(non-substituted)
allyl	H	OH	CH_2COOMe	4-F
allyl	H	OH	CH_2COOMe	5-F
allyl	H	OH	CH_2COOMe	6-F
allyl	H	OH	CH_2COOMe	7-F
allyl	H	OH	CH_2COOMe	5,6-F
allyl	H	OH	CH_2COOMe	4,5,6,7-F
allyl	H	OH	CH_2COOMe	4-Cl
allyl	H	OH	CH_2COOMe	5-Cl
allyl	H	OH	CH_2COOMe	6-Cl
allyl	H	OH	CH_2COOMe	7-Cl
allyl	H	OH	CH_2COOMe	5,6-Cl
allyl	H	OH	CH_2COOMe	4-Me
allyl	H	OH	CH_2COOMe	5-Me
allyl	H	OH	CH_2COOMe	6-Me
allyl	H	OH	CH_2COOMe	7-Me
allyl	H	OH	CH_2COOMe	5,6-Me
allyl	H	OH	CH_2COOMe	4-OMe
allyl	H	OH	CH_2COOMe	5-OMe
allyl	H	OH	CH_2COOMe	6-OMe
allyl	H	OH	CH_2COOMe	7-OMe
allyl	H	OH	CH_2COOMe	5,6-OMe

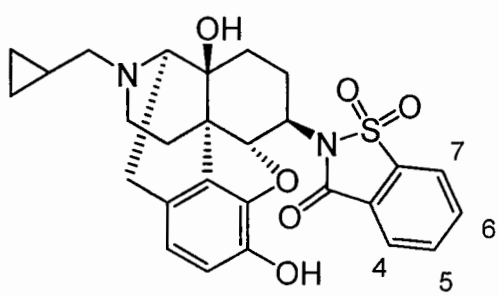
Among the compounds represented by Formula (I) used in the present invention, specific examples of the compound wherein -X- is a carbon chain having

three carbon atoms (one of the carbon atoms is replaced by sulfur atom) constituting a part of the ring structure, Y is -C(=O), Z is valence bond, four R^4s bound to the same sulfur atom cooperatively represent two oxygen atoms to form sulfone group, two R^4s cooperatively form a benzene fused ring which is non-substituted or substituted by one or more R^5s; R^9 is hydrogen, R^{10} and R^{11} are bound to form -O-, that is, the examples of the compounds represented by the following Formula (Ic) are shown in Table 3.



(1c)

Among the compounds represented by Formula (Ic), the compound wherein R^1 is cyclopropylmethyl, R^2 and R^3 are hydroxy, the benzene ring is not substituted, and the configuration of the bond at the 6-position is β, that is, the compound of the following formula:



is named N-[17-(cyclopropylmethyl)-4,5α-epoxy-3,14-dihydroxymorphinan-6β-yl]-*O*-sulfonebenzimide.

Table 3

R^1	R^2	R^3	R^5
CPM	OH	OH	(non-substituted)
CPM	OH	OH	4-F
CPM	OH	OH	5-F
CPM	OH	OH	6-F
CPM	OH	OH	7-F
CPM	OH	OH	5,6-F
CPM	OH	OH	4,5,6,7-F
CPM	OH	OH	4-Cl
CPM	OH	OH	5-Cl
CPM	OH	OH	6-Cl
CPM	OH	OH	7-Cl
CPM	OH	OH	5,6-Cl
CPM	OH	OH	4-Me
CPM	OH	OH	5-Me
CPM	OH	OH	6-Me
CPM	OH	OH	7-Me
CPM	OH	OH	5,6-Me
CPM	OH	OH	4-OMe
CPM	OH	OH	5-OMe
CPM	OH	OH	6-OMe
CPM	OH	OH	7-OMe
CPM	OH	OH	5,6-OMe
allyl	OH	OH	(non-substituted)
allyl	OH	OH	4-F
allyl	OH	OH	5-F
allyl	OH	OH	6-F
allyl	OH	OH	7-F
allyl	OH	OH	5,6-F
allyl	OH	OH	4,5,6,7-F
allyl	OH	OH	4-Cl
allyl	OH	OH	5-Cl
allyl	OH	OH	6-Cl
allyl	OH	OH	7-Cl
allyl	OH	OH	5,6-Cl
allyl	OH	OH	4-Me
allyl	OH	OH	5-Me
allyl	OH	OH	6-Me
allyl	OH	OH	7-Me
allyl	OH	OH	5,6-Me
allyl	OH	OH	4-OMe
allyl	OH	OH	5-OMe
allyl	OH	OH	6-OMe
allyl	OH	OH	7-OMe
allyl	OH	OH	5,6-OMe

Table 3 (continued)

R^1	R^2	R^3	R^5
CPM	H	OH	(non-substituted)
CPM	H	OH	4-F
CPM	H	OH	5-F
CPM	H	OH	6-F
CPM	H	OH	7-F
CPM	H	OH	5,6-F
CPM	H	OH	4,5,6,7-F
CPM	H	OH	4-Cl
CPM	H	OH	5-Cl
CPM	H	OH	6-Cl
CPM	H	OH	7-Cl
CPM	H	OH	5,6-Cl
CPM	H	OH	4-Me
CPM	H	OH	5-Me
CPM	H	OH	6-Me
CPM	H	OH	7-Me
CPM	H	OH	5,6-Me
CPM	H	OH	4-OMe
CPM	H	OH	5-OMe
CPM	H	OH	6-OMe
CPM	H	OH	7-OMe
CPM	H	OH	5,6-OMe
allyl	H	OH	(non-substituted)
allyl	H	OH	4-F
allyl	H	OH	5-F
allyl	H	OH	6-F
allyl	H	OH	7-F
allyl	H	OH	5,6-F
allyl	H	OH	4,5,6,7-F
allyl	H	OH	4-Cl
allyl	H	OH	5-Cl
allyl	H	OH	6-Cl
allyl	H	OH	7-Cl
allyl	H	OH	5,6-Cl
allyl	H	OH	4-Me
allyl	H	OH	5-Me
allyl	H	OH	6-Me
allyl	H	OH	7-Me
allyl	H	OH	5,6-Me
allyl	H	OH	4-OMe
allyl	H	OH	5-OMe
allyl	H	OH	6-OMe
allyl	H	OH	7-OMe
allyl	H	OH	5,6-OMe

Table 3 (continued)

R^1	R^2	R^3	R^5
CPM	OH	OH	(non-substituted)
CPM	OH	OH	4-F
CPM	OH	OH	5-F
CPM	OH	OH	6-F
CPM	OH	OH	7-F
CPM	OH	OH	5,6-F
CPM	OH	OH	4,5,6,7-F
CPM	OH	OH	4-Cl
CPM	OH	OH	5-Cl
CPM	OH	OH	6-Cl
CPM	OH	OH	7-Cl
CPM	OH	OH	5,6-Cl
CPM	OH	OH	4-Me
CPM	OH	OH	5-Me
CPM	OH	OH	6-Me
CPM	OH	OH	7-Me
CPM	OH	OH	5,6-Me
CPM	OH	OH	4-OMe
CPM	OH	OH	5-OMe
CPM	OH	OH	6-OMe
CPM	OH	OH	7-OMe
CPM	OH	OH	5,6-OMe
allyl	OH	OH	(non-substituted)
allyl	OH	OH	4-F
allyl	OH	OH	5-F
allyl	OH	OH	6-F
allyl	OH	OH	7-F
allyl	OH	OH	5,6-F
allyl	OH	OH	4,5,6,7-F
allyl	OH	OH	4-Cl
allyl	OH	OH	5-Cl
allyl	OH	OH	6-Cl
allyl	OH	OH	7-Cl
allyl	OH	OH	5,6-Cl
allyl	OH	OH	4-Me
allyl	OH	OH	5-Me
allyl	OH	OH	6-Me
allyl	OH	OH	7-Me
allyl	OH	OH	5,6-Me
allyl	OH	OH	4-OMe
allyl	OH	OH	5-OMe
allyl	OH	OH	6-OMe
allyl	OH	OH	7-OMe
allyl	OH	OH	5,6-OMe

Table 3 (continued)

R^1	R^2	R^3	R^5
CPM	H	OH	(non-substituted)
CPM	H	OH	4-F
CPM	H	OH	5-F
CPM	H	OH	6-F
CPM	H	OH	7-F
CPM	H	OH	5,6-F
CPM	H	OH	4,5,6,7-F
CPM	H	OH	4-Cl
CPM	H	OH	5-Cl
CPM	H	OH	6-Cl
CPM	H	OH	7-Cl
CPM	H	OH	5,6-Cl
CPM	H	OH	4-Me
CPM	H	OH	5-Me
CPM	H	OH	6-Me
CPM	H	OH	7-Me
CPM	H	OH	5,6-Me
CPM	H	OH	4-OMe
CPM	H	OH	5-OMe
CPM	H	OH	6-OMe
CPM	H	OH	7-OMe
CPM	H	OH	5,6-OMe
allyl	H	OH	(non-substituted)
allyl	H	OH	4-F
allyl	H	OH	5-F
allyl	H	OH	6-F
allyl	H	OH	7-F
allyl	H	OH	5,6-F
allyl	H	OH	4,5,6,7-F
allyl	H	OH	4-Cl
allyl	H	OH	5-Cl
allyl	H	OH	6-Cl
allyl	H	OH	7-Cl
allyl	H	OH	5,6-Cl
allyl	H	OH	4-Me
allyl	H	OH	5-Me
allyl	H	OH	6-Me
allyl	H	OH	7-Me
allyl	H	OH	5,6-Me
allyl	H	OH	4-OMe
allyl	H	OH	5-OMe
allyl	H	OH	6-OMe
allyl	H	OH	7-OMe
allyl	H	OH	5,6-OMe

Table 3 (continued)

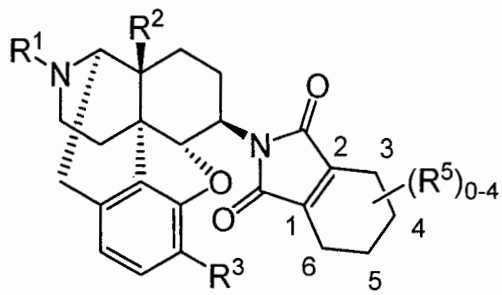
R^1	R^2	R^3	R^5
CPM	OH	OH	(non-substituted)
CPM	OH	OH	4-F
CPM	OH	OH	5-F
CPM	OH	OH	6-F
CPM	OH	OH	7-F
CPM	OH	OH	5,6-F
CPM	OH	OH	4,5,6,7-F
CPM	OH	OH	4-Cl
CPM	OH	OH	5-Cl
CPM	OH	OH	6-Cl
CPM	OH	OH	7-Cl
CPM	OH	OH	5,6-Cl
CPM	OH	OH	4-Me
CPM	OH	OH	5-Me
CPM	OH	OH	6-Me
CPM	OH	OH	7-Me
CPM	OH	OH	5,6-Me
CPM	OH	OH	4-OMe
CPM	OH	OH	5-OMe
CPM	OH	OH	6-OMe
CPM	OH	OH	7-OMe
CPM	OH	OH	5,6-OMe
allyl	OH	OH	(non-substituted)
allyl	OH	OH	4-F
allyl	OH	OH	5-F
allyl	OH	OH	6-F
allyl	OH	OH	7-F
allyl	OH	OH	5,6-F
allyl	OH	OH	4,5,6,7-F
allyl	OH	OH	4-Cl
allyl	OH	OH	5-Cl
allyl	OH	OH	6-Cl
allyl	OH	OH	7-Cl
allyl	OH	OH	5,6-Cl
allyl	OH	OH	4-Me
allyl	OH	OH	5-Me
allyl	OH	OH	6-Me
allyl	OH	OH	7-Me
allyl	OH	OH	5,6-Me
allyl	OH	OH	4-OMe
allyl	OH	OH	5-OMe
allyl	OH	OH	6-OMe
allyl	OH	OH	7-OMe
allyl	OH	OH	5,6-OMe

Table 3 (continued)

CPM	H	OH	(non-substituted)
CPM	H	OH	4-F
CPM	H	OH	5-F
CPM	H	OH	6-F
CPM	H	OH	7-F
CPM	H	OH	5,6-F
CPM	H	OH	4,5,6,7-F
CPM	H	OH	4-Cl
CPM	H	OH	5-Cl
CPM	H	OH	6-Cl
CPM	H	OH	7-Cl
CPM	H	OH	5,6-Cl
CPM	H	OH	4-Me
CPM	H	OH	5-Me
CPM	H	OH	6-Me
CPM	H	OH	7-Me
CPM	H	OH	5,6-Me
CPM	H	OH	4-OMe
CPM	H	OH	5-OMe
CPM	H	OH	6-OMe
CPM	H	OH	7-OMe
CPM	H	OH	5,6-OMe
allyl	H	OH	(non-substituted)
allyl	H	OH	4-F
allyl	H	OH	5-F
allyl	H	OH	6-F
allyl	H	OH	7-F
allyl	H	OH	5,6-F
allyl	H	OH	4,5,6,7-F
allyl	H	OH	4-Cl
allyl	H	OH	5-Cl
allyl	H	OH	6-Cl
allyl	H	OH	7-Cl
allyl	H	OH	5,6-Cl
allyl	H	OH	4-Me
allyl	H	OH	5-Me
allyl	H	OH	6-Me
allyl	H	OH	7-Me
allyl	H	OH	5,6-Me
allyl	H	OH	4-OMe
allyl	H	OH	5-OMe
allyl	H	OH	6-OMe
allyl	H	OH	7-OMe
allyl	H	OH	5,6-OMe

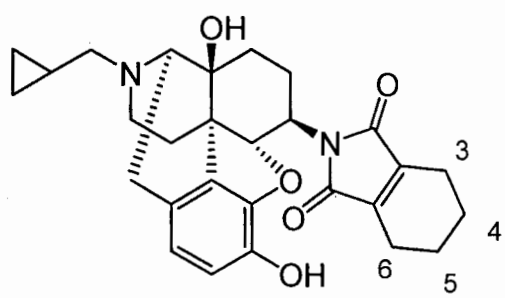
Among the compounds represented by Formula (I) according to the present invention, specific examples of the compounds wherein -X- is a carbon chain having

two carbon atoms constituting a part of the ring structure, Y and Z are -C(=O), two R^4s form cyclohexene fused ring which is not substituted or substituted by one or more R^5s, R^9 is hydrogen, R^{10} and R^{11} are bound to form -O-, that is, the examples of the compounds represented by the following Formula (Id) are shown in Table 4.



(1d)

Among the compounds represented by Formula (Id), the compound wherein R^1 is cyclopropylmethyl, R^2 and R^3 are hydroxy, the cyclohexene ring is not substituted, and the configuration of the bond at the 6-position is β, that is, the compound of the following formula:



is named N-[17-(cyclopropylmethyl)-4,5α-epoxy-3,14-dihydroxymorphinan-6β-yl]-3,4,5,6-tetrahydrophthalimide.

Table 4

R^1	R^2	R^3	R^5
CPM	OH	OH	(non-substituted)
CPM	OH	OH	3-F
CPM	OH	OH	4-F
CPM	OH	OH	3,6-F
CPM	OH	OH	4,5-F
CPM	OH	OH	3,4,5,6-F
CPM	OH	OH	3-Cl
CPM	OH	OH	4-Cl
CPM	OH	OH	3,6-Cl
CPM	OH	OH	4,5-Cl
CPM	OH	OH	3-Br
CPM	OH	OH	4-Br
CPM	OH	OH	3,6-Br
CPM	OH	OH	4,5-Br
CPM	OH	OH	3-Me
CPM	OH	OH	4-Me
CPM	OH	OH	3,6-Me
CPM	OH	OH	4,5-Me
CPM	OH	OH	3-OMe
CPM	OH	OH	4-OMe
CPM	OH	OH	3,6-OMe
CPM	OH	OH	4,5-OMe
CPM	OH	OH	3-OH
CPM	OH	OH	4-OH
CPM	OH	OH	3,6-OH
CPM	OH	OH	4,5-OH
CPM	OH	OH	3-NO_2
CPM	OH	OH	4-NO_2
CPM	OH	OH	3,6-NO_2
CPM	OH	OH	4,5-NO_2
CPM	OH	OH	3-NH_2
CPM	OH	OH	4-NH_2
CPM	OH	OH	3,6-NH_2
CPM	OH	OH	4,5-NH_2
allyl	OH	OH	(non-substituted)
allyl	OH	OH	3-F
allyl	OH	OH	4-F
allyl	OH	OH	3,6-F
allyl	OH	OH	4,5-F
allyl	OH	OH	3,4,5,6-F
allyl	OH	OH	3-Cl
allyl	OH	OH	4-Cl
allyl	OH	OH	3,6-Cl
allyl	OH	OH	4,5-Cl
allyl	OH	OH	3-Br

Table 4 (continued)

R^1	R^2	R^3	R^5
allyl	OH	OH	4-Br
allyl	OH	OH	3,6-Br
allyl	OH	OH	4,5-Br
allyl	OH	OH	3-Me
allyl	OH	OH	4-Me
allyl	OH	OH	3,6-Me
allyl	OH	OH	4,5-Me
allyl	OH	OH	3-OMe
allyl	OH	OH	4-OMe
allyl	OH	OH	3,6-OMe
allyl	OH	OH	4,5-OMe
allyl	OH	OH	3-OH
allyl	OH	OH	4-OH
allyl	OH	OH	3,6-OH
allyl	OH	OH	4,5-OH
allyl	OH	OH	3-NO_2
allyl	OH	OH	4-NO_2
allyl	OH	OH	3,6-NO_2
allyl	OH	OH	4,5-NO_2
allyl	OH	OH	3-NH_2
allyl	OH	OH	4-NH_2
allyl	OH	OH	3,6-NH_2
allyl	OH	OH	4,5-NH_2
CPM	H	OH	(non-substituted)
CPM	H	OH	3-F
CPM	H	OH	4-F
CPM	H	OH	3,6-F
CPM	H	OH	4,5-F
CPM	H	OH	3,4,5,6-F
CPM	H	OH	3-Cl
CPM	H	OH	4-Cl
CPM	H	OH	3,6-Cl
CPM	H	OH	4,5-Cl
CPM	H	OH	3-Br
CPM	H	OH	4-Br
CPM	H	OH	3,6-Br
CPM	H	OH	4,5-Br
CPM	H	OH	3-Me
CPM	H	OH	4-Me
CPM	H	OH	3,6-Me
CPM	H	OH	4,5-Me
CPM	H	OH	3-OMe
CPM	H	OH	4-OMe
CPM	H	OH	3,6-OMe

Table 4 (continued)

R^1	R^2	R^3	R^5
CPM	H	OH	4,5-OMe
CPM	H	OH	3-OH
CPM	H	OH	4-OH
CPM	H	OH	3,6-OH
CPM	H	OH	4,5-OH
CPM	H	OH	3-NO_2
CPM	H	OH	4-NO_2
CPM	H	OH	3,6-NO_2
CPM	H	OH	4,5-NO_2
CPM	H	OH	3-NH_2
CPM	H	OH	4-NH_2
CPM	H	OH	3,6-NH_2
CPM	H	OH	4,5-NH_2
allyl	H	OH	(non-substituted)
allyl	H	OH	3-F
allyl	H	OH	4-F
allyl	H	OH	3,6-F
allyl	H	OH	4,5-F
allyl	H	OH	3,4,5,6-F
allyl	H	OH	3-Cl
allyl	H	OH	4-Cl
allyl	H	OH	3,6-Cl
allyl	H	OH	4,5-Cl
allyl	H	OH	3-Br
allyl	H	OH	4-Br
allyl	H	OH	3,6-Br
allyl	H	OH	4,5-Br
allyl	H	OH	3-Me
allyl	H	OH	4-Me
allyl	H	OH	3,6-Me
allyl	H	OH	4,5-Me
allyl	H	OH	3-OMe
allyl	H	OH	4-OMe
allyl	H	OH	3,6-OMe
allyl	H	OH	4,5-OMe
allyl	H	OH	3-OH
allyl	H	OH	4-OH
allyl	H	OH	3,6-OH
allyl	H	OH	4,5-OH
allyl	H	OH	3-NO_2
allyl	H	OH	4-NO_2
allyl	H	OH	3,6-NO_2
allyl	H	OH	4,5-NO_2
allyl	H	OH	3-NH_2

Table 4 (continued)

R^1	R^2	R^3	R^5
allyl	H	OH	4-NH_2
allyl	H	OH	3,6-NH_2
allyl	H	OH	4,5-NH_2
CPM	OAc	OH	(non-substituted)
CPM	OAc	OH	3-F
CPM	OAc	OH	4-F
CPM	OAc	OH	3,6-F
CPM	OAc	OH	4,5-F
CPM	OAc	OH	3,4,5,6-F
CPM	OAc	OH	3-Cl
CPM	OAc	OH	4-Cl
CPM	OAc	OH	3,6-Cl
CPM	OAc	OH	4,5-Cl
CPM	OAc	OH	3-Br
CPM	OAc	OH	4-Br
CPM	OAc	OH	3,6-Br
CPM	OAc	OH	4,5-Br
CPM	OAc	OH	3-Me
CPM	OAc	OH	4-Me
CPM	OAc	OH	3,6-Me
CPM	OAc	OH	4,5-Me
CPM	OAc	OH	3-OMe
CPM	OAc	OH	4-OMe
CPM	OAc	OH	3,6-OMe
CPM	OAc	OH	4,5-OMe
CPM	OAc	OH	3-OH
CPM	OAc	OH	4-OH
CPM	OAc	OH	3,6-OH
CPM	OAc	OH	4,5-OH
CPM	OAc	OH	3-NO_2
CPM	OAc	OH	4-NO_2
CPM	OAc	OH	3,6-NO_2
CPM	OAc	OH	4,5-NO_2
CPM	OAc	OH	3-NH_2
CPM	OAc	OH	4-NH_2
CPM	OAc	OH	3,6-NH_2
CPM	OAc	OH	4,5-NH_2
allyl	OAc	OH	(non-substituted)
allyl	OAc	OH	3-F
allyl	OAc	OH	4-F
allyl	OAc	OH	3,6-F
allyl	OAc	OH	4,5-F
allyl	OAc	OH	3,4,5,6-F
allyl	OAc	OH	3-Cl

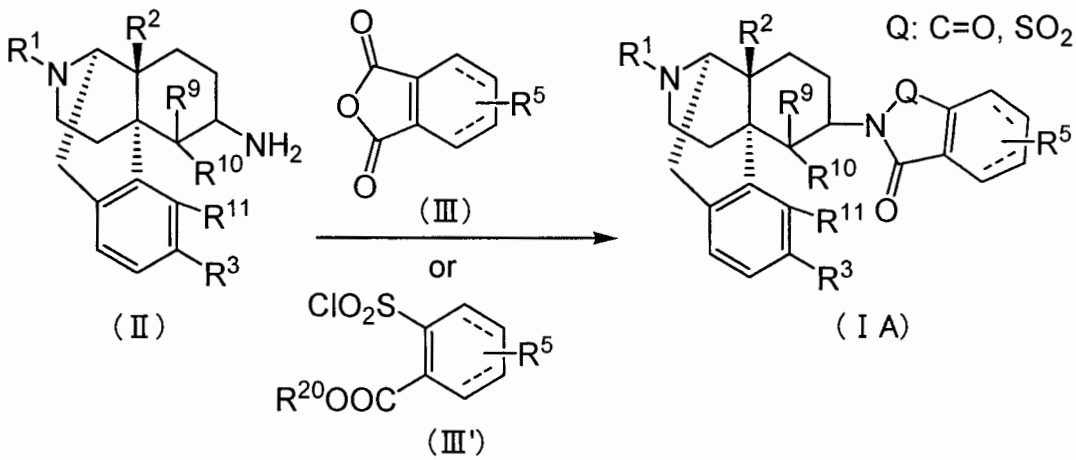
Table 4 (continued)

R^1	R^2	R^3	R^5
allyl	OAc	OH	4-Cl
allyl	OAc	OH	3,6-Cl
allyl	OAc	OH	4,5-Cl
allyl	OAc	OH	3-Br
allyl	OAc	OH	4-Br
allyl	OAc	OH	3,6-Br
allyl	OAc	OH	4,5-Br
allyl	OAc	OH	3-Me
allyl	OAc	OH	4-Me
allyl	OAc	OH	3,6-Me
allyl	OAc	OH	4,5-Me
allyl	OAc	OH	3-OMe
allyl	OAc	OH	4-OMe
allyl	OAc	OH	3,6-OMe
allyl	OAc	OH	4,5-OMe
allyl	OAc	OH	3-OH
allyl	OAc	OH	4-OH
allyl	OAc	OH	3,6-OH
allyl	OAc	OH	4,5-OH
allyl	OAc	OH	3-NO_2
allyl	OAc	OH	4-NO_2
allyl	OAc	OH	3,6-NO_2
allyl	OAc	OH	4,5-NO_2
allyl	OAc	OH	3-NH_2
allyl	OAc	OH	4-NH_2
allyl	OAc	OH	3,6-NH_2
allyl	OAc	OH	4,5-NH_2

The morphinan derivatives represented by the above-described Formula (I), having a nitrogen-containing cyclic group used as the effective ingredient of the antipruritic according to the present invention may be produced by the methods hereinbelow described.

Among the compounds represented by the Formula (I) according to the present invention, the cyclic imide and sulfoneimide derivatives represented by Formula (IA) (wherein R^1, R^2, R^3, R^5, R^9, R^{10} and R^{11} represent the same meanings as described above, and the broken lines represent single bond or aromatic fused ring) may be produced by reacting a primary amine represented by Formula (II) (wherein R^1, R^2, R^3, R^9, R^{10} and R^{11} represent the same meanings as described

above) and an acid anhydride represented by Formula (III) (wherein R^5 represents the same meanings as described above) or a sulfonic acid derivative represented by Formula (III') (wherein R^{20} represents C_1-C_5 alkyl, and R^5 represents the same meaning as described above), as shown in Scheme 1. As required, the reaction may be carried out in the presence of an acid or a base.



The acid anhydride (III) or the sulfonic acid derivative (III') may be used in an amount of 0.5 to 50 equivalents, preferably 1 to 20 equivalents, with respect to the primary amine (II. When R^3 is hydroxy, the hydroxy group may be protected by an appropriate protective group such as methoxymethyl), and especially, good results are obtained when they are used in an amount of 1 to 10 equivalents. As the solvent, aprotic polar solvents such as DMF, dimethylacetamide and DMSO; ether solvents such as diethylether, THF, DME and dioxane; hydrocarbon solvents such as benzene, toluene and xylene; halogen-containing solvents such as dichloromethane, chloroform and 1,2-dichloroethane; alcohols such as methanol, ethanol, propanol and butanol; and acid solvents such as acetic acid and propionic acid may be employed. Among these, DMF, toluene, acetic acid and chloroform are preferred.

As the base to be made to coexist as required, inorganic bases such as sodium carbonate, potassium carbonate, cesium carbonate and sodium acetate; and organic bases such as triethylamine, diisopropylethylamine, pyridine and 4-dimethylaminopyridine may be used. Among these, triethylamine, pyridine,

potassium carbonate and sodium carbonate are preferred. The base is used in amount of 1 to 30 equivalents, preferably 1 to 10 equivalents with respect to the substrate. On the other hand, as the acid, inorganic acids such as hydrochloric acid, sulfuric acid and phosphoric acid; carboxylic acids such as acetic acid, propionic acid and benzoic acid; and sulfonic acids such as methanesulfonic acid, benzenesulfonic acids and *p*-toluenesulfonic acid may be used. Among these, carboxylic acids such as acetic acid, propionic acid and benzoic acid are preferred, and acetic acid is especially preferred. The acid is used in amount of 1 to 30 equivalents, preferably 1 to 10 equivalents with respect to the substrate. A process in which acetic acid or the like is used as the solvent is also preferred. In this case, excessive acid coexists.

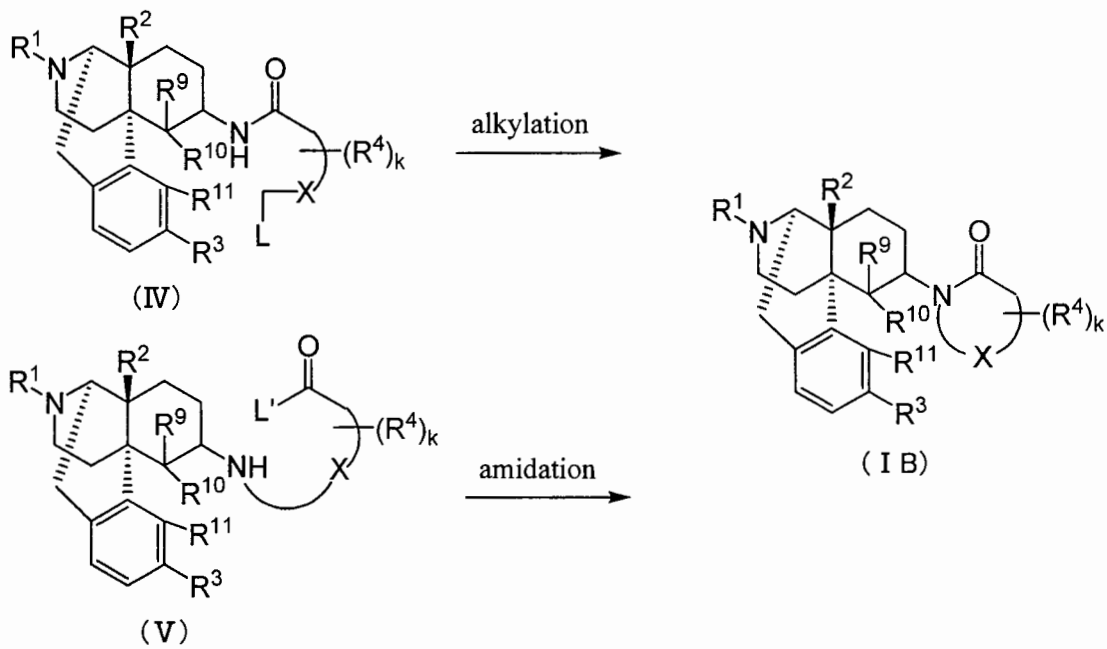
The reaction may usually be carried out at -20°C to 200°C and preferably at 0°C to 150°C at which satisfactory results are obtained. The reaction time may appropriately be selected depending on the conditions such as reaction temperature, satisfactory results are usually obtained when the reaction time is about 30 minutes to 30 hours. The concentration of the substrate (II) in the reaction system is not restricted, and usually about 1 mmol/L to 1 mol/L is preferred.

The primary amine represented by Formula (II) used as the starting material of Scheme 1 may be synthesized by the method described in, for example, J. Med. Chem. 20, 1100 (1977)、J.Org.Chem. 45, 3366 (1980).

Among the compounds represented by Formula (IA) (wherein R^1, R^2, R^3, R^5, R^9, R^{10} and R^{11} represent the same meanings as described above), the imide derivatives may also be produced by Mitsunobu reaction described in Tetrahedron. 50, 9757 (1994).

Among the compounds represented by Formula (I), the cyclic amide compounds (IB) (wherein R^1, R^2, R^3, R^4, R^9, R^{10}, R^{11}, k and X represent the same meanings as described above) wherein Y is -C(=O)- and Z is valence bond may be produced by the usual alkylation reaction of amide group or amidation reaction of

amino group so as to attain intramolecular cyclization, from the compound represented by Formula (IV) (wherein R^1, R^2, R^3, R^4, R^9, R^{10}, R^{11}, k and X represent the same meanings as described above, L is chlorine, bromine, iodine, OTs or OMs) or the compound represented by Formula (V) (wherein R^1, R^2, R^3, R^4, R^9, R^{10}, R^{11}, k and X represent the same meanings as described above, L' is chlorine or OR^{12} (wherein R^{12} is hydrogen, C_1-C_5 alkoxy, C_7-C_{13} aralkyloxy or C_1-C_5 alkanoyloxy), as shown by Scheme 2 below. The compounds represented by Formula (IV) or (V) used as the starting materials of the reaction shown in Scheme 2 may be obtained by the method described in WO93/15081 and so on.



Scheme 2

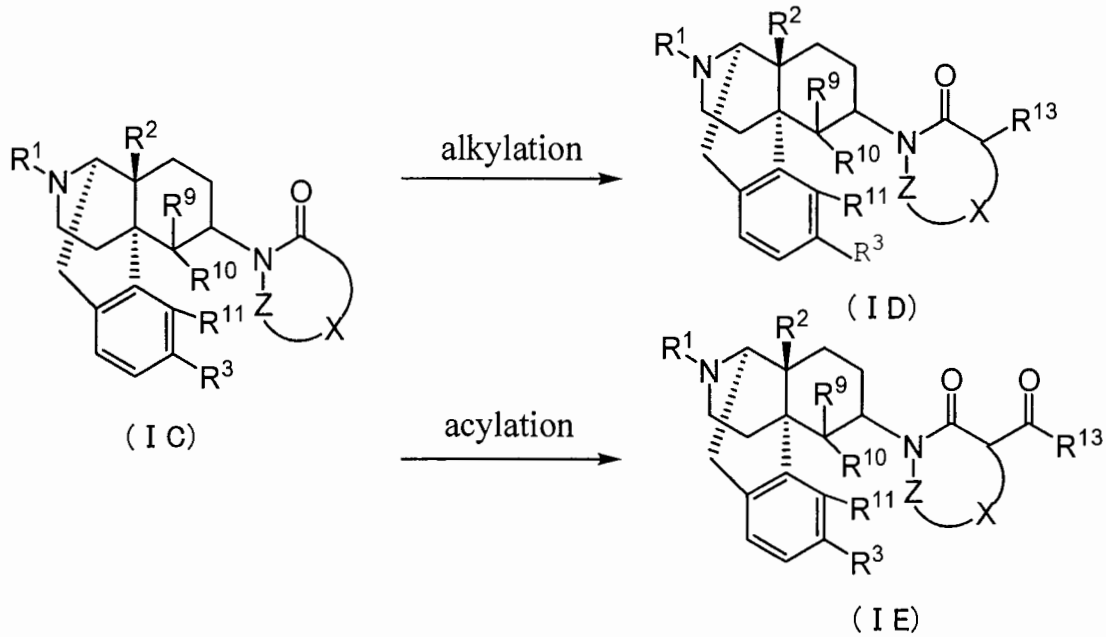
The alkylation or amidation may be carried out by a general method in which a base is made to coexist in a solvent.

As the base, inorganic bases such as potassium carbonate, cesium carbonate, sodium hydroxide and potassium hydroxide; metal hydrides such as sodium hydride and potassium hydride; metal alkoxides such as sodium ethoxide and potassium t-butoxide; and organic bases such as triethylamine, diisopropylethylamine, pyridine and 4-dimethylaminopyridine may be used. The base is used in an amount of 1 to

30 equivalents, preferably 1 to 10 equivalents with respect to the substrate. In case of amidation reaction, satisfactory results may be obtained without using a base in some cases.

As the solvent, aprotic polar solvents such as DMF, dimethylacetoamide and DMSO; ether solvents such as diethyl ether, THF, DME and dioxane; hydrocarbon solvents such as benzene and toluene; and halogen-containing solvents such as dichloromethane, chloroform and 1,2-dichloroethane may be used. Among these, DMF, THF and toluene are preferred. As for the reaction temperature, satisfactory results may be usually obtained at -20°C to 200°C, preferably 0°C to 150°C. The reaction time is appropriately selected depending on the conditions such as reaction temperature, and satisfactory results are usually obtained when the reaction time is about 30 minutes to 100 hours. The concentration of the substrate (IV) or (V) in the reaction mixture is not restricted, and usually 1 mmol/L to 1 mol/L is preferred.

Among the compounds represented by Formula (I) (wherein R^1, R^2, R^3, R^4, R^9, R^{10}, R^{11}, X, Y, Z and k represent the same meanings as described above), the compounds wherein Y is -C(=O)-, that is, the compounds represented by Formula (ID) or (IE) (wherein R^1, R^2, R^3, R^9, R^{10}, R^{11}, X and Z represent the same meanings as described above, R^{13} is C_1-C_5 alkyl or C_7-C_{13} aralkyl) may be produced by alkylating or acylating the compounds represented by Formula (IC) (wherein R^1, R^2, R^3, R^9, R^{10}, R^{11}, X and Z represent the same meanings as described above) in a solvent in the co-presence of a base, as shown in Scheme 3 below. The compounds of Formula (IC) used as a starting material of Scheme 3 may be obtained by the methods shown in Schemes 1 and 2.



Scheme 3

An alkylation agent or acylation agent may preferably be used in an amount of 1 to 20 equivalents, and satisfactory results are obtained by using the alkylation agent or acylation agent in an amount of 1 to 10 equivalents.

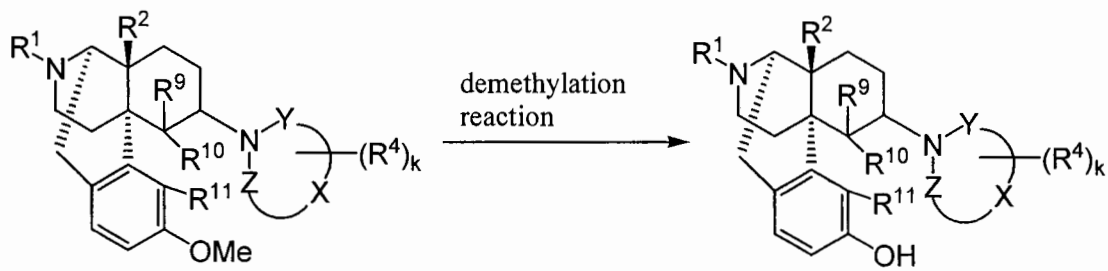
As the base, organic lithium reagents such as methyl lithium, butyl lithium and LDA; metal hydrides such as sodium hydride and potassium hydride; and metal alkoxide such as sodium ethoxide, potassium t-butoxide may be used, and LDA and butyl lithium are preferred. The base may be used in an amount of 1 to 30 equivalents, preferably 1 to 10 equivalents with respect to the substrate.

As the solvent, aprotic polar solvents such as DMF, dimethylacetoamide and DMSO; ether solvents such as diethyl ether, THF, DME and dioxane; and hydrocarbon solvents such as pentane, hexane, benzene and toluene may be used. Among these, THF and DME are preferred.

As for the reaction temperature, satisfactory results may be usually obtained at -100°C to 200°C, preferably -80°C to 150°C. The reaction time is appropriately selected depending on the conditions such as reaction temperature, and satisfactory results are usually obtained when the reaction time is about 30 minutes to 30 hours.

The concentration of the substrate (IC) in the reaction mixture is not restricted, and usually 1 mmol/L to 1 mol/L is preferred.

When synthesizing the compounds represented by Formula (I) wherein R^3 is hydroxy, that is, the compounds represented by Formula (IG) (wherein R^1, R^2, R^4, R^9, R^{10}, R^{11}, X, Y, Z and k represent the same meanings as described above), the compounds may be synthesized through the compounds of Formula (IF) (wherein R^1, R^2, R^4, R^9, R^{10}, R^{11}, X, Y, Z and k represent the same meanings as described above), wherein R^3 is methoxy, in order to protect the phenol moiety. In this case, the deprotection may be carried out by the usual demethylation reaction of phenolic methyl ether, as shown in Scheme 4, more particularly, by (1) a method in which boron tribromide is used, or (2) a method in which an alkylthiol is used under basic condition.



(I F)　　(I G)

Scheme 4

In the method (1), the amount of the boron tribromide is preferably 1 to 20 equivalents, and satisfactory results are obtained by using boron tribromide in an amount of 1 to 7 equivalents. As the reaction solvent, halogen-containing solvents such as dichloromethane, chloroform and 1,2-dichloroethane are preferred, and dichloromethane is preferred. The reaction temperature is preferably -70°C to 50°C, and satisfactory results are obtained when the reaction temperature is -50°C to 40°C. The reaction time is preferably 10 minutes to 10 hours, and satisfactory results are obtained when the reaction time is 30 minutes to 5 hours. The concentration of the

compound (IF) in the reaction system is not restricted, and usually 1 mmol/L to 1 mol/L is preferred.

In the method (2), as the reagent, an alkylthiol such as ethanethiol, propanethiol or butanethiol is preferred, and propanethiol is especially preferred. The amount of the alkylthiol is preferably 1 to 20 equivalents, and satisfactory results are obtained by using alkylthiol in an amount of 1 to 7 equivalents. As the base, potassium t-butoxide, sodium hydride and potassium hydride are preferred, and potassium t-butoxide is especially preferred. The amount of the base is preferably 1 to 20 equivalents, and satisfactory results are obtained by using the base in an amount of 1 to 7 equivalents. As the reaction solvent, aprotic polar solvents such as DMF and dimethylacetoamide; and ether solvents such as THF and DME are preferred, and DMF which is an aprotic solvent is particularly preferred. The reaction temperature is preferably 50°C to 200°C, and satisfactory results are obtained when the reaction temperature is 80°C to 150°C. The reaction time is preferably 1 hour to 15 hours, and satisfactory results are obtained when the reaction time is 2 to 8 hours. The concentration of the compound (IF) in the reaction system is not restricted, and usually 1 mmol/L to 1 mol/L is preferred.

The fact that the morphinan derivatives having the nitrogen-containing cyclic group, represented by Formula (I) are effective against pruritus can be confirmed by the fact that they have action to inhibit scratching behavior in animals. Although the action to inhibit scratching behavior in animals may be confirmed by the method described in a reference [Eur. J. Pharmacol., vol 477, 29-35 (2003)], the method is not restricted thereto.

The antipruritic according to the present invention may be used against atopic dermatitis, neurogenic dermatitis, contact dermatitis, seborrheic dermatitis, autosensitization dermatitis, caterpillar dermatitis, asteatosis, senile pruritus, insect sting, photosensitive dermatosis, urticaria, prurigo, herpes blister, impetigo, eczema,

tinea, lichen, psoriasis, scabies, and acne vulgaris, as well as against organ diseases and medical treatments accompanying pruritus, such as malignant tumors, diabetes mellitus, hepatic diseases, renal failure, hemodialysis, gout, thyroid diseases, hemopathy and sideropenia. In addition, they may be used against the pruritus due to pregnancy or vermination, and against the pruritus induced by drugs and by psychogenic reasons. The antipruritic according to the present invention may also be applied to the pruritus accompanying ophthalmic or otorhinolaryngologic diseases. The antipruritic according to the present invention may also be applied to mammals (e.g., mouse, rat, hamster, rabbit, cat, dog, bovine, sheep, monkey and human).

When administering the antipruritic according to the present invention, the compound described in the present invention may be administered individually or in combination with one or more substances which are used for the therapy or prevention of the disease, or used for the alleviation or inhibition of the symptoms. Examples of such substances include anthelmintics such as fipronil, lufenuron, imidacloprid, avermectins (e.g., abamectin, ivermectin, doramectin, milbemycins, organic phosphate and pyrethroid; antihistamines such as chlorophenylamine, trimeprazine, diphenhydramine and doxylamine; antifungals such as fluconazole, ketoconazole, itraconazole, griseofulvin and amphotericin B; antibacterial agents such as enrofloxacin, marbofloxacin, ampicillin and amoxicillin; antiinflammatory agents such as prednisolone, betamethasone, carprofen, clobetasol, diflorasone, hydrocortisone, dexamethasone, ketoprofen and meloxicam; antiallergic drugs such as mequitazine, ketotifen, azelastine, oxatomide and fexofenadine; therapeutic agents against atopic dermatitis such as tacrolimus; supplementary foods such as γ- linoleic acid; emollients; and humectant, although the substances are not restricted thereto.

When the antipruritic according to the present invention is clinically used, the drug may be in the form of the free base or its salt *per se*, or additives such as vehicles, stabilizers, preservatives, buffering agents, solubilizers, emulsifiers,

diluents and isotonic agents may be admixed appropriately. Administration forms thereof include oral preparations such as tablets, capsules, granules, powders and syrups; parenteral preparations such as injection solutions, suppositories and liquids; and topical preparations such as ointments, creams and patches. When used for the treatments of dermatoses, external preparations are preferred. The external preparations may be prepared by mixing the effective ingredient with one or more of fats (preferably, plant oils, animal oils, waxes, fatty acids, fatty alcohols, mineral oils, turpentine oils, vaselines, etc.), solvents (preferably, water, ethanol, glycerin, propylene glycol, isopropyl alcohol, ether, etc.), preserving agents (preferably, paraoxybenzoic acid ester, benzoic acid, salicylic acid, sorbic acid, benzalkonium, benzethonium, propyleneglycol, chlorobuthanol, benzyl alcohol, ethanol, etc.), stabilizers (preferably, tocopherol, butylhydroxyanisol, dibutylhydroxytoluene, sulfites, edetic acid disodium, etc.), anionic surfactants (preferably, potassium soap, medical soap, zinc undecylenate, calcium stearate, magnesium stearate, aluminum monostearate, calcium linolate, sodium laurylsulfate, etc.), non-ionic surfactants (preferably, glyceryl monostearate, sorbitan fatty acid partial esters, sugar fatty acid esters, stearic acid polyoxyl 40, macrogolic acids, lauromacrogol, polyoxyethylene160, polyoxypropylene30glycol, polyoxyethylene hardened castor oils, polyoxyethylene sorbitan fatty acid partial esters, etc.), cationic surfactants (preferably, benzalkonium chloride, benzethonium chloride, cetyl piridinium chloride, etc.), powders (preferably, zinc oxide, zinc powder in starch, kaolin, bismuth hyponitrite, titanium oxide, titanium dioxide, sulfur, anhydrous silicic acid, tarc, etc.), preservatives (preferably, paraoxybenzoic acid esters, sorbic acid, p-chloro-m-xylenol, Irgasan, hexachlorophene, etc.), emulsifiers (preferably, arabic gum powder, tragacanth powder, bentonite, carboxymethylcellulose sodium, methylcellulose, etc.), and moisturizers (preferably, glycerin, propylene glycol, polyethylene glycol, 1,3-butylene glycol, sorbitol, polypyrrolidone carboxylic acid sodium, sodium lactate, sodium hyaluronate, chitin derivatives, urea, amino acids,

sugar amino acids, etc) to form a base, and formulating the base into the form of ointment, cream, pack, liniment or patch. The preparation may also be in the form of external liquid. Further, the preparation may be made as a solution for topical ophthalmic use.

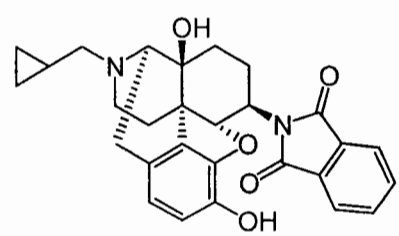
The antipruritic according to the present invention preferably contains the effective ingredient in an amount of 0.00001 to 90% by weight, more preferably 0.0001 to 70% by weight. Although the administration dose is appropriately selected depending on the symptom, age, body weight, administration method and the like, in case of injection solution or external preparation, 0.1 μg to 1 g per day for an adult, and in case of oral preparation, 1 μg to 10 g per day for an adult, in terms of the amount of the effective ingredient, may be administered at one time or in several times.

The present invention will now be described concretely by way of examples.

Examples

Reference Example 1

Synthesis of N-[(17-cyclopropylmethyl)-4,5α-epoxy-3,14-dihydroxy-morphinan-6β-yl]-phthalimide · hydrochloric acid salt (Compound 1)



1

In 7 mL of DMF, 150 mg (0.44 mmol) of 6β-naltrexamine was dissolved, and 71 mg (0.48 mmol) of phthalic anhydride and 0.92 mL (0.66 mmol) of triethylamine were added, followed by stirring the mixture at 140°C for 4 hours. After allowing the reaction solution to cool to room temperature, saturated aqueous sodium hydrogen carbonate solution was added and the resulting mixture was extracted with

ethyl acetate. Organic layers were combined, washed with water and saturated saline, dried over anhydrous magnesium sulfate, and concentrated to obtain a crude product. The obtained crude product was purified by silica gel column chromatography to obtain 120 mg (yield: 58%) of free base compound (6). An aliquot thereof was converted to hydrochloric acid salt to obtain the captioned compound 1.

^{1}H-NMR (ppm) (300 MHz, $CDCl_3$)

7.8-7.9 (2H, m), 7.7-7.8 (2H, m), 6.76 (1H, d, J = 7.9 Hz), 6.63 (1H, d, J = 8.2 Hz), 5.18 (1H, d, J = 8.5 Hz), 4.0-4.1 (1H, m), 3.11 (1H, d, J = 5.6 Hz), 3.05 (1H, d, J = 18.8 Hz), 2.6-2.9 (3H, m), 2.3-2.4 (3H, m), 2.15 (1H, dt, J = 12.0, 3.5 Hz), 1.4-1.7 (4H, m), 0.8-0.9 (1H, m), 0.5-0.6 (2H, m), 0.1-0.2 (2H, m) (free form)

IR (cm^{-1}) (KBr)

3320, 1769, 1708, 1626, 1504, 1466, 1428, 1379, 1323, 1271, 1240, 1190, 1173, 1075

Elementary Analysis:

Formula: C28H28N2O5 · 1.0 HCl · 1.0 H2O

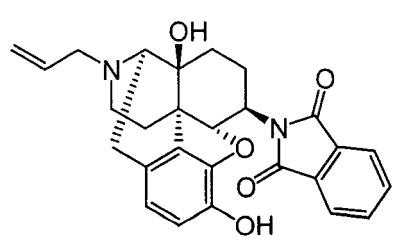
Calcd.: C:63.81, H:5.93, N:5.32, Cl:6.73

Found: C:63.72, H:6.03, N:5.40, Cl:6.49

Mass (EI): 472 (M^+)

Reference Example 2

Synthesis of N-[(17-allyl)-4,5α-epoxy-3,14-dihydroxy-morphinan-6β-yl]-phthalimide · tartaric acid salt (Compound 2)



2

The same procedure as in Reference Example 1 was repeated except that 6β-naloxamine was used in place of 6β-naltrexamine to obtain 24 mg (yield: 34%) of free form of Compound 2. This product was converted to tartaric acid salt to obtain the captioned compound 2.

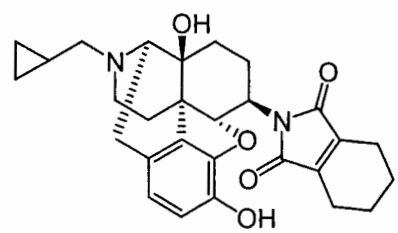
^{1}H-NMR (ppm) (300 MHz, $CDCl_3$)

7.75-7.8 (2H, m), 7.6-7.7 (2H, m), 6.72 (1H, d, J = 8.2 Hz), 6.59 (1H, d, J = 8.2 Hz), 5.7-5.8 (1H, m), 5.1-5.2 (3H, m), 4.0-4.05 (1H, m), 3.0-3.1 (3H, m), 2.45-2.9 (5H, m), 2.0-2.3 (2H, m), 1.6-1.7 (1H, m), 1.4-1.5 (2H, m) (free form)

Mass (ESI): 459 (M^++1)

Reference Example 3

Synthesis of N-[(17-cyclopropylmethyl)-4,5α-epoxy-3,14-dihydroxy-morphinan-6β-yl]-3,4,5,6-tetrahydrophthalimide · tartaric acid salt (Compound 3)



3

In 3.3 mL of chloroform, 113 mg (0.33 mmol) of 6β-naltrexamine was dissolved, and 58 mg (0.38 mmol) of 3,4,5,6-tetrahydrophthalic anhydride and 114 μL (0.82 mmol) of triethylamine were added, followed by stirring the mixture at room temperature for 50 minutes. Thereafter, 234 μL (1.68 mmol) of triethylamine and 158 μL (1.68 mmol) of acetic anhydride were added to this reaction solution, followed by heating the solution to reflux for 1 hour. After allowing the reaction solution to cool to room temperature, the solution was concentrated by an evaporator, and then 3 mL of methanol and 300 μL of 28 % aqueous ammonia were added, followed by stirring the mixture at room temperature for 4 hours. Thereafter, water was added and the resulting mixture was extracted with chloroform. Organic layers

were combined, washed with water and saturated saline, dried over anhydrous magnesium sulfate and concentrated to obtain a crude product. The obtained crude product was purified by silica gel column chromatography to obtain 121 mg (yield: 77 %) of free form of compound 3. This product was converted to methanesulfonic acid salt to obtain the captioned compound 3.

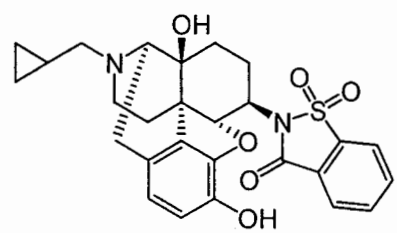
^{1}H-NMR (ppm) (300 MHz, $CDCl_3$)

0.12 (2H, m), 0.52 (2H, m), 0.84 (1H, m), 1.43 (3H, m), 1.65 (1H, m), 1.76 (4H, br), 2.12 (3H, td, J = 12.0, 3.6 Hz), 2.26-2.38 (7H, m), 2.63 (3H,m), 3.03 (1H, d, J = 18.4 Hz), 3.08 (1H, d, J = 5.6 Hz), 3.83 (1H, ddd, J = 13.2, 8.4, 3.6 Hz), 5.05(1H, d, J = 8.4 Hz), 6.60 (1H, d, J = 8.4 Hz) (free form)

Mass (ESI) : 477 (M^++1)

Reference Example 4

Synthesis of [N-(17-cyclopropylmethyl)-4,5α-epoxy-3,14-dihydroxy-morphinan-6β-yl]-O-sulfonebenzimide · tartaric acid salt (Compound 4)



4

In 10 mL of chloroform, 203 mg (0.53 mmol) of 6β-amino-(17-cyclopropylmethyl)-4,5α-epoxy-3-methoxymethoxy-morphinan-14-ol was dissolved, and 0.15 mL of triethylamine and 136 mg of methyl-(2-chlorosulfonyl)-benzoate were added at 0 °C, followed by stirring the mixture at room temperature for 8 hours, and then the mixture was heated to reflux for 30 minutes. After allowing the reaction solution to cool to room temperature, saturated aqueous sodium hydrogen carbonate solution was added and the resulting mixture was extracted with chloroform. Organic layers were combined, washed with saturated saline, dried

over anhydrous magnesium sulfate and concentrated to obtain a crude product. The obtained crude product was purified by silica gel column chromatography to obtain 219 mg (yield: 71 %) of 2-[(17-cyclopropylmethyl-4,5α-epoxy-14-hydroxy-3-methoxymethoxy-morphinan-6β-yl)-sulfamoyl]-benzoic acid methyl ester.

In 10 mL of DMF, 91mg (0.16 mmol) of the obtained 2-[(17-cyclopropylmethyl-4,5α-epoxy-14-hydroxy-3-methoxymethoxy-morphinan-6β-yl)-sulfamoyl]-benzoic acid methyl ester was dissolved, and 352 mg of potassium carbonate was added, followed by stirring the mixture at 80 °C for 3 hours. After allowing the reaction solution to cool to room temperature, the solution was filtered through celite (trademark) and the filtrate was concentrated to obtain N-[(17-cyclopropylmethyl)-4,5α-epoxy-14-hydroxy-3-methoxymethoxy-morphinan-6β-yl]-O-sulfonebenzimide as a crude product.

In 2 mL of 2-propanol and 2 mL of chloroform, the obtained crude product was dissolved and 0.2 mL of concentrated hydrochloric acid was added, followed by stirring the mixture at room temperature for 13 hours. Saturated aqueous sodium hydrogen carbonate solution was added and the resulting mixture was extracted with chloroform. Organic layers were combined, washed with saturated saline, dried over anhydrous magnesium sulfate and concentrated to obtain a crude product. The obtained crude product was purified by silica gel column chromatography to obtain 67 mg (yield 85 %: 2 steps) of free form of captioned compound 4. This product was converted to tartaric acid salt to obtain the captioned compound 4.

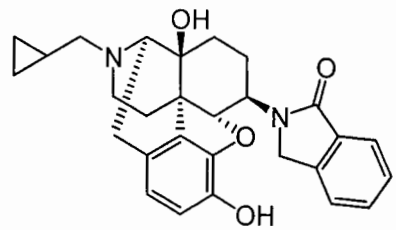
^{1}H-NMR (ppm) (300 MHz, $CDCl_3$)

8.06-8.08 (m, 1H), 7.82-7.97 (m, 3H), 6.80 (d, 1H, J = 8.1 Hz), 6.65 (d, 1H, J = 8.1 Hz), 5.28 (d, 1H, J = 8.3 Hz), 3.92 (ddd, 1H, J = 3.9, 8.3, 13.1 Hz), 3.11 (d, 1H, J = 5.6 Hz), 3.06 (d, 1H, J = 18.3 Hz), 2.78-2.87 (m, 1H), 2.60-2.70 (m, 2H), 2.32-2.39 (m, 3H), 2.13-2.20 (m, 1H), 1.46-1.76 (m, 4H), 0.82-0.88 (m, 1H), 0.52-0.57 (m, 2H), 0.12-0.15 (m, 2H) (free form)

Mass (ESI) : 509 (M^++1)

Reference Example 5

Synthesis of 2-[(17-cyclopropylmethyl)-4,5α-epoxy-3,14-dihydroxy-morphinan-6β-yl]-2,3-dihydro-isoindole-1-one · tartaric acid salt (Compound 5)



5

In a mixed solution of 5 mL of methanol and 5 mL of chloroform, 156 mg (0.33 mmol) of N-[(17-cyclopropylmethyl)-4,5α-epoxy-3,14-dihydroxy-morphinan-6β-yl]-phthalimide obtained in Reference Example 1 was dissolved, and 61 mg (1.61 mmol) of sodium borohydride was added at 0 °C, followed by stirring the mixture for 2 hours. Thereafter, saturated aqueous sodium hydrogen carbonate solution was added and the resulting mixture was extracted with chloroform. Organic layers were combined, washed with saturated saline, dried over anhydrous magnesium sulfate and concentrated to obtain a crude product. The obtained crude product was purified by silica gel column chromatography to obtain 130 mg (yield 83 %) of 2-[(17-cyclopropylmethyl)-4,5α-epoxy-3,14-dihydroxy-morphinan-6β-yl]-3-hydroxy-2,3-dihydro-isoindole-1-one (diastereomer mixture).

In a mixed solution of 7 mL of methylene chloride and 25 mL of chloroform, 150 mg (0.32 mmol) of the obtained purified product was dissolved, 0.22 mL (1.73 mmol) of boron trifluoride ether complex and 0.28 mL (1.73 mmol) of triethylsilane were added at 0 °C, followed by stirring the mixture for 22 hours. Thereafter, saturated aqueous sodium hydrogen carbonate solution was added and the resulting mixture was extracted with chloroform. Organic layers were combined, washed with saturated saline, dried over anhydrous magnesium sulfate and concentrated to

obtain a crude product. The obtained crude product was purified by silica gel column chromatography to obtain 55 mg (yield 38 %) of free form of captioned compound 5. This product was converted to tartaric acid salt to obtain the captioned compound 5.

^{1}H-NMR (ppm) (300 MHz, $CDCl_3$)

7.85 (d, J = 8.2 Hz, 1H), 7.58-7.45 (m, 3H), 6.79 (d, J = 8.2 Hz, 1H), 6.62 (d, J = 8.2 Hz, 1H), 4.68 (d, J = 8.2 Hz, 1H), 4.52 (d, J = 16.8 Hz, 1H), 4.44 (d, J = 16.8 Hz, 1H), 4.27 (ddd, J = 12.6, 8.2, 4.4 Hz, 1H), 3.11 (d, J = 5.5 Hz, 1H), 3.06 (d, J = 18.4 Hz, 1H), 2.70-2.59 (m, 2H), 2.39 (d, J = 6.6 Hz, 2H), 2.31-2.12 (m, 3H), 1.72-1.49 (m, 4H), 0.93-0.79 (m, 1H), 0.58-0.50 (m, 2H), 0.17-0.11 (m, 2H) (free form)

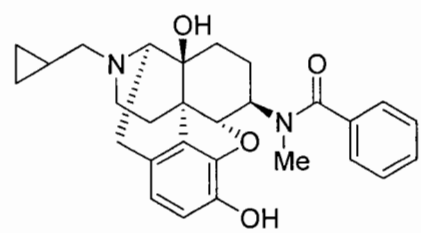
IR (cm^{-1}) (KBr)

3075, 3004, 2925, 2818, 1658, 1622, 1498, 1455, 1377, 1330, 1307, 1279, 1228, 1188, 1153, 1117, 1069, 1051, 1034, 981, 943, 919, 884, 859, 740

Mass (EI) : 458 (M^+)

Reference Example 6

Synthesis of 17-cyclopropylmethyl-4,5α-epoxy-3,14-dihydroxy-6β-(N-methylbenzamido)-morphinan · hydrochloric acid salt (Compound 7)



7

In 5 mL of chloroform, 194 mg (0.54 mmol) of 17-cyclopropylmethyl-4,5α-epoxy-3,14-dihydroxy-6β-methylamino-morphinan was dissolved, and 0.16 mL (1.11 mmol) of triethylamine and 0.13 mL (1.09 mmol) of benzoyl chloride were added, followed by stirring the mixture at room temperature for 1 hour. Then 5 mL of methanol and 1.5 mL of 2N aqueous NaOH solution were added to the reaction

solution, followed by stirring the mixture at room temperature for 3 hours. Thereafter, water was added and the resulting mixture was extracted with chloroform. Organic layers were combined, washed with saturated saline, dried over anhydrous magnesium sulfate and concentrated to obtain a crude product. The obtained crude product was purified by silica gel column chromatography to obtain 237 mg (yield 95 %) of free form of the captioned compound 7. This product was converted to hydrochloric acid salt to obtain the captioned compound 7.

^{1}H-NMR (ppm) (400 MHz, DMSO-d6)

7.4-7.2 (m, 5H), 6.65 (d, J = 8.1 Hz, 1H), 6.50 (d, J = 8.1 Hz, 1H), 4.94 (d, J = 8.0 Hz, 1H), 3.74 (m, 1H), 3.3-3.1 (m, 2H), 3.03 (s, 3H), 3.0-2.8 (m, 4H), 2.5-2.3 (m, 1H), 2.2-2.1 (m, 1H), 1.65-1.55 (m, 1H), 1.45-1.35 (m, 2H), 1.3-1.2 (m, 1H), 1.1-0.9 (m, 2H), 0.7-0.3 (m, 4H)

Mass (ESI): 461 ($M+1^+$)

Example 1

Inhibitory Effect of Scratching Behavior Induced by Substance-P

Male ddY mice were purchased when they were 4 weeks old, and used in the experiments when they became 5 weeks old after acclimation. One day before experiment, each mouse had hair on the rostral back skin clipped with a hair clipper. Each of test drugs was dissolved in 10% DMSO. Either the test drug or vehicle was administered subcutaneously into the rostral back of the mouse, and 30 minutes later, Substance-P (250 nmom/site) dissolved in PBS (phosphate buffered saline) was administered intradermally into the hair-clipped skin at a dose of about 50 μL. Immediately thereafter, each mouse was put into a cage for observation (10*14*22cm), and the subsequent behavior of each mouse was recorded by an unattended video camera for 30 minutes. The video tape was replayed, and the number of times that the mouse scratched at or around the Substance-P-administered site with its hind limb was counted. In the experiment, each group consisted of 8

mice. In cases where there was a statistically significant difference in the mean number of scratching between the solvent-administered group and the test drug-administered group, the test drug was judged to have an antipruritic effect. The results are shown in terms of the predicted administration dosage at which the number of scratching was reduced to half of that in the solvent-administered group (Table 5).

Table 5

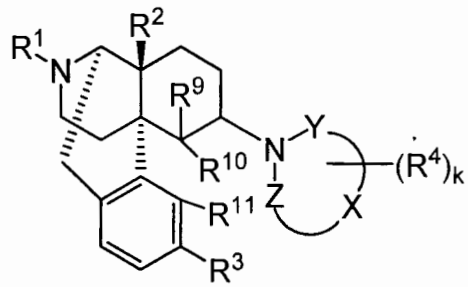
Compound	ED50 (mg/kg, sc)
1	0.0034
2	0.32
3	0.0033
4	0.0081
5	0.015
6	0.0029
7	0.55(Reference Example)

Industrial Availability

Since the antipruritic according to the present invention has an excellent antipruritic effect and has small side effects, it is useful for treatment of pruritus accompanying various diseases.

CLAIMS

1. An antiprurtic comprising as an effective ingredient a morphinan derivative having a nitrogen-containing cyclic group of the Formula (I):



(I)

[wherein R^1 is hydrogen, C_1-C_5 alkyl, C_4-C_7 cycloalkylalkyl, C_6-C_8 cycloalkenylalkyl, C_6-C_{12} aryl, C_7-C_{13} aralkyl, C_3-C_7 alkenyl, furanylalkyl (wherein the number of carbon atoms in the alkyl moiety is 1 to 5), thienylalkyl (wherein the number of carbon atoms in the alkyl moiety is 1 to 5) or pyridylalkyl (wherein the number of carbon atoms in the alkyl moiety is 1 to 5);

R^2 and R^3 are independently hydrogen, hydroxy, C_1-C_5 alkoxy, C_3-C_7 alkenyloxy, C_7-C_{13} aralkyloxy or C_1-C_5 alkanoyloxy;

Y and Z independently represent valence bond or -C(=O)-;

-X- represents a C_2-C_7 carbon chain (one or more of the carbon atoms therein may be replaced by (a) nitrogen, oxygen or sulfur atom(s), and the carbon chain may contain (an) unsaturated bond(s)) constituting a part of the ring structure;

k is an integer of 0 to 8;

R^4 is(are) (a) substituent(s) in the number of k on the nitrogen-containing ring, which independently represent(s) fluorine, chlorine, bromine, iodine, nitro, hydroxy, C_1-C_5 alkyl, C_7-C_{13} cycloalkylalkyl, C_6-C_{12} aryl, C_7-C_{13} aralkyl, C_7-C_{13} aralkyloxy, C_1-C_5 alkoxy, trifluoromethyl, trifluoromethoxy, cyano, isothiocyanato, SR^6, SOR^6, SO_2R^6, $(CH_2)_pOR^6$, $(CH_2)_pCOR^6$, $(CH_2)_pCO_2R^6$, $SO_2NR^7R^8$, $CONR^7R^8$, $(CH_2)_pNR^7R^8$ or $(CH_2)_pN(R^7)COR^8$, or among the R^4s in the number of k, two R^4s bound to the same

carbon atom or to the same sulfur atom cooperatively represent one oxygen atom to form carbonyl or sulfoxide, or two R^4s bound to the same carbon atom cooperatively represent one sulfur atom to form thiocarbonyl, or four R^4s bound to the same sulfur atom cooperatively represent two oxygen atoms to form sulfone, or among the R^4s in the number of k, two R^4s bound to adjacent carbon atoms, respectively, cooperatively form benzene fused ring, pyridine fused ring, naphthalene fused ring, cyclopropane fused ring, cyclobutane fused ring, cyclopentane fused ring, cyclopentene fused ring, cyclohexane fused ring, cyclohexene fused ring, cycloheptane fused ring or cycloheptene fused ring, each of said fused rings is non-substituted or substituted by 1 or more R^5s, wherein R^5(s) independently represent(s) fluorine, chlorine, bromine, iodine, nitro, hydroxy, C_1-C_5 alkyl, C_1-C_5 alkoxy, trifluoromethyl, trifluoromethoxy, cyano, C_6-C_{12} aryl, isothiocyanato, SR^6, SOR^6, SO_2R^6, $(CH_2)_pOR^6$, $(CH_2)_pCOR^6$, $(CH_2)_pCO_2R^6$, $SO_2NR^7R^8$, $CONR^7R^8$, $(CH_2)_pNR^7R^8$ or $(CH_2)_pN(R^7)COR^8$;

R^9 is hydrogen, C_1-C_5 alkyl, C_1-C_5 alkenyl, C_7-C_{13} aralkyl, C_1-C_3 hydroxyalkyl, $(CH_2)_pOR^6$ or $(CH_2)_pCO_2R^6$;

R^{10} and R^{11} are bound to form -O-, -S- or -CH_2-, or R^{10} is hydrogen and R^{11} is hydrogen, hydroxy, C_1-C_5 alkoxy or C_1-C_5 alkanoyloxy;

p is an integer of 0 to 5;

R^6 is hydrogen, C_1-C_5 alkyl, C_3-C_7 alkenyl, C_6-C_{12} aryl or C_7-C_{13} aralkyl; and

R^7 and R^8 are independently hydrogen, C_1-C_5 alkyl or C_7-C_{13} aralkyl, and the Formula (I) includes (+), (-) and (±) isomers]

or a pharmaceutically acceptable acid addition salt thereof.

2. The antipruritic according to claim 1, wherein in said Formula (I), X is a C_2-C_7 carbon chain (which may contain (an) unsaturated bond(s)) constituting a part of the ring structure.

3. The antipruritic according to claim 1 or 2, wherein in said Formula (I), Y is -C(=O)- and Z is valence bond.

4. The antipruritic according to claim 1 or 2, wherein in said Formula (I), both Y and Z are -C(=O)-.

5. The antipruritic according to claim 4, wherein in said Formula (I), R^1 is hydrogen, C_4-C_7 cycloalkylalkyl, C_6-C_8 cycloalkenylalkyl, C_6-C_{12} aryl or C_3-C_7 alkenyl; and two R^4s bound to adjacent carbon atoms, respectively, cooperatively form benzene fused ring, pyridine fused ring, naphthalene fused ring, cyclopropane fused ring, cyclobutane fused ring, cyclopentane fused ring, cyclopentene fused ring, cyclohexane fused ring, cyclohexene fused ring, cycloheptane fused ring or cycloheptene fused ring, each of said fused rings is non-substituted or substituted by 1 or more R^5s.

6. The antipruritic according to claim 4, wherein in said Formula (I), R^1 is hydrogen, cyclopropylmethyl, cyclobutylmethyl, cyclopentylmethyl, cyclohexylmethyl, allyl or prenyl; R^2 and R^3 are hydrogen, hydroxy, methoxy, ethoxy, allyloxy, benzyloxy, acetoxy or propionoxy; k is 2, two R^4s cooperatively form benzene fused ring or cyclohexene fused ring, which is non-substituted or substituted by 1 to 4 R^5s; R^5(s) is(are) independently fluorine, chlorine, bromine, iodine, nitro, methyl, ethyl, propyl, benzyl, hydroxy, methoxy, ethoxy, trifluoromethyl, trifluoromethoxy, cyano, phenyl, isothiocyanato, SR^6, SOR^6, SO_2R^6, $(CH_2)_pOR^6$, $(CH_2)_pCOR^6$, $(CH_2)_pCO_2R^6$, $SO_2NR^7R^8$, $CONR^7R^8$, $(CH_2)_pNR^7R^8$ or $(CH_2)_pN(R^7)COR^8$; R^6 is hydrogen, methyl, ethyl, propyl or phenyl; R^7 and R^8 are independently hydrogen, methyl, ethyl, propyl or benzyl; R^9 is hydrogen or methyl; R^{10} and R^{11} are bound to form -O-, or R^{10} is hydrogen and R^{11} is hydrogen, hydroxy or methoxy.

7. The antipruritic according to claim 4, wherein in said Formula (I), R^1 is hydrogen, cyclopropylmethyl, cyclobutylmethyl or allyl; R^2 and R^3 are independently hydrogen, hydroxy, methoxy or acetoxy; k is 2, two R^4s cooperatively form benzene fused ring or cyclohexene fused ring which is non-substituted or substituted by 1 to 4

R^5s; R^5(s) is(are) independently fluorine, chlorine, bromine, iodine, nitro, methyl, ethyl, propyl, benzyl, hydroxy, methoxy, ethoxy, trifluoromethyl, trifluoromethoxy, cyano, phenyl, isothiocyanato, SR^6, SOR^6, SO_2R^6, $(CH_2)_pOR^6$, $(CH_2)_pCOR^6$, $(CH_2)_pCO_2R^6$, $SO_2NR^7R^8$, $CONR^7R^8$, $(CH_2)_pNR^7R^8$ or $(CH_2)_pN(R^7)COR^8$; R^6 is hydrogen, methyl, ethyl, propyl or phenyl; R^7 and R^8 are independently hydrogen, methyl, ethyl, propyl or benzyl; R^9 is hydrogen or methyl; R^{10} and R^{11} are bound to form -O-.

8. Use of said morphinan derivative having a nitrogen-containing cyclic group or the pharmaceutically acceptable acid addition salt thereof recited in any one of claims 1 to 7 for the production of antipruritics.