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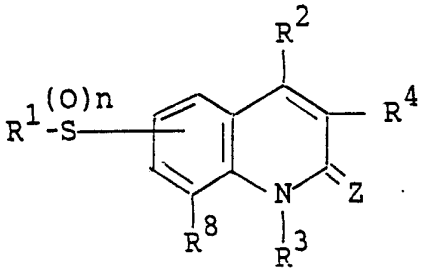

(I)

(57) Abstract

Quinoline derivatives of formula (I), wherein R^1 is lower alkyl or aryl which may have suitable substituent(s), R^2 is hydroxy, protected hydroxy, lower alkoxy, etc., R^3 is hydrogen, lower alkyl, lower alkoxy(lower)- alkyl or ar(lower)alkyl and R^8 is hydrogen, or R^3 and R_8 are linked together to form lower alkylene, R^4 is an organic group, Z is O or S, and n is 0, 1 or 2; and pharmaceutically acceptable salts thereof which are useful as a medicament.

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DESCRIPTION

QUINOLINE DERIVATIVES

TECHNICAL FIELD

This invention relates to new quinoline derivatives and pharmaceutically acceptable salts thereof which are useful as a medicament.

BACKGROUND ART

Some quinoline derivatives have been known as described, for example, in U.S. Patent 4,547,511 and U.S. Patent 4,127,574.

DISCLOSURE OF INVENTION

This invention relates to new quinoline derivatives. More particularly, this invention relates to new quinoline derivatives and pharmaceutically acceptable salts thereof which have pharmacological activities, processes for preparation thereof, a pharmaceutical composition comprising the same and a use of the same.

Accordingly, one object of this invention is to provide the new and useful quinoline derivatives and pharmaceutically acceptable salts thereof which possess a strong immunomodulating activity (e.g. an inhibitory activity on the production of an autoantibody, etc.), anti-inflammatory activity and anti-cancer activity.

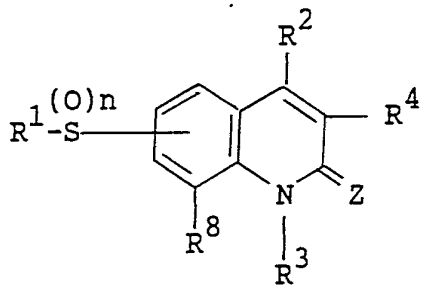
Another object of this invention is to provide processes for preparation of the quinoline derivatives and salts thereof.

A further object of this invention is to provide a pharmaceutical composition comprising said quinoline derivatives or a pharmaceutically acceptable salt thereof.

Still further object of this invention is to provide

a use of said quinoline derivatives or a pharmaceutically acceptable salt thereof as a medicament for the treatment and/or prevention of inflammatory conditions, various pains, collagen diseases, autoimmune diseases, various immunity diseases, cancer and the like in human being and animals.

The object quinoline derivatives of the present invention are novel and can be represented by the following general formula (I) :



(I)

wherein R^1 is lower alkyl or aryl which may have suitable substituent(s),

R^2 is hydroxy, protected hydroxy, lower alkoxy, halogen, amino, substituted amino, mercapto or protected mercapto,

R^3 is hydrogen, lower alkyl, lower alkoxy(lower)-alkyl or ar(lower)alkyl and

R^8 is hydrogen, or

R^3 and R^8 are linked together to form lower alkylene,

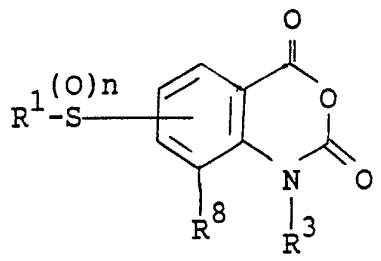
R^4 is an organic group,

Z is O or S, and

n is 0, 1 or 2.

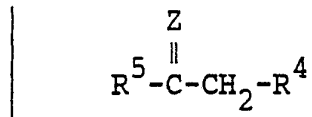
The object compound (I) of the present invention can be prepared by the following processes.

Process (1)



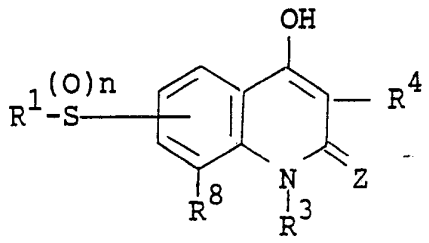
(II)

or a salt thereof



(III)

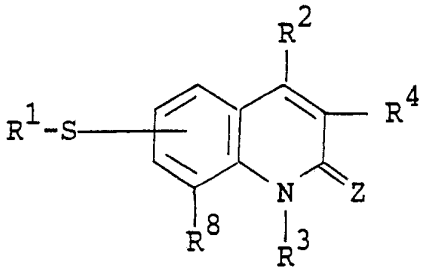
or a salt thereof



(Ia)

or a salt thereof

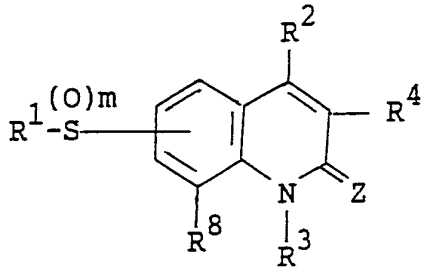
Process (2)



(Ib)

or a salt thereof

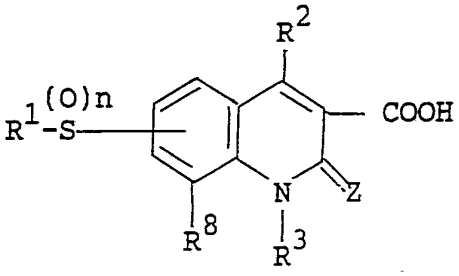
↓ oxidation



(Ic)

or a salt thereof

Process (3)

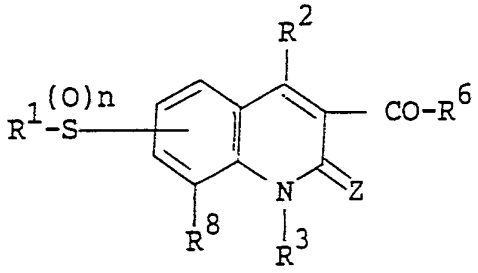


(Id)

or its reactive derivative

at the carboxy group or a salt thereof

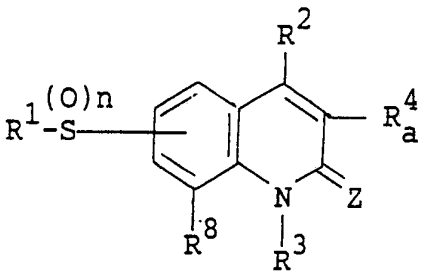
↓ Amidation reaction



(Ie)

or a salt thereof

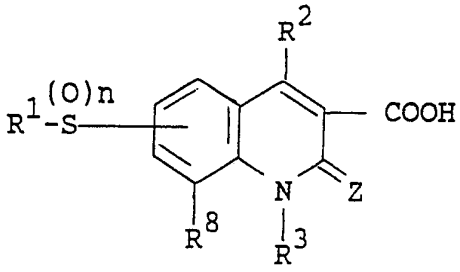
Process (4)



(If)

or a salt thereof

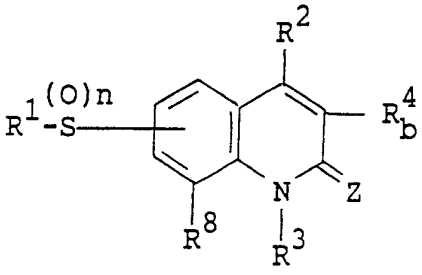
↓ Elimination reaction of the carboxy protective group in R_a^4



(Id)

or a salt thereof

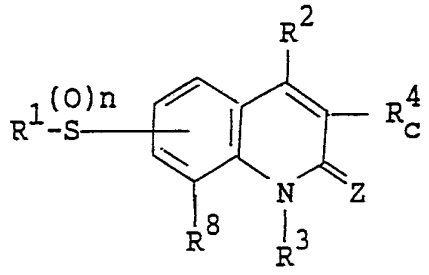
Process (5)



(Ig)

or a salt thereof

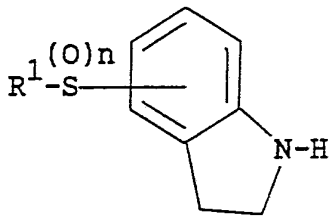
Elimination reaction of the carboxy protective group



(Ih)

or a salt thereof

Process (6)



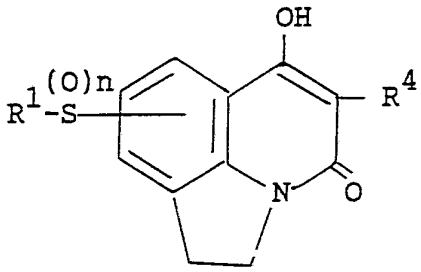
(IV)

or a salt thereof

R^4-CH(COX^1)$_2$

(V)

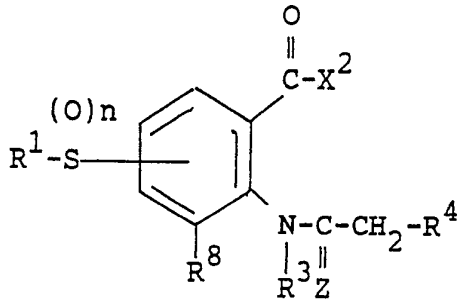
or a salt thereof



(Ii)

or a salt thereof

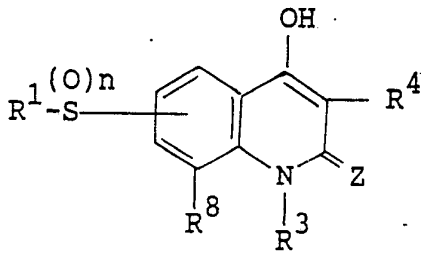
Process (7)



(VI)

or a salt thereof

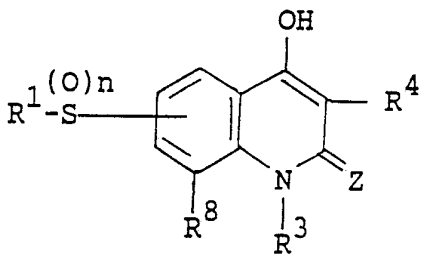
↓ Cyclization



(Ia)

or a salt thereof

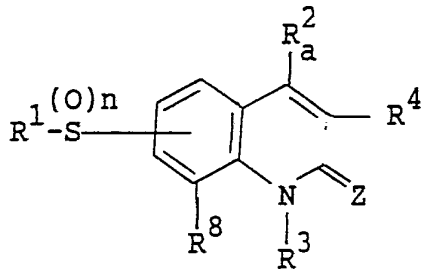
Process (8)



(Ia)

or a salt thereof

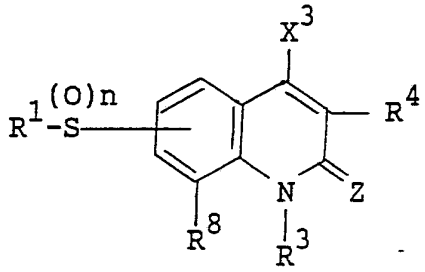
Halogenation



(Ij)

or a salt thereof

Process (9)



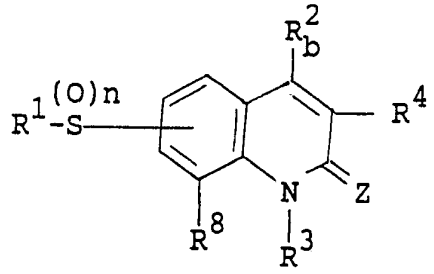
(Ik)

or a salt thereof

$H - R_b^2$

(VII)

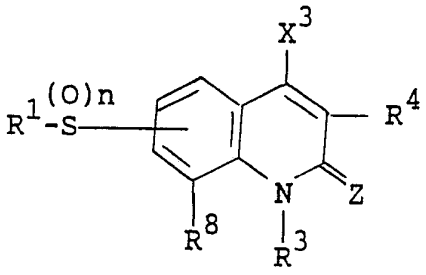
or a salt thereof



(Iℓ)

or a salt thereof

Process (10)

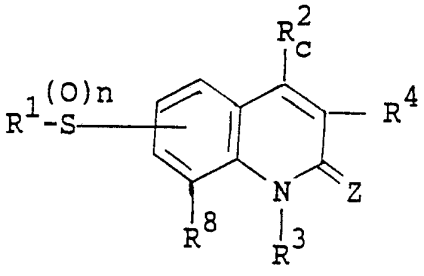


(Ik)

or a salt thereof

① $R^2_c - M^1$ (VIII)

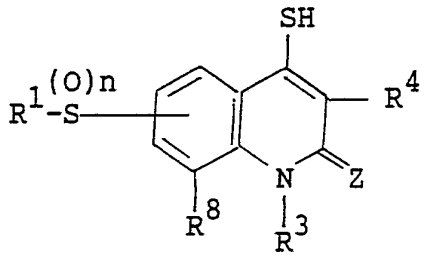
or a salt thereof



(Im)

or a salt thereof

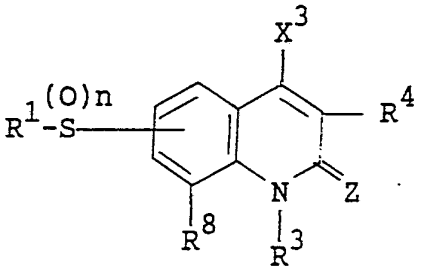
(2) Elimination reaction of the mercapto protective group



(In)

or a salt thereof

Process (11)



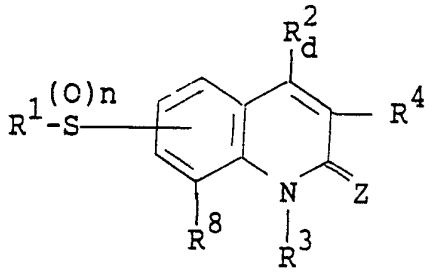
(Ik)

or a salt thereof

$R_d^2 - M^2$

(IX)

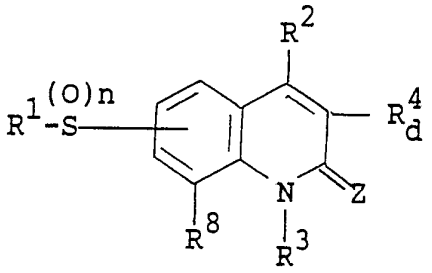
or a salt thereof



(Io)

or a salt thereof

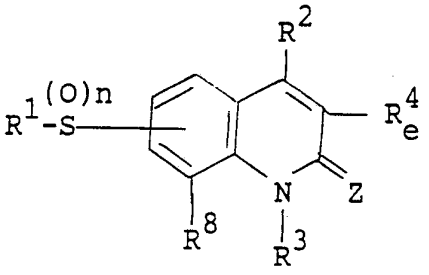
Process (12)



(Ip)

or a salt thereof

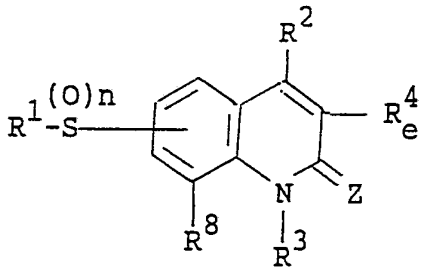
Reduction



(Iq)

or a salt thereof

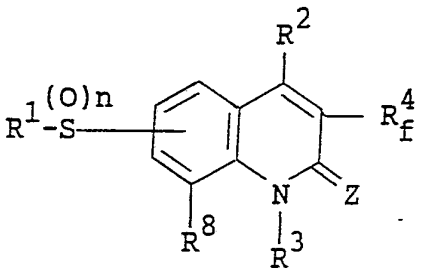
Process (13)



(Iq)

or a salt thereof

↓ Acylation



(Ir)

or a salt thereof

wherein R^1, R^2, R^3, R^4, R^8, Z and n are each as defined above,

$R^2_{a_2}$ is halogen,

R^2_b is amino or substituted amino,

$R^2_{c_2}$ is protected mercapto,

R^2_d is lower alkoxy,

$R^4_{a_4}$ is protected carboxy,

R^4_b is acyl having protected carboxy,

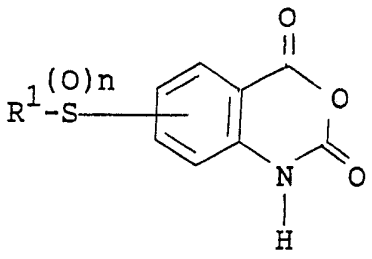
$R^4_{c_4}$ is acyl having carboxy,

R^4_d is acyl having nitro,

R^4_e is acyl having amino,
R^4_f is acyl having acylamino,
R^5 is a leaving group,
a group of the formula : $-CO-R^6$ is amidated carboxy,
X^1, X^2 and X^3 are each as a leaving group,
M^1 and M^2 are each as an alkali metal and
m is 1 or 2.

The starting compounds or salts thereof can be prepared by the following processes.

Process (A)



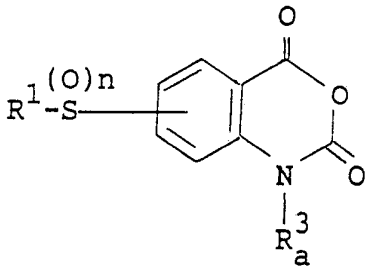
(IIa)

or a salt thereof

$R^3_a - X^4$

(X)

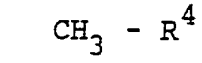
or a salt thereof



(IIb)

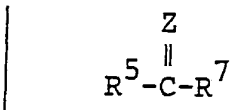
or a salt thereof

Process (B)



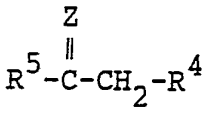
(XI)

or a salt thereof



(XII)

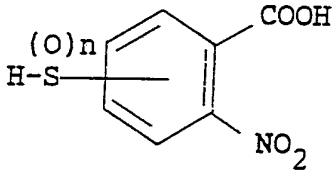
or a salt thereof



(III)

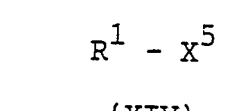
or a salt thereof

Process (C)



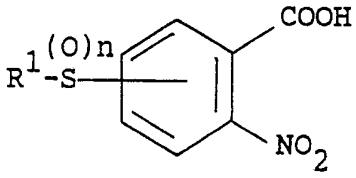
(XIII)

or a salt thereof



(XIV)

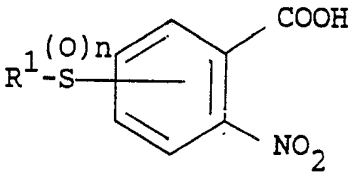
or a salt thereof



(XV)

or a salt thereof

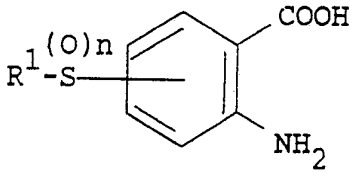
Process (D)



(XV)

or a salt thereof

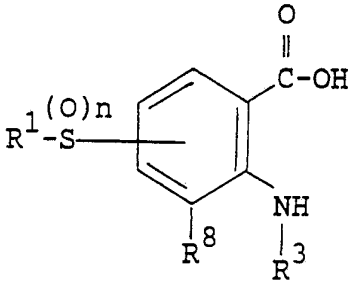
↓ Reduction



(XVIb)

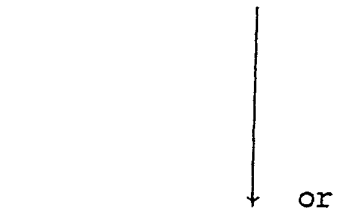
or a salt thereof

Process (E)



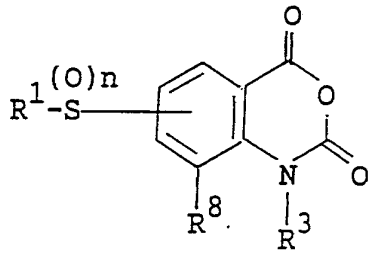
(XVIa)

or a salt thereof



(XVII)

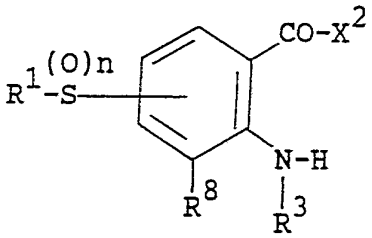
or a salt thereof



(II)

or a salt thereof

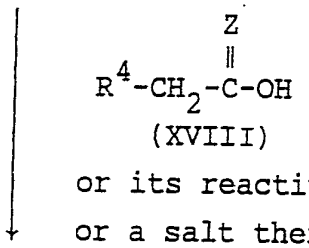
Process (F)



(XVIc)

or its reactive derivative,

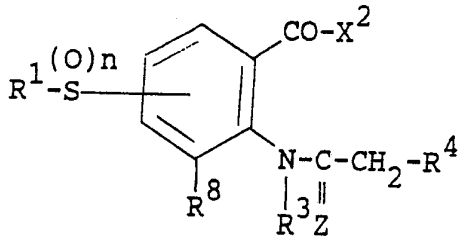
or a salt thereof



(XVIII)

or its reactive derivative,

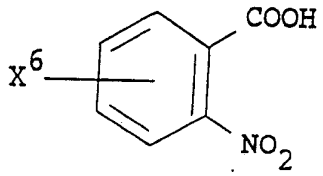
or a salt thereof



(VI)

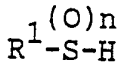
or a salt thereof

Process (G)



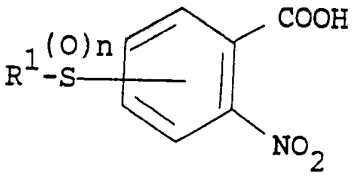
(XIX)

or a salt thereof



(XX)

or a salt thereof



(XV)

or a salt thereof

Process (H)

$R^4-CH_2-R^{12}$

(XXII)

or a salt thereof

↓ Elimination reaction of the carboxy protective group

R^4-CH_2-COOH

(XVIIIa)

or a salt thereof

wherein R^1, R^3, R^4, R^5, R^8, X^2, Z and n are each as defined above,

R^3_a is lower alkyl, lower alkoxy(lower)alkyl, or ar(lower)alkyl,

R^7, R^9, R^{10}, X^4, X^5 and X^6 are each as a leaving group, and

R^{12} is protected carboxy.

Suitable pharmaceutically acceptable salts of the object compound (I) are conventional non-toxic salts and may include e.g. a salt with a base or an acid addition salt such as a salt with an inorganic base, for example, an alkali metal salt (e.g. sodium salt, potassium salt, etc.), an alkaline earth metal salt (e.g. calcium salt, magnesium salt, etc.) an ammonium salt; a salt with an organic base, for example, an organic amine salt (e.g. triethylamine salt, pyridine salt, picoline salt, ethanolamine salt, triethanolamine salt, dicyclohexylamine

salt, N,N'-dibenzylethylenediamine salt, etc.);
an inorganic acid addition salt (e.g. hydrochloride, hydrobromide, sulfate, phosphate, etc.);
an organic carboxylic or sulfonic acid addition salt (e.g. formate, acetate, trifluoroacetate, maleate, tartrate, methanesulfonate, benzenesulfonate, toluenesulfonate, etc.); a salt with a basic or acidic amino acid (e.g. arginine, aspartic acid, glutamic acid, etc.).

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

The term "lower" is used to intend a group having 1 to 6 carbon atom(s), unless otherwise provided.

The term "higher" is used to intend a group having 7 to 20 carbon atoms, unless otherwise provided.

Suitable "lower alkyl" and "lower alkyl moiety" in the terms "lower alkoxy(lower)alkyl and "ar(lower)alkyl" may include straight or branched one such as methyl, ethyl, propyl, isopropyl, butyl, t-butyl, pentyl, neopentyl, hexyl, and the like, in which more preferable example may be C_1-C_5 alkyl.

Suitable "lower alkoxy" and "lower alkoxy moiety" in the term "lower alkoxy(lower)alkyl may include methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, t-butoxy, pentyloxy, t-pentyloxy, hexyloxy and the like.

Suitable "aryl" and "aryl moiety" in the term "ar(lower)alkyl" may include phenyl, naphthyl and the like.

Suitable "lower alkylene" may include straight or branched one such as methylene, ethylene, trimethylene, tetramethylene, pentamethylene, hexamethylene, methylmethylene, ethylethylene, propylene, and the like, in which more preferable example may be C_1-C_4 alkylene and

the most preferable one may be ethylene.

Suitable "halogen" may include chlorine, bromine, iodine and fluorine.

Suitable "alkali metal" may include sodium, potassium and the like.

Suitable substituent in the term "aryl which may have suitable substituent(s)" may include lower alkyl (e.g., methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tert-butyl, pentyl, neopentyl, tert-pentyl, hexyl, etc.), lower alkoxy (e.g., methoxy, ethoxy, propoxy, isopropoxy, isobutoxy, tert-butoxy, pentyloxy, neopentyloxy, tert-pentyloxy, hexyloxy, etc.), lower alkenyl (e.g., vinyl, 1-propenyl, allyl, 1-methylallyl, 1 or 2 or 3-butenyl, 1 or 2 or 3 or 4-pentenyl, 1 or 2 or 3 or 4 or 5-hexenyl, etc.), lower alkynyl (e.g., ethynyl, 1-propynyl, propargyl, 1-methylpropargyl, 1 or 2 or 3-butynyl, 1 or 2 or 3 or 4-pentynyl, 1 or 2 or 3 or 4 or 5-hexynyl, etc.), mono(or di or tri)halo(lower)alkyl (e.g. fluoromethyl, difluoromethyl, trifluoromethyl, chloromethyl, dichloromethyl, trichloromethyl, bromomethyl, dibromomethyl, tribromomethyl, 1 or 2-fluoroethyl, 1 or 2-bromoethyl, 1 or 2-chloroethyl, 1,1-difluoroethyl, 2,2-difluoroethyl, etc.), mono(or di or tri)halo(lower)alkoxy (e.g., fluoromethoxy, difluoromethoxy, trifluoromethoxy, chloromethoxy, dichloromethoxy, trichloromethoxy, bromomethoxy, dibromomethoxy, tribromomethoxy, etc.), halogen (e.g., chlorine, bromine, fluorine and iodine), carboxy, protected carboxy, hydroxy, protected hydroxy, aryl (e.g., phenyl, naphthyl, etc.), ar(lower)alkyl such as phenyl(lower)alkyl (e.g., benzyl, phenethyl, phenylpropyl, etc.), carboxy(lower)alkyl wherein lower alkyl moiety can be referred to the ones as exemplified above, protected carboxy(lower)alkyl wherein lower alkyl moiety can be referred to the ones as exemplified above and protected

carboxy moiety can be referred to the ones as exemplified below, amino, protected amino, di(lower)alkylamino (e.g., dimethylamino, diethylamino, diisopropylamino, ethylmethylamino, isopropylmethylamino, ethylisopropylamino, etc.), hydroxy(lower)alkyl, protected hydroxy(lower)alkyl, nitro, acyl, cyano, mercapto, lower alkylthio (e.g., methylthio, ethylthio, propylthio, isopropylthio, butylthio, etc.), imino, and the like.

Suitable "acyl" may include carbamoyl, thiocarbamoyl, aliphatic acyl group and acyl group containing an aromatic ring, which is referred to as aromatic acyl, or heterocyclic ring, which is referred to as heterocyclic acyl.

Suitable example of said acyl may be illustrated as follows :-

Carbamoyl; Thiocarbamoyl;

Aliphatic acyl such as lower or higher alkanoyl (e.g. formyl, acetyl, propanoyl, butanoyl, 2-methylpropanoyl, pentanoyl, 2,2-dimethylpropanoyl, hexanoyl, heptanoyl, octanoyl, nonanoyl, decanoyl, undecanoyl, dodecanoyl, tridecanoyl, tetradecanoyl, pentadecanoyl, hexadecanoyl, heptadecanoyl, octadecanoyl, nonadecanoyl, icosanoyl, etc.);

lower or higher alkoxycarbonyl (e.g. methoxycarbonyl, ethoxycarbonyl, t-butoxycarbonyl, t-pentyloxycarbonyl, heptyloxycarbonyl, etc.);

lower or higher alkylsulfonyl (e.g. methylsulfonyl, ethylsulfonyl, etc.);

lower or higher alkoxysulfonyl (e.g. methoxysulfonyl, ethoxysulfonyl, etc.); aminosulfonyl; or the like.

Aromatic acyl such as

aroyl (e.g. benzoyl, toluoyl, naphthoyl, etc.);

ar(lower)alkanoyl [e.g. phenyl(lower)alkanoyl (e.g.

phenylacetyl, phenylpropanoyl, phenylbutanoyl, phenylisobutylyl, phenylpentanoyl, phenylhexanoyl, etc.), naphthyl(lower)alkanoyl (e.g. naphthylacetyl, naphthylpropanoyl, naphthylbutanoyl, etc.), etc.];

ar(lower)alkenoyl [e.g. phenyl(lower)alkenoyl (e.g. phenylpropenoyl, phenylbutenoyl, phenylmethacryloyl, phenylpentenoyl, phenylhexenoyl, etc.), naphthyl(lower)alkenoyl (e.g. naphthylpropenoyl, naphthylbutenoyl, naphthylpentenoyl, etc.), etc.];

ar(lower)alkoxycarbonyl [e.g. phenyl(lower)alkoxycarbonyl (e.g. benzyloxycarbonyl, etc.), etc.];

ar(lower)cycloalkylcarbonyl [e.g. phenyl(lower)cycloalkylcarbonyl (e.g., 1-phenyl-1-cyclopropylcarbonyl, 1-phenyl-1-cyclopentylcarbonyl, etc.), etc.];

aryloxycarbonyl (e.g., phenoxycarbonyl, naphthyloxycarbonyl, etc.);

aryloxy(lower)alkanoyl (e.g. phenoxyacetyl, phenoxypropionyl, etc.);

arylglyoxyloyl (e.g. phenylglyoxyloyl, naphthylglyoxyloyl, etc.);

arenesulfonyl (e.g. benzenesulfonyl, p-toluenesulfonyl, etc.);

ar(lower)alkylsulfonyl [e.g. phenyl(lower)alkylsulfonyl, (e.g. benzylsulfonyl, etc.), etc.]; or the like.

Heterocyclic acyl such as heterocycliccarbonyl; heterocyclic(lower)alkanoyl (e.g., heterocyclicacetyl, heterocyclcpropanoyl, heterocyclicbutanoyl, heterocyclicpentanoyl, heterocyclichexanoyl, etc.); heterocyclic(lower)alkenoyl (e.g. heterocyclicpropenoyl, heterocyclicbutenoyl, heterocyclicpentenoyl,

heterocyclichexenoyl, etc.);
heterocyclicglyoxyloyl (e.g. thiazolylglyoxyloyl, thienylglyoxyloyl, etc.); or the like; in which suitable heterocyclic moiety in the terms "heterocycliccarbonyl", "heterocyclic(lower)alkanoyl", "heterocyclic(lower)alkenoyl" and "heterocyclicglyoxyloyl" as mentioned above means, in more detail, saturated or unsaturated, monocyclic or polycyclic heterocyclic group containing at least one hetero-atom such as an oxygen, sulfur, nitrogen atom and the like.

And, especially preferable heterocyclic group may be heterocyclic group such as

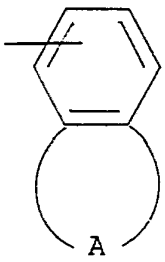
unsaturated 3 to 8-membered (more preferably 5 or 6-membered) heteromonocyclic group containing 1 to 4-nitrogen atom(s), for example, pyrrolyl, pyrrolinyl, imidazolyl, pyrazolyl, pyridyl and its N-oxide, dihydropyridyl, pyrimidyl, pyrazinyl, pyridazinyl, triazolyl (e.g. 4H-1,2,4-triazolyl, 1H-1,2,3-triazolyl, 2H-1,2,3-triazolyl, etc.), tetrazolyl (e.g. 1H-tetrazolyl, 2H-tetrazolyl, etc.), etc.;
saturated 3 to 8-membered (more preferably 5 or 6-membered) heteromonocyclic group containing 1 to 4 nitrogen atom(s), for example, pyrrolidinyl, imidazolidinyl, piperidyl, piperazinyl, etc.;
unsaturated condensed heterocyclic group containing 1 to 4 nitrogen atom(s), for example, indolyl, isoindolyl, indolinyl, indolizinyl, benzimidazolyl, quinolyl, isoquinolyl, indazolyl, benzotriazolyl, etc.;
unsaturated 3 to 8-membered (more preferably 5 or 6-membered) heteromonocyclic group containing 1 to 2 oxygen atom(s) and 1 to 3 nitrogen atom(s), for example, oxazolyl, isoxazolyl, oxadiazolyl (e.g. 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl, 1,2,5-oxadiazolyl, etc.) etc.;
saturated 3 to 8-membered (more preferably 5 or 6-

membered) heteromonocyclic group containing 1 to 2 oxygen atom(s) and 1 to 3 nitrogen atom(s), for example, morpholinyl, sydnonyl, etc.;
unsaturated condensed heterocyclic group containing 1 to 2 oxygen atom(s) and 1 to 3 nitrogen atom(s), for example, benzoxazolyl, benzoxadiazolyl, benzoxazinyl (e.g. 2H-1,4-benzoxazinyl, etc.), dihydrobenzoxazinyl (e.g. 2H-3,4-dihydro-1,4-benzoxazinyl, etc.), etc.;
unsaturated 3 to 8-membered (more preferably 5 or 6-membered) heteromonocyclic group containing 1 to 2 sulfur atom(s) and 1 to 3 nitrogen atom(s), for example, thiazolyl, isothiazolyl, thiadiazolyl (e.g. 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,3,4-thiadiazolyl, 1,2,5-thiadiazolyl, etc.), dihydrothiadiazolyl, etc.;
saturated 3 to 8-membered (more preferably 5 or 6-membered) heteromonocyclic group containing 1 to 2 sulfur atom(s) and 1 to 3 nitrogen atom(s), for example, thiazolidinyl, etc.;
unsaturated 3 to 8-membered (more preferably 5 or 6-membered) heteromonocyclic group containing 1 to 2 sulfur atom(s), for example, thienyl, dihydrodithiinyl, dihydrodithionyl, etc.;
unsaturated condensed heterocyclic group containing 1 to 2 sulfur atom(s) and 1 to 3 nitrogen atom(s), for example, benzothiazolyl, benzothiadiazolyl, benzothiazinyl (e.g. 2H-1,4-benzothiazinyl, etc.), dihydrobenzothiazinyl (e.g. 2H-3,4-dihydrobenzothiazinyl, etc.), etc.;
unsaturated 3 to 8-membered (more preferably 5 or 6-membered) heteromonocyclic group containing an oxygen atom, for example, furyl, etc.;
unsaturated condensed heterocyclic group containing 1 to 2 oxygen atom(s), for example, benzodioxolyl (e.g. 1,3-benzodioxolyl, etc.), etc.;
unsaturated 3 to 8-membered (more preferably 5 or

6-membered) heteromonocyclic group containing an oxygen atom and 1 to 2 sulfur atom(s), for example, dihydrooxathiinyl, etc.;
unsaturated condensed heterocyclic group containing 1 to 2 sulfur atom(s), for example, benzothienyl, benzodithiinyl, etc.;
unsaturated condensed heterocyclic group containing an oxygen atom and 1 to 2 sulfur atom(s), for example benzoxathiinyl, etc.; and the like.

The acyl moiety as stated above may have one to ten, same or different, suitable substituent(s) such as lower alkyl;
lower alkoxy (e.g. methoxy, ethoxy, propoxy, etc.);
lower alkylthio (e.g. methylthio, ethylthio, etc.);
lower alkylamino (e.g. methylamino, etc.); lower cycloalkyl (e.g. cyclopentyl, cyclohexyl, etc.); lower cycloalkenyl (e.g. cyclohexenyl, etc.); halogen; amino; protected amino; hydroxy; protected hydroxy; cyano; nitro; carboxy; protected carboxy; sulfo; sulfamoyl; imino; oxo; amino(lower)alkyl (e.g. aminomethyl, aminoethyl, etc.); carbamoyloxy; hydroxy(lower)alkyl (e.g. hydroxymethyl, 1 or 2-hydroxyethyl, 1 or 2 or 3-hydroxypropyl, etc.); ar(lower)alkyl [e.g. phenyl(lower)alkyl (e.g., benzyl, phenylpropyl, phenylbutyl, etc.), etc.];
aryl which may have 1 to 3, same or different, suitable substituent(s) [e.g., lower alkyl; halogen; lower alkoxy; lower alkylthio, di(lower)alkylamino (e.g., dimethylamino, diethylamino, dipropylamino, etc.); cyano; mono(or di or tri)halo(lower)alkyl (e.g., fluoromethyl, chloromethyl, bromomethyl, difluoromethyl, dichloromethyl, dibromomethyl, trifluoromethyl, trichloromethyl, tribromomethyl, 1-(or 2-)fluoroethyl, 1-(or 2-)chloromethyl, 1-(or 2-)bromomethyl, etc.);
mono(or di or tri)halo(lower)alkoxy (e.g.,

fluoromethoxy, chloromethoxy, bromomethoxy, difluoromethoxy, dichloromethoxy, dibromomethoxy, trifluoromethoxy, trichloromethoxy, tribromomethoxy, 1-(or 2-)fluoroethoxy, 1-(or 2-)chloroethoxy, 1-(or 2-)bromoethoxy, etc.);
carboxy; protected carboxy [e.g., esterified carboxy {e.g. lower alkoxycarbonyl (e.g., methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, etc.), etc.}, etc.]; acyl [e.g., lower alkanoyl (e.g., formyl, acetyl, propanoyl, butanoyl, etc.), etc.]; nitro; amino; protected amino [e.g. acylamino {e.g., lower alkanoylamino (e.g., formylamino, acetylamino, etc.), etc.}, etc.]; etc.];
a group of the formula :



(in which A is lower alkylene as exemplified above);
heterocyclic group which may have suitable substituent(s) [e.g., lower alkyl; lower alkoxy; lower alkylthio; lower alkylamino; lower cycloalkyl; lower cycloalkenyl; halogen; amino; protected amino, etc.]; or the like.

Suitable "protected hydroxy" may be acyloxy group or the like.

Suitable "protected mercapto" may be acylthio group or the like.

Suitable "substituted amino" may be protected amino or lower alkylamino or the like.

Suitable "protected amino" may be acylamino group or the like.

Suitable "acyl moiety" in the terms "acyloxy",

"acylthio" and "acylamino" can be referred to the ones as exemplified above.

Suitable "lower alkyl moiety" in the term "lower alkylamino" can be referred to the ones as exemplified above.

Suitable "leaving group" may include lower alkoxy (e.g. methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, t-butoxy, pentoxy, etc.), aryloxy (e.g. phenoxy, napthoxy, etc.), an acid residue or the like, and suitable examples of "acid residue" may be halogen (e.g. chlorine, bromine, iodine, etc.), sulfonyloxy (e.g. methanesulfonyloxy, benzenesulfonyloxy, toluenesulfonyloxy, etc.) or the like.

Suitable "amidated carboxy" may include carbamoyl which may be substituted with one or two suitable substituent(s), a group of the formula : -CO-N< (wherein a group of the formula : -N< is a heterocyclic group containing at least one nitrogen atom), and the like.

Suitable "organic group" may include lower alkyl, lower alkenyl, lower alkynyl, aryl, ar(lower)alkyl, carboxy, ar(lower)alkylsulfinyl, ar(lower)alkylthio, cyano, acyl, heterocyclic group which may have suitable substituent(s), and the like.

Suitable "lower alkyl" and "lower alkyl moiety" in the terms "ar(lower)alkyl", "ar(lower)alkylsulfinyl" and "ar(lower)alkylthio" can be referred to the ones as exemplified above.

Suitable "lower alkenyl" may include vinyl, 1-propenyl, allyl, 1-methylallyl, 1 or 2 or 3-butenyl, 1 or 2 or 3 or 4-pentenyl, 1 or 2 or 3 or 4 or 5-hexenyl and the like.

Suitable "lower alkynyl" may include ethynyl, 1-propynyl, propargyl, 1-methylpropargyl, 1 or 2 or 3 butynyl, 1 or 2 or 3 or 4-pentynyl, 1 or 2 or 3 or 4 or

5-hexynyl and the like.

Suitable "aryl" and "aryl moiety" in the terms "ar(lower)alkyl", "ar(lower)alkylsulfinyl" and "ar(lower)alkylthio" can be referred to the ones as exemplified above.

Suitable "acyl" can be referred to the ones as exemplified above.

Suitable "heterocyclic group" can be referred to the ones as exemplified above.

Suitable "substituent" in the term "heterocyclic group which may have suitable substituent(s)" may include lower alkyl (e.g., methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tert-butyl, pentyl, neopentyl, tert-pentyl, hexyl, etc.), lower alkoxy (e.g., methoxy, ethoxy, propoxy, isopropoxy, isobutoxy, tert-butoxy, pentyloxy, neopentyloxy, tert-pentyloxy, hexyloxy, etc.), lower alkenyl (e.g., vinyl, 1-propenyl, allyl, 1-methylallyl, 1 or 2 or 3-butenyl, 1 or 2 or 3 or 4-pentenyl, 1 or 2 or 3 or 4 or 5-hexenyl, etc.), lower alkynyl (e.g., ethynyl, 1-propynyl, propargyl, 1-methylpropargyl, 1 or 2 or 3-butynyl, 1 or 2 or 3 or 4-pentynyl, 1 or 2 or 3 or 4 or 5-hexynyl, etc.), mono(or di or tri)halo(lower)alkyl (e.g. fluoromethyl, difluoromethyl, trifluoromethyl, chloromethyl, dichloromethyl, trichloromethyl, bromomethyl, dibromomethyl, tribromomethyl, 1 or 2-fluoroethyl, 1 or 2-bromoethyl, 1 or 2-chloroethyl, 1,1-difluoroethyl, 2,2-difluoroethyl, etc.), halogen (e.g., chlorine, bromine, fluorine and iodine), carboxy, protected carboxy, hydroxy, protected hydroxy, aryl (e.g., phenyl, naphthyl, etc.), ar(lower)alkyl such as phenyl(lower)alkyl (e.g., benzyl, phenethyl, phenylpropyl, etc.), carboxy(lower)alkyl wherein lower alkyl moiety can be referred to the ones as exemplified above, protected carboxy(lower)alkyl wherein lower alkyl moiety can be referred to the ones as exemplified above and protected

carboxy moiety can be referred to the ones as exemplified below, amino, protected amino, di(lower)alkylamino (e.g., dimethylamino, diethylamino, diisopropylamino, ethylmethylamino, isopropylmethylamino, ethylisopropylamino, etc.), hydroxy(lower)alkyl, protected hydroxy(lower)alkyl, nitro, acyl, cyano, mercapto, lower alkylthio (e.g., methylthio, ethylthio, propylthio, isopropylthio, butylthio, etc.), imino, and the like.

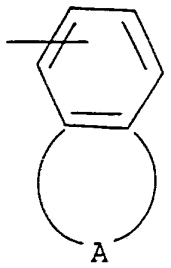
Suitable "substituent" in the term "carbamoyl which may be substituted with one or two suitable substituent(s)" may include lower alkyl;
lower alkoxy (e.g. methoxy, ethoxy, propoxy, etc.);
lower alkylthio (e.g. methylthio, ethylthio, etc.);
lower alkylamino (e.g. methylamino, etc.);
lower cycloalkyl (e.g. cyclopentyl, cyclohexyl, etc.);
lower cycloalkenyl (e.g. cyclohexenyl, etc.); halogen;
amino; protected amino; hydroxy; protected hydroxy; cyano;
nitro; carboxy; protected carboxy; sulfo; sulfamoyl;
imino; oxo; amino(lower)alkyl (e.g. aminomethyl, aminoethyl, etc.); carbamoyloxy; hydroxy(lower)alkyl (e.g. hydroxymethyl, 1 or 2-hydroxyethyl, 1 or 2 or 3 hydroxypropyl, etc.);
ar(lower)alkyl [e.g., phenyl(lower)alkyl (e.g., benzyl, phenylpropyl, phenylbutyl, etc.), etc.];
aryl which may have 1 to 3, same or different, suitable substituent(s) [e.g., lower alkyl; halogen; lower alkoxy; lower alkylthio; di(lower)alkylamino (e.g., dimethylamino, diethylamino, dipropylamino, etc.); cyano;
mono(or di or tri)halo(lower)alkyl (e.g., fluoromethyl, chloromethyl, bromomethyl, difluoromethyl, dichloromethyl, dibromomethyl, trifluoromethyl, trichloromethyl, tribromomethyl, 1-(or 2-)fluoroethyl, 1-(or 2-)chloromethyl, 1-(or 2-)bromomethyl etc.);

mono(or di or tri)halo(lower)alkoxy (e.g., fluoromethoxy, chloromethoxy, bromomethoxy,

difluoromethoxy, dichloromethoxy, dibromomethoxy, trifluoromethoxy, trichloromethoxy, tribromomethoxy, 1-(or 2-)fluoroethoxy, 1-(or 2-)chloroethoxy, 1-(or 2-)bromoethoxy, etc.);

carboxy; protected carboxy [e.g. esterified carboxy {e.g., lower alkoxycarbonyl (e.g., methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, etc.), etc.}, etc.], acyl [e.g., lower alkanoyl (e.g., formyl, acetyl, propanoyl, butanoyl, etc.), etc.]; nitro; amino; protected amino [e.g. acylamino {e.g., lower alkanoylamino (e.g., formylamino, acetylamino, etc.), etc.}, etc.], etc.];

a group of the formula :



(in which A is lower alkylene as exemplified above); or heterocyclic group which may have suitable substituent(s) [e.g. lower alkyl; lower alkoxy; lower alkylthio; lower alkylamino; lower cycloalkyl, lower cycloalkenyl; halogen; amino; protected amino, etc.]; or the like.

Suitable "heterocyclic group" can be referred to the ones as exemplified above.

Suitable "protected carboxy" may include esterified carboxy and the like. An suitable examples of said ester moiety may be the ones such as lower alkyl ester (e.g., methyl ester, ethyl ester, propyl ester, isopropyl ester, butyl ester, isobutyl ester, t-butyl ester, pentyl ester, t-pentyl ester, hexyl ester, 1-cyclopropylethyl ester, etc.);

lower alkenyl ester (e.g., vinyl ester, allyl ester, etc.);

lower alkynyl ester (e.g., ethynyl ester, propynyl ester,

etc.);
lower alkoxyalkyl ester (e.g., methoxymethyl ester, ethoxymethyl ester, isopropoxymethyl ester, 1-methoxyethyl ester, 1-ethoxyethyl ester, etc.);
lower alkylthioalkyl ester (e.g., methylthiomethyl ester, ethylthiomethyl ester, ethylthioethyl ester, isopropylthiomethyl ester, etc.);
mono(or di or tri)halo(lower)alkyl ester (e.g. 2-iodoethyl ester, 2,2,2-trichloroethyl ester, etc.);
lower alkanoyloxy(lower)alkyl ester (e.g., acetoxymethyl ester, propionyloxymethyl ester, butyryloxymethyl ester, valeryloxymethyl ester, pivaloyloxymethyl ester, hexanoyloxymethyl ester, 2-acetoxyethyl ester, 2-propionyloxyethyl ester, etc.);
lower alkanesulfonyl(lower)alkyl ester (e.g. mesylmethyl ester, 2-mesylethyl ester etc.);
ar(lower)alkyl ester, for example, phenyl(lower)alkyl ester which may have one or more suitable substituent(s) (e.g., benzyl ester, 4-methoxybenzyl ester, 4-nitrobenzyl ester, phenethyl ester, trityl ester, benzhydryl ester, bis(methoxyphenyl)methyl ester, 3,4-dimethoxybenzyl ester, 4-hydroxy-3,5-di-t-butylbenzyl ester, etc.);
aryl ester which may have one or more suitable substituent(s) such as substituted or unsubstituted phenyl ester (e.g., phenyl ester, tolyl ester, t-butylphenyl ester, xylyl ester, mesityl ester, cumenyl ester, 4-chlorophenyl ester, 4-methoxyphenyl ester, etc.);
tri(lower)alkyl silyl ester;
lower alkylthioester (e.g. methylthioester, ethylthioester, etc.) and the like.

Suitable "heterocyclic group containing at least one nitrogen atom" may include

unsaturated 3 to 8-membered (more preferably 5 or 6-membered) heteromonocyclic group containing 1 to 4-nitrogen atom(s), for example, pyrrolyl, pyrrolinyl,

imidazolyl, pyrazolyl, dihydropyridyl, pyrazinyl, pyridazinyl, triazolyl (e.g. 4H-1,2,4-triazolyl, 1H-1,2,3-triazolyl, 2H-1,2,3-triazolyl, etc.), tetrazolyl (e.g. 1H-tetrazolyl, 2H-tetrazolyl, etc.), etc.;
saturated 3 to 8-membered (more preferably 5 or 6-membered) heteromonocyclic group containing 1 to 4 nitrogen atom(s), for example pyrrolidinyl, imidazolidinyl, piperidyl, piperazinyl, etc.;
unsaturated condensed heterocyclic group containing 1 to 4 nitrogen atom(s), for example, indolyl, isoindolyl, indolinyl, benzimidazolyl, indazolyl, benzotriazolyl, etc.;
saturated 3 to 8-membered (more preferably 5 or 6-membered) heteromonocyclic group containing 1 to 2 oxygen atom(s) and 1 to 3 nitrogen atom(s), for example, morpholinyl, etc.;
unsaturated 3 to 8-membered (more preferably 5 or 6-membered) heteromonocyclic group containing 1 to 2 sulfur atom(s) and 1 to 3 nitrogen atom(s), for example, dihydrothiazinyl, etc.;
saturated 3 to 8-membered (more preferably 5 or 6-membered) heteromonocyclic group containing 1 to 2 sulfur atom(s) and 1 to 3 nitrogen atom(s), for example, thiazolidinyl, etc.;
unsaturated condensed heterocyclic group containing 1 to 2 oxygen atom(s) and 1 to 3 nitrogen atom(s), for example, benzoxazolyl, benzoxadiazolyl, benzoxazinyl, dihydrobenzoxazinyl (e.g. 2H-3,4-dihydro-1,4-benzoxazinyl, etc.);
unsaturated condensed heterocyclic group containing 1 to 2 sulfur atom(s) and 1 to 3 nitrogen atom(s), for example benzothiazolyl, benzothiadiazolyl, benzothiazinyl, dihydrobenzothiazinyl (e.g., 2H-3,4-dihydrobenzothiazinyl, etc.), etc.; and the like.

The processes for preparing the object and starting compounds are explained in detail in the following.

Process (1)

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

The reaction is usually carried out in a conventional solvent such as chloroform, ether, tetrahydrofuran, benzene, N,N-dimethylformamide, N,N-dimethylacetamide or any other organic solvent which does not adversely influence the reaction.

The reaction temperature is not critical and the reaction is usually carried out under cooling to heating.

The reaction is usually carried out in the presence of an inorganic or an organic base such as an alkali metal hydroxide, an alkali metal hydrogencarbonate, alkali metal carbonate, alkali metal hydride (e.g., sodium hydride, etc.), alkali metal acetate, di(lower)alkylamine (e.g., diisopropylamine, etc.), tri(lower)alkylamine, pyridine base (e.g., pyridine, lutidine, picoline, dimethylaminopyridine, etc.), N-(lower)alkylmorpholine, N,N-di(lower)alkylbenzylamine, N,N-di(lower)alkylaniline or the like.

Process (2)

The compound (Ic) or a salt thereof can be prepared by subjecting the compound (Ib) or a salt thereof to oxidation reaction.

Oxidation is carried out in a conventional manner, which is capable of oxidizing a sulfur atom to an oxidized sulfur atom, and suitable oxidizing reagent may be oxygen acid such as periodate (e.g. sodium periodate, potassium periodate, etc.), peroxy acid such as peroxybenzoic acids (e.g. peroxybenzoic acid, m-chloroperoxybenzoic acid, etc.), and the like.

The reaction is usually carried out in a conventional solvent such as water, alcohol (e.g., methanol, ethanol,

isopropyl alcohol, etc.), tetrahydrofuran, dioxane, dichloromethane, chloroform, N,N-dimethyl acetamide, N,N-dimethylformamide or any other organic solvent which does not adversely influence the reaction. Among these solvents, hydrophilic solvents may be used in a mixture with water.

The reaction temperature is not critical and the reaction is usually carried out under cooling to heating.

Process (3)

The compound (Ie) or a salt thereof can be prepared by subjecting the compound (Id) or its reactive derivative at the carboxy group or a salt thereof to amidation reaction.

Suitable amidating reagent to be used in the present amidation reaction may include a compound of the formula :

$$H - R^6 \qquad \text{(XXIII)}$$

(wherein R^6 is as defined above)
or its reactive derivative or a salt thereof, and the like.

Suitable reactive derivative of the compound (XXIII) may include Schiff's base type imino or its tautomeric enamine type isomer formed by the reaction of the compound (XXIII) with a carbonyl compound such as aldehyde, ketone or the like; a silyl derivative formed by the reaction of the compound (XXIII) with a silyl compound such as bis(trimethylsilyl)acetamide, mono(trimethylsilyl)-acetamide [e.g. N-(trimethylsilyl)acetamide], bis(trimethylsilyl)urea or the like;
a derivative formed by reaction of the compound (XXIII) with phosphorus trichloride or phosgene, and the like.

Suitable reactive derivative at the carboxy group of the compound (Id) may include an acid halide, an acid

anhydride, an activated amide, an activated ester, and the like. Suitable examples of the reactive derivatives may be an acid chloride; an acid azide; a mixed acid anhydride with an acid such as substituted phosphoric acid [e.g. dialkylphosphoric acid, phenylphosphoric acid, diphenylphosphoric acid, dibenzylphosphoric acid, halogenated phosphoric acid, etc.], dialkylphosphorous acid, sulfurous acid, thiosulfuric acid, sulfuric acid, sulfonic acid [e.g. methanesulfonic acid, etc.], aliphatic carboxylic acid [e.g. acetic acid, propionic acid, butyric acid, isobutyric acid, pivalic acid, pentanoic acid, isopentanoic acid, 2-ethylbutyric acid, trichloroacetic acid, etc.] or aromatic carboxylic acid [e.g. benzoic acid, etc.]; a symmetrical acid anhydride; an activated amide with imidazole, 4-substituted imidazole, dimethylpyrazole, triazole or tetrazole; or an activated ester [e.g. cyanomethyl ester, methoxymethyl ester, dimethyliminomethyl [$(CH_3)_2\overset{+}{N}=CH-$] ester, vinyl ester, ethyl ester, propargyl ester, p-nitrophenyl ester, 2,4-dinitrophenyl ester, trichlorophenyl ester, pentachlorophenyl ester, mesylphenyl ester, phenylazophenyl ester, phenyl thioester, p-nitrophenyl thioester, p-cresyl thioester, carboxymethyl thioester, pyranyl ester, pyridyl ester, piperidyl ester, 8-quinolyl thioester, etc.], or an ester with a N-hydroxy compound [e.g. N,N-dimethyl hydroxylamine, 1-hydroxy-2-(1H)-pyridone, N-hydroxysuccinimide, N-hydroxyphthalimide, 1-hydroxy-1H-benzotriazole, etc.], and the like. These reactive derivatives can optionally be selected from them according to the kind of the compound (Id) to be used.

The reaction is usually carried out in a conventional solvent such as water, alcohol [e.g. methanol, ethanol, etc.], acetone, dioxane, acetonitrile, chloroform,

methylene chloride, ethylene chloride, tetrahydrofuran, toluene, ethyl acetate, N,N-dimethylformamide, pyridine or any other organic solvent which does not adversely influence the reaction. These conventional solvent may also be used in a mixture with water. When the base and/or the starting compound are in liquid, they can be used also as a solvent.

In this reaction, when the compound (Id) is used in a free acid form or its salt form, the reaction is preferably carried out in the presence of a conventional condensing agent such as N,N'-dicyclohexylcarbodiimide; N-cyclohexyl-N'-morpholinoethylcarbodiimide; N-cyclohexyl-N'-(4-diethylaminocyclohexyl)carbodiimide; N,N'-diethylcarbodiimide, N,N'-diisopropylcarbodiimide; N-ethyl-N'-(3-dimethylaminopropyl)carbodiimide; N,N'-carbonyl-bis(2-methylimidazole); pentamethyleneketene-N-cyclohexylimine; diphenylketene-N-cyclohexylimine; ethoxyacetylene; 1-alkoxy-1-chloroethylene; trialkyl phosphite; ethyl polyphosphate; isopropyl polyphosphate; phosphorus oxychloride (phosphoryl chloride); phosphorus trichloride; thionyl chloride; oxalyl chloride; lower alkyl haloformate [e.g. ethyl chloroformate, isopropyl chloroformate, etc.]; triphenylphosphine; 2-ethyl-7-hydroxybenzisoxazolium salt; 2-ethyl-5-(m-sulfophenyl)isoxazolium hydroxide intramolecular salt; 1-(p-chlorobenzenesulfonyloxy)-6-chloro-1H-benzotriazole; so-called Vilsmeier reagent prepared by the reaction of N,N-dimethylformamide with thionyl chloride, phosgene, trichloromethyl chloroformate, phosphorus oxychloride, etc.; or the like.

The reaction may also be carried out in the presence of an inorganic or organic base such as an alkali metal bicarbonate, tri(lower)alkylamine, pyridine, N-(lower)alkylmorpholine, N,N-di(lower)alkylbenzylamine, or the like.

The reaction temperature is not critical, and the reaction is usually carried out under cooling to heating.

Process (4)

The compound (Id) or a salt thereof can be prepared by subjecting the compound (If) or a salt thereof to elimination reaction of the carboxy protective group in R_a^4.

This reaction is carried out in accordance with a conventional method such as hydrolysis, reduction or the like.

The hydrolysis is preferably carried out in the presence of a base or an acid including Lewis acid. Suitable base may include an inorganic base and an organic base such as an alkali metal [e.g. sodium, potassium, etc.], an alkaline earth metal [e.g. magnesium, calcium, etc.], the hydroxide or carbonate or bicarbonate thereof, trialkylamine [e.g. trimethylamine, triethylamine, etc.], picoline, 1,5-diazabicyclo[4.3.0]non-5-ene, 1,4-diazabicyclo[2.2.2]octane, 1,8-diazabicyclo[5.4.0]-undec-7-ene, or the like.

Suitable acid may include an organic acid [e.g. formic acid, acetic acid, propionic acid, trichloroacetic acid, trifluoroacetic acid, etc.] and an inorganic acid [e.g. hydrochloric acid, hydrobromic acid, sulfuric acid, hydrogen chloride, hydrogen bromide, etc.]. The elimination using Lewis acid such as trihaloacetic acid [e.g. trichloroacetic acid, trifluoroacetic acid, etc.] or the like is preferably carried out in the presence of cation trapping agent [e.g. anisole, phenol, etc.].

The reaction is usually carried out in a solvent such as water, an alcohol [e.g. methanol, ethanol, etc.], methylene chloride, tetrahydrofuran, a mixture thereof or any other solvent which does not adversely affect the reaction. A liquid base or acid can be also used as the

solvent. The reaction temperature is not critical and the reaction is usually carried out under cooling to warming.

The reduction method applicable for the elimination reaction may include chemical reduction and catalytic reduction.

Suitable reducing agents to be used in chemical reduction are a combination of metal [e.g. tin, zinc, iron, etc.] or metallic compound [e.g. chromium chloride, chromium acetate, etc.] and an organic or inorganic acid [e.g. formic acid, acetic acid, propionic acid, trifluoroacetic acid, p-toluenesulfonic acid, hydrochloric acid, hydrobromic acid, etc.].

Suitable catalysts to be used in catalytic reduction are conventional ones such as platinum catalysts [e.g. platinum plate, spongy platinum, platinum black, colloidal platinum, platinum oxide, platinum wire, etc.], palladium catalysts [e.g. spongy palladium, palladium black, palladium oxide, palladium on carbon, colloidal palladium, palladium on barium sulfate, palladium on barium carbonate, etc.], nickel catalysts [e.g. reduced nickel, nickel oxide, Raney nickel, etc.], cobalt catalysts [e.g. reduced cobalt, Raney cobalt, etc.], iron catalysts [e.g. reduced iron, Raney iron, etc.], copper catalysts [e.g. reduced copper, Raney copper, Ullman copper, etc.] and the like.

The reduction is usually carried out in a conventional solvent which does not adversely affect the reaction such as water, methanol, ethanol, propanol, N,N-dimethylformamide, or a mixture thereof. Additionally, in case that the above-mentioned acids to be used in chemical reduction are in liquid, they can also be used as a solvent, further, a suitable solvent to be used in catalytic reduction may be the above-mentioned solvent, and other conventional solvent such as diethyl ether, dioxane, tetrahydrofuran, etc., or a mixture thereof.

The reaction temperature of this reduction is not critical and the reaction is usually carried out under cooling to heating.

Process (5)

The compound (Ih) or a salt thereof can be prepared by subjecting the compound (Ig) or a salt thereof to elimination reaction of the carboxy protective group in R_b^4.

This elimination can be carried out in a similar manner to that of the aforementioned Process (4), and therefore the reagents to be used and the reaction conditions (e.g., solvent, reaction temperature, etc.) can be referred to those of the Process (4).

Process (6)

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

This reaction is usually carried out in a solvent such as water, alcohol (e.g., methanol, ethanol, etc.), benzene, N,N-dimethylformamide, tetrahydrofuran, toluene, methylene chloride, ethylene dichloride, chloroform, diethyl ether or any other solvent which does not adversely affect the reaction.

The reaction temperature is not critical and the reaction is usually carried out under warming to heating.

When the starting compound is in liquid, it can be also used as a solvent.

Process (7)

The compound (Ia) or a salt thereof can be prepared by subjecting the compound (VI) or a salt thereof to cyclization reaction.

This reaction is usually carried out in a solvent

such as water, alcohol (e.g., methanol, ethanol, etc.), benzene, N,N-dimethylformamide, tetrahydrofuran, toluene, methylene chloride, ethylene dichloride, chloroform, dioxane, diethyl ether or any other solvent which does not adversely affect the reaction. These conventional solvent may also be used in a mixture with water.

The reaction temperature is not critical and the reaction is usually carried out under cooling to heating.

The reaction is usually carried out by a method using an inorganic or an organic base such as an alkali metal (e.g., sodium, potassium, etc.), an alkali metal hydroxide (e.g., sodium hydroxide, potassium hydroxide, etc.), an alkali metal hydrogencarbonate (e.g., sodium hydrogencarbonate, potassium hydrogencarbonate, etc.), alkali metal carbonate (e.g., sodium carbonate, potassium carbonate, etc.), tri(lower)alkylamine (e.g., trimethylamine, triethylamine, diisopropylethylamine, etc.), alkali metal hydride (e.g., sodium hydride, etc.), alkali metal (lower)alkoxide (e.g., sodium methoxide, sodium ethoxide, etc.), pyridine (e.g., pyridine, lutidine, picoline, dimethylaminopyridine, etc.), N-(lower)alkylmorpholine, N,N-di(lower)alkylbenzylamine, N,N-di(lower)alkylaniline or the like.

When the base and/or the starting compound are in liquid, they can be used also as a solvent.

Process (8)

The compound (Ij) or a salt thereof can be prepared by subjecting the compound (Ia) or a salt thereof to halogenation reaction.

This halogenation is usually carried out by using a conventional halogenating agent such as halogen (e.g., chlorine, bromine, etc.), phosphorus trihalide (e.g., phosphorus tribromide, phosphorus trichloride, etc.), phosphorus pentahalide, (e.g., phosphorus pentachloride,

phosphorus pentabromide, etc.), phosphorus oxychloride (e.g., phosphoryl trichloride, phosphoryl monochloride, etc.), thionyl halide (e.g., thionyl chloride, thionyl bromide, etc.), oxalyl halide (e.g., oxalyl chloride, oxalyl bromide, etc.) and the like.

This reaction is usually carried out in a solvent such as water, alcohol (e.g., methanol, ethanol, isopropyl alcohol, etc.), benzene, dioxane, N,N-dimethylformamide, tetrahydrofuran, methylene chloride, ethylene dichloride, chloroform, diethyl ether or any other solvent which does not adversely affect the reaction.

The reaction temperature is not critical and the reaction is usually carried out under cooling to heating.

When the starting compound is in liquid, it can be also used as a solvent.

Process (9)

The compound (Iℓ) or a salt thereof can be prepared by reacting the compound (Ik) or a salt thereof with the compound (VII) or a salt thereof.

This reaction is usually carried out in a solvent such as water, alcohol (e.g., methanol, ethanol, etc.), benzene, N,N-dimethylformamide, tetrahydrofuran, toluene, methylene chloride, ethylene dichloride, chloroform, diethyl ether or any other solvent which does not adversely affect the reaction.

The reaction temperature is not critical and the reaction is usually carried out under warming to heating.

When the starting compound is in liquid, it can be also used as a solvent.

Process (10) - (1)

The compound (Im) or a salt thereof can be prepared by reacting the compound (Ik) or a salt thereof with the compound (VIII) or a salt thereof.

This reaction is usually carried out in a solvent such as water, alcohol (e.g., methanol, ethanol, etc.), benzene, N,N-dimethylformamide, tetrahydrofuran, toluene, methylene chloride, acetone, ethylene dichloride, chloroform, diethyl ether or any other solvent which does not adversely affect the reaction.

The reaction temperature is not critical and the reaction is usually carried out under cooling to heating.

Process (10) - (2)

The compound (In) or a salt thereof can be prepared by subjecting the compound (Im) or a salt thereof to elimination reaction of the mercapto protective group.

This elimination can be carried out in a similar manner to that of the aforementioned Process (4), and therefore the reagents to be used and the reaction conditions (e.g., solvent, reaction temperature, etc.) can be referred to those of the Process (4).

Process (11)

The compound (Io) or a salt thereof can be prepared by reacting the compound (Ik) or a salt thereof with the compound (IX) or a salt thereof.

This reaction is usually carried out in a solvent such as water, alcohol (e.g., methanol, ethanol, etc.), benzene, N,N-dimethylformamide, tetrahydrofuran, toluene, methylene chloride, ethylene dichloride, chloroform, diethyl ether or any other solvent which does not adversely affect the reaction.

The reaction temperature is not critical and the reaction is usually carried out under cooling to heating.

Process (12)

The compound (Iq) or a salt thereof can be prepared by subjecting the compound (Ip) or a salt thereof to

reduction reaction.

Reduction is carried out in a conventional manner, including chemical reduction and catalytic reduction.

Suitable reducing reagent to be used in chemical reduction are hydrides (e.g., hydrogen iodide, hydrogen sulfide, lithium aluminum hydride, sodium borohydride, sodium cyanoborohydride, etc.) or a combination of a metal (e.g., tin, zinc, iron, etc.) or metallic compound (e.g., chromium chloride, chromium acetate, etc.) and an organic acid or an inorganic acid (e.g., formic acid, acetic acid, propionic acid, trifluoroacetic acid, p-toluenesulfonic acid, hydrochloric acid, hydrobromic acid, etc.).

Suitable catalysts to be used in catalytic reduction are conventional ones such as platinum catalysts (e.g., platinum plate, spongy platinum, platinum black, colloidal platinum, platinum oxide, platinum wire, etc.), palladium catalysts (e.g., spongy palladium, palladium black, palladium oxide, palladium on carbon, colloidal palladium, palladium on barium sulfate, palladium on barium carbonate, etc.), nickel catalysts (e.g., reduced nickel, nickel oxide, Raney nickel, etc.), cobalt catalysts (e.g., reduced cobalt, Raney cobalt, etc.), iron catalysts (e.g., reduced iron, Raney iron, etc.), copper catalysts (e.g., reduced copper, Raney copper, Ullman copper, etc.) and the like.

The reduction is usually carried out in a conventional solvent which does not adversely influence the reaction such as water, alcohol (e.g., methanol, ethanol, propanol, etc.), tetrahydrofuran, dioxane, N,N-dimethylformamide, or a mixture thereof.

Additionally, in case that the above-mentioned acids to be used in chemical reduction are in liquid, they can also be used as a solvent.

Further, a suitable solvent to be used in catalytic reduction may be the above-mentioned solvent, and other

conventional solvent such as diethyl ether, dioxane, tetrahydrofuran, etc. or a mixture thereof.

The reaction temperature is not critical and the reaction is usually carried out under cooling to warming.

Process (13)

The compound (Ir) or a salt thereof can be prepared by subjecting the compound (Iq) or its reactive derivative at the amino group or a salt thereof to acylation reaction.

Suitable acylating agent to be used in the present acylation reaction may include the compound of the formula :

$$R^{11} - OH \qquad (XXI)$$

(wherein R^{11} is acyl)

or its reactive derivative or a salt thereof.

Suitable reactive derivative at the amino group of the compound (Iq) may include Schiff's base type imino or its tautomeric enamine type isomer formed by the reaction of the compound (Iq) with a carbonyl compound such as aldehyde, ketone or the like; a silyl derivative formed by the reaction of the compound (Iq) with a silyl compound such as N,O-bis(trimethylsilyl)acetamide, N-trimethylsilylacetamide or the like; a derivative formed by the reaction of the compound (Iq) with phosphorus trichloride or phosgene, and the like.

Suitable reactive derivative of the compound (XXI) may include an acid halide, an acid anhydride, an activated amide, an activated ester, isocyanate, and the like. The suitable example may be an acid chloride, an acid azide; a mixed acid anhydride with an acid such as substituted phosphoric acid (e.g. dialkylphosphoric acid, phenylphosphoric acid, diphenylphosphoric acid,

dibenzylphosphoric acid, halogenated phosphoric acid, etc.), dialkylphosphorous acid, sulfurous acid, thiosulfuric acid, alkanesulfonic acid (e.g. methanesulfonic acid, ethanesulfonic acid, etc.), sulfuric acid, alkylcarbonic acid, aliphatic carboxylic acid (e.g. pivalic acid, pentanoic acid, isopentanoic acid, 2-ethylbutyric acid or trichloroacetic acid, etc.) or aromatic carboxylic acid (e.g. benzoic acid, etc.); a symmetrical acid anhydride; an activated amide with imidazole, 4-substituted imidazole, dimethylpyrazole, triazole or tetrazole; or an activated ester (e.g. cyanomethyl ester, methoxymethyl ester, dimethyliminomethyl [$(CH_3)_2\overset{+}{N}=CH-$] ester, vinyl ester, propargyl ester, p-nitrophenyl ester, 2,4-dinitrophenyl ester, trichlorophenyl ester, pentachlorophenyl ester, mesylphenyl ester, phenylazophenyl ester, phenyl thioester, p-nitrophenyl thioester, p-cresyl thioester, carboxymethyl thioester, pyranyl ester, pyridyl ester, piperidyl ester, 8-quinolyl thioester, etc.), or an ester with a N-hydroxy compound (e.g. N,N-dimethylhydroxylamine, 1-hydroxy-2-(1H)-pyridone, N-hydroxysuccinimide, N-hydroxybenzotriazole, N-hydroxyphthalimide, 1-hydroxy-6-chloro-1H-benzotriazole, etc.); substituted or unsubstituted aryl isocyanate; substituted or unsubstituted aryl isothiocyanate, and the like. These reactive derivatives can optionally be selected from them according to the kind of the compound (XXI) to be used.

The reaction is usually carried out in a conventional solvent such as water, acetone, dioxane, acetonitrile, chloroform, methylene chloride, ethylene chloride, tetrahydrofuran, ethyl acetate, N,N-dimethylformamide, pyridine or any other organic solvents which do not adversely influence the reaction. These conventional solvents may also be used in a mixture with water.

When the compound (XXI) is used in free acid form or its salt form in the reaction, the reaction is preferably carried out in the presence of a conventional condensing agent such as N,N'-dicyclohexylcarbodiimide; N-cyclohexyl-N'-morpholinoethylcarbodiimide; N-cyclohexyl-N'-(4-diethylaminocyclohexyl)carbodiimide; N,N'-diethylcarbodiimide; N,N'-diisopropylcarbodiimide; N-ethyl-N'-(3-dimethylaminopropyl)carbodiimide; N,N-carbonylbis-(2-methylimidazole); pentamethyleneketene-N-cyclohexylimine, diphenylketene-N-cyclohexylimine; ethoxyacetylene; 1-alkoxy-1-chloroethylene; trialkyl phosphite; ethyl polyphosphate; isopropyl polyphosphate; phosphorus oxychloride (phosphoryl chloride); phosphorus trichloride; thionyl chloride; oxalyl chloride; triphenylphosphine; 2-ethyl-7-hydroxybenzisoxazolium salt; 2-ethyl-5-(m-sulfophenyl)isoxazolium hydroxide intra-molecular salt; 1-(p-chlorobenzenesulfonyloxy)-6-chloro-1H-benzotriazole; so-called Vilsmeier reagent prepared by the reaction of N,N-dimethylformamide with thionyl chloride, phosgene, phosphorus oxychloride, etc.; or the like.

The reaction may also be carried out in the presence of an inorganic or organic base such as an alkali metal bicarbonate, tri(lower)alkylamine, pyridine, N-(lower)alkylmorphorine, N,N-di(lower)alkylbenzylamine, or the like. The reaction temperature is not critical and the reaction is usually carried out under cooling to heating.

Process (A)

The compound (IIb) or a salt thereof can be prepared by reacting the compound (IIa) or a salt thereof with the compound (X) or a salt thereof.

The reaction is usually carried out in a conventional solvent such as alcohols (e.g. methanol, ethanol, ethylene

glycol, etc.), chloroform, ether, tetrahydrofuran, benzene, N,N-dimethylformamide, N,N-dimethylacetamide or any other organic solvent which does not adversely influence the reaction.

The reaction temperature is not critical and the reaction is usually carried out under cooling to heating.

The reaction is usually carried out in the presence of an inorganic or an organic base such as an alkali metal hydroxide, an alkali metal hydrogencarbonate, alkali metal carbonate, alkali metal hydride (e.g. sodium hydride, etc.), alkali metal acetate, tri(lower)alkylamine, pyridine base (e.g. pyridine, lutidine, picoline, dimethylaminopyridine, etc.), N-(lower)alkylmorpholine, N,N-di(lower)alkylbenzylamine, N,N-di(lower)alkylaniline or the like. When the base and/or the starting compound are in liquid, they can be used also as a solvent.

Process (B)

The compound (III) or a salt thereof can be prepared by reacting the compound (XI) or a salt thereof with the compound (XII) or a salt thereof.

The reaction is usually carried out in a conventional solvent such as alcohols (e.g. methanol, ethanol, ethylene glycol, etc.), chloroform, ether, tetrahydrofuran, benzene, hexane or any other organic solvent which does not adversely influence the reaction.

The reaction temperature is not critical and the reaction is usually carried out under cooling to warming.

The reaction is usually carried out in the presence of an inorganic or an organic base such as an alkali metal hydroxide, an alkali metal hydrogencarbonate, alkali metal carbonate, alkali metal acetate, tri(lower)alkylamine, lower alkyl alkali metal (e.g. n-butyl lithium, etc.), pyridine base (e.g. pyridine, lutidine, picoline, dimethylaminopyridine, etc.), N-(lower)alkylmorpholine,

N,N-di(lower)alkylbenzylamine, N,N-di(lower)alkylaniline or the like. When the base and/or the starting compound are in liquid, they can be used also as a solvent.

Process (C)

The compound (XV) or a salt thereof can be prepared by reacting the compound (XIII) or a salt thereof with the compound (XIV) or a salt thereof.

This reaction is usually carried out in a solvent such as water, alcohol (e.g., methanol, ethanol, etc.), benzene, N,N-dimethylformamide, tetrahydrofuran, toluene, methylene chloride, ethylene dichloride, chloroform, dioxane, diethyl ether or any other solvent which does not adversely affect the reaction. These conventional solvent may also be used in a mixture with water.

The reaction temperature is not critical and the reaction is usually carried out under cooling to heating.

The reaction is usually carried out in the presence of an inorganic or an organic base such as an alkali metal (e.g., sodium, potassium, etc.), an alkali metal hydroxide (e.g., sodium hydroxide, potassium hydroxide, etc.), an alkali metal hydrogencarbonate (e.g., sodium hydrogencarbonate, potassium hydrogencarbonate, etc.), alkali metal carbonate (e.g., sodium carbonate, potassium carbonate, etc.), tri(lower)alkylamine (e.g., trimethylamine, triethylamine, diisopropylethylamine, etc.), alkali metal hydride (e.g., sodium hydride, etc.), alkali metal (lower)alkoxide (e.g., sodium methoxide, sodium ethoxide, etc.), pyridine (e.g., pyridine, lutidine, picoline, dimethylaminopyridine, etc.), N-(lower)alkylmorpholine, N,N-di(lower)alkylbenzylamine, N,N-di(lower)alkylaniline or the like.

When the base and/or the starting compound are in liquid, they can be used also as a solvent.

Process (D)

The compound (XVIb) or a salt thereof can be prepared by subjecting the compound (XV) or a salt thereof to reduction reaction.

This reaction can be carried out in the manner disclosed in Preparation 5 or similar manners thereto.

Process (E)

The compound (II) or a salt thereof can be prepared by reacting the compound (XVIa) or a salt thereof with the compound (XVII) or a salt thereof.

This reaction is usually carried out in a solvent such as water, alcohol (e.g., methanol, ethanol, etc.), benzene, N,N-dimethylformamide, tetrahydrofuran, toluene, methylene chloride, ethylene dichloride, chloroform, dioxane, diethyl ether or any other solvent which does not adversely affect the reaction. These conventional solvent may also be used in a mixture with water.

The reaction temperature is not critical and the reaction is usually carried out under cooling to heating.

The reaction is usually carried out in the presence of an inorganic or an organic base such as an alkali metal (e.g., sodium, potassium, etc.), an alkali metal hydroxide (e.g., sodium hydroxide, potassium, hydroxide, etc.), an alkali metal hydrogencarbonate (e.g., sodium hydrogencarbonate, potassium hydrogencarbonate, etc.), alkali metal carbonate (e.g., sodium carbonate, potassium carbonate, etc.), tri(lower)alkylamine (e.g., trimethylamine, triethylamine, diisopropylethylamine, etc.), alkali metal hydride (e.g., sodium hydride, etc.), alkali metal (lower)alkoxide (e.g., sodium methoxide, sodium ethoxide, etc.), pyridine (e.g., pyridine, lutidine, picoline, dimethylaminopyridine, etc.), N-(lower)alkylmorpholine, N,N-di(lower)alkylbenzylamine, N,N-di(lower)alkylaniline or the like.

When the base and/or the starting compound and in liquid, they can be used also as a solvent.

Process (F)

The compound (VI) or a salt thereof can be prepared by reacting the compound (XVIc) or its reactive derivative, or a salt thereof with the compound (XVIII) or its reactive derivative, or a salt thereof.

Suitable reactive derivative of the compound (XVIc) may include Schiff's base type imino or its tautomeric enamine type isomer formed by the reaction of the compound (XVIc) with a carbonyl compound such as aldehyde, ketone or the like; a silyl derivative formed by the reaction of the compound (XVIc) with a silyl compound such as bis(trimethylsilyl)acetamide, mono(trimethylsilyl)-acetamide [e.g. N-(trimethylsilyl)acetamide], bis(trimethylsilyl)urea or the like; a derivative formed by reaction of the compound (XVIc) with phosphorus trichloride or phosgene, and the like.

Suitable reactive derivative of the compound (XVIII) may include a conventional one such as an acid halide, an acid anhydride, an activated amide, an activated ester, and the like.

Suitable examples of the reactive derivatives may be an acid chloride; an acid azide; a mixed acid anhydride with an acid such as substituted phosphoric acid [e.g. dialkylphosphoric acid, phenylphosphoric acid, diphenylphosphoric acid, dibenzylphosphoric acid, halogenated phosphoric acid, etc.], dialkylphosphorous acid, sulfurous acid, thiosulfuric acid, sulfuric acid, sulfonic acid [e.g. methanesulfonic acid, etc.], aliphatic carboxylic acid [e.g. acetic acid, propionic acid, butyric acid, isobutyric acid, pivalic acid, pentanoic acid, isopentanoic acid, 2-ethylbutyric acid, trichloroacetic acid, etc.] or aromatic carboxylic acid [e.g. benzoic

acid, etc.]; a symmetrical acid anhydride; an activated amide with imidazole, 1-hydroxy-1H-benzotriazole, 4-substituted imidazole, dimethylpyrazole, triazole or tetrazole; or an activated ester [e.g. cyanomethyl ester, methoxymethyl ester, dimethyliminomethyl [$(CH_3)_2\overset{+}{N}=CH-$] ester, vinyl ester, propargyl ester, p-nitrophenyl ester, 2,4-dinitrophenyl ester, trichlorophenyl ester, pentachlorophenyl ester, mesylphenyl ester, phenylazophenyl ester, phenyl thioester, p-nitrophenyl thioester, p-cresyl thioester, benzothiazolyl thioester, carboxymethyl thioester, pyranyl ester, pyridyl ester, piperidyl ester, 8-quinolyl thioester, etc.], or an ester with a N-hydroxy compound [e.g. N,N-dimethylhydroxylamine, 1-hydroxy-2-(1H)-pyridone, N-hydroxysuccinimide, N-hydroxyphthalimide, 1-hydroxy-1H-benzotriazole, etc.], and the like. These reactive derivatives can optionally be selected from them according to the kind of the compound (XVIII) to be used.

The reaction is usually carried out in a conventional solvent such as water, alcohol [e.g. methanol, ethanol, etc.], acetone, dioxane, acetonitrile, chloroform, methylene chloride, ethylene chloride, tetrahydrofuran, ethyl acetate, N,N-dimethylformamide, pyridine or any other organic solvent which does not adversely influence the reaction. These conventional solvent may also be used in a mixture with water.

In this reaction, when the compound (XVIII) is used in a free acid form or its salt form, the reaction is preferably carried out in the presence of a conventional condensing agent such as N,N'-dicyclohexylcarbodiimide; N-cyclohexyl-N'-morpholinoethylcarbodiimide; N-cyclohexyl-N'-(4-diethylaminocyclohexyl)carbodiimide; N,N'-diethylcarbodiimide; N,N'-diisopropylcarbodiimide; N-ethyl-N'-(3-dimethylaminopropyl)carbodiimide; N,N'-carbonyl-bis(2-methylimidazole);

pentamethyleneketene-N-cyclohexylimine; diphenylketene-N-cyclohexylimine; ethoxyacetylene; 1-alkoxy-1-chloroethylene; trialkyl phosphite; ethyl polyphosphate; isopropyl polyphosphate; phosphorus oxychloride (phosphoryl chloride); phosphorus trichloride; thionyl chloride; oxalyl chloride; lower alkyl haloformate [e.g. ethyl chloroformate, isopropyl chloroformate, etc.]; triphenylphosphine; 2-ethyl-7-hydroxybenzisoxazolium salt; 2-ethyl-5-(m-sulfophenyl)isoxazolium hydroxide intramolecular salt; 1-(p-chlorobenzenesulfonyloxy)-6-chloro-1H-benzotriazole; so-called Vilsmeier reagent prepared by the reaction of N,N-dimethylformamide with thionyl chloride, phosgene, trichloromethyl chloroformate, phosphorus oxychloride, etc.; or the like.

The reaction may also be carried out in the presence of an inorganic or organic base such as an alkali metal bicarbonate, tri(lower)alkylamine, pyridine, N-(lower)alkylmorpholine, N,N-di(lower)alkylbenzylamine, or the like.

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

Process (G)

The compound (XV) or a salt thereof can be prepared by reacting the compound (XIX) or a salt thereof with the compound (XX) or a salt thereof.

This reaction can be carried out in the manner disclosed in Preparation 9 or similar manners thereto.

Process (H)

The compound (XVIIIa) or a salt thereof can be prepared by subjecting the compound (XXII) or a salt thereof to elimination reaction of the carboxy protective group.

This reaction can be carried out in the manner

disclosed in Preparation 11 or similar manners thereto.

Suitable salts of the object and starting compounds and their reactive derivatives in Processes (1)~(13) and (A)~(H) can be referred to the ones as exemplified for the compound (I).

The new quinoline derivatives (I) and a pharmaceutically acceptable salt thereof of the present invention possess a strong immunomodulating activity (e.g. an inhibitory activity on the production of an autoantibody, etc.), anti-inflammatory activity and anti-cancer activity and and therefore are useful as an immunomodulating agent (e.g. an inhibitor on the production of an autoantibody, etc.), anti-inflammatory agent and anti-cancer agent.

Accordingly, the new quinoline derivatives (I) and a pharmaceutically acceptable salt thereof can be used for the treatment and/or prevention of inflammatory conditions, various pains, collagen diseases, autoimmune diseases, various immunity diseases, cancer [e.g. lung carcinoma, stomach carcinoma, colon cancer, renal carcinoma, hepatoma, etc.], and the like in human beings or animals, and more particularly for the treatment and/or prevention of inflammation and pain in joint and muscle [e.g. rheumatoid arthritis, rheumatoid spondylitis, osteoarthritis, gouty arthritis, etc.], inflammatory skin condition [e.g. sunburn, eczema, etc.], inflammatory eye condition [e.g. conjunctivitis etc.], lung disorder in which inflammation is involved [e.g. asthma, bronchitis, pigeon fancier's disease, farmer's lung, etc.], condition of the gastrointestinal tract associated with inflammation [e.g. aphthous ulcer, Crohn's disease, atrophic gastritis, gastritis varialoforme, ulcerative colitis, coeliac disease, regional ileitis, irritable bowel syndrome, etc.], gingivitis, (inflammation, pain and tumescence after operation or injury), pyrexia, pain and other

conditions associated with inflammation, rejection by transplantation, systemic lupus erythematosus, scleroderma, polymyositis, polychondritis, periarteritis nodosa, ankylosing spondytis, inflammatory chronic renal condition [e.g. glomerulonephritis, membranous nephritis, etc.], rheumatic fever, Sjögren's syndorome, Behcet disease, thyroiditis, type I diabetes, dermatomyositis, chronic active hepatitis, myasthenia gravis, idiopathic sprue, Grave's disease, multiple sclerosis, primary billiary cirrhoris, Reiter's syndrome, autoimmune hematological disorders [e.g. hemolytic anemia, pure red cell anemia, idiopathic thrombocytopenia, aplastic anemia, etc.], myasthenia gravis, uveitis, contact dermatitis, psoriasis, Kawasaki disease, sarcoidosis, Wegner's granulomatosis, Hodgkin's disease, cancer [e.g. lung carcinoma, stomach carcinoma, colon cancer, renal carcinoma, hepatoma, etc.], and the like.

In order to show the utilities of the quinoline derivatives (I) and a pharmaceutically acceptable salt thereof of the present invention, pharmacological test data of the representative compound of the quinoline derivatives (I) are illustrated in the following.

Inhibitory activity on the production of an anti-DNA-antibody and on the leakage of a proteinuria.

1. Test method

Six weeks old female (57BL/6 x DBA/2)F_1 and DBA/2 mice were used. Graft-varsus-host (GVH) disease was induced in (57BL/6 x DBA/2)F_1 mice with two injections of DBA/2 spleen cells given 5 days apart. Each injection contained 5 x 10^7 cells. From 3 days after the second cell injection, drug was administered orally once a day for 8 weeks.

As an indication of autoimmune disease, 4 weeks after

the last cell injection anti-single strand DNA antibodies were measured by enzyme-linked immunosorbent assay (ELISA) using the procedure reported by T. Fujitsu et al. (International J. Immunopharmacol, 8 897 (1986)). To assess the renal disease, 8 weeks after the last cell injection proteinuria were measured. The concentration of serum albumin in the urine was determined by the single radial immunodiffusion method using rabbit anti-mouse serum albumin antiserum. Ten mice were used per group. The activity of the compound was expressed as a % inhibition of anti-DNA antibody and proteinuria.

2. Test compound

1-Methyl-2-oxo-3-(N-methyl-N-phenylcarbamoyl)-4-hydroxy-6-methylsulfinyl-1,2-dihydroquinoline

3. Test result

Dose (mg/kg)	Inhibition (%)	
	anti-DNA antibody	proteinuria
100	68*	100*

* : Significantly different from control group at $P<0.01$

Inhibitory activity on B16 melanoma metastases

1. Test Method

According to the experimental schedule as exemplified below, the experiment was carried out.

Mouse B16 melanoma cells ($5x10^5$ cells) were inoculated intravenously to 8 weeks old female (C57BL/6) mice on day 0.

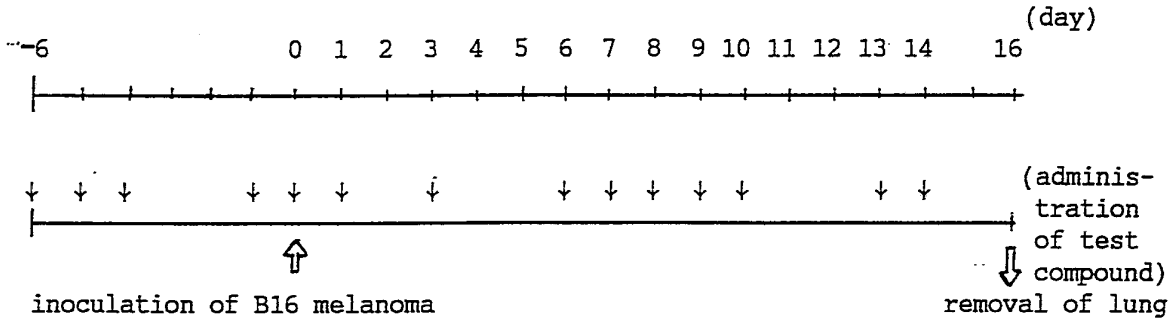
The animals were sacrificed at day 16 and tumor

colonies established in lung were counted in a dissection microscope.

The test compound was administered orally once a day.

Effects of test compound on tumors were assessed by the numbers of colonies compared to control.

experimental schedule



2. Test compound

1-methyl-2-oxo-3-(N-methyl-N-phenylcarbamoyl)-4-hydroxy-6-methylthio-1,2-dihydroquinoline

3. Test result

Dose (mg/kg)	inhibition (%)
10	34*
100	63

* Significantly different from control group at $P<0.01$

For therapeutic administration, the object compounds (I) of the present invention and pharmaceutically acceptable salts thereof are used in a form of the conventional pharmaceutical preparation in admixture with a conventional pharmaceutically acceptable carrier such as an organic or inorganic solid or liquid excipient which is

suitable for oral, parenteral or external administration. The pharmaceutical preparation may be compounded in a solid form such as granule, capsule, tablet, dragee or suppository, or in a liquid form such as solution, suspension or emulsion for injection, ingestion, eye drops, etc. If needed, there may be included in the above preparation auxiliary substance such as stabilizing agent, wetting or emulsifying agent, buffer or any other commonly used additives.

The effective ingredient may usually be administered with a unit dose of 0.01 mg/kg to 500 mg/kg, preferably 0.01 mg/kg to 10 mg/kg, 1 to 4 times a day. However, the above dosage may be increased or decreased according to age, weight and conditions of the patient or the administering method.

Preferred embodiments of the object compound (I) are as follows.

R^1 is lower alkyl or phenyl which may have suitable substituent(s) [more preferably phenyl which may have halogen; most preferably phenyl or halophenyl],

R^2 is hydroxy, protected hydroxy [more preferably acyloxy], lower alkoxy, halogen, amino, lower alkylamino, protected amino [more preferably acylamino], mercapto, or protected mercapto [more preferably acylthio; most preferably lower alkanoylthio],

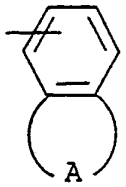
R^3 is hydrogen, lower alkyl, lower alkoxy(lower)alkyl, or ar(lower)alkyl [more preferably phenyl(lower)alkyl; most preferably benzyl],

R^8 is hydrogen, or

R^3 and R^8 are linked together to form lower alkylene,

R^4 is acyl [more preferably carbamoyl which may be substituted with one or two suitable substituent(s)

selected from the group consisting of lower alkyl; phenyl which may have 1 to 3 (more preferably 1 or 2) suitable substituent(s) selected from the group consisting of lower alkyl, halogen, lower alkoxy, lower alkylthio, acyl, di(lower)alkylamino, cyano, mono(or di or tri)halo(lower)alkyl, mono(or di or tri)halo(lower)-alkoxy, carboxy, protected carboxy, nitro, amino and acylamino; heterocyclic group which may have lower alkyl; phenyl(lower)alkyl; lower cycloalkyl and a group of the formula :



(in which A is lower alkylene);
thiocarbamoyl which may be substituted with one or two suitable substituent(s) selected from the group consisting of lower alkyl and aryl;
lower alkoxycarbonyl;
aminosulfonyl which may be substituted with one or two suitable substituent(s) selected from the group consisting of lower alkyl and aryl;
aroyl; ar(lower)cycloalkylcarbonyl;
ar(lower)alkylsulfonyl; or heterocycliccarbonyl;
most preferably carbamoyl which may be substituted with one or two suitable substituent(s) selected from the group consisting of lower alkyl, phenyl, mono(or di)(lower)alkylphenyl, mono(or di)halophenyl, (lower)alkoxyphenyl, lower alkylthiophenyl, lower alkanoylphenyl, di(lower)alkylaminophenyl, cyanophenyl, trihalo(lower)alkylphenyl, trihalo(lower)alkoxyphenyl, carboxyphenyl, lower alkoxycarbonylphenyl, nitrophenyl, aminophenyl, lower alkanoylaminophenyl, pyridyl, lower alkylpyrazolyl, pyrrolyl, thiazolyl, thiadiazolyl, benzodioxolyl, phenyl(lower)alkyl, lower cycloalkyl and

indanyl; thiocarbamoyl which may be substituted with one or two suitable substituent(s) selected from the group consisting of lower alkyl and phenyl;
lower alkoxycarbonyl;
aminosulfonyl which may be substituted with one or two suitable substituent(s) selected from the group consisting of lower alkyl and phenyl;
benzoyl; phenyl(lower)cycloalkylcarbonyl;
phenyl(lower)alkylsulfonyl;
indolinylcarbonyl, dihydrobenzoxazinylcarbonyl; or dihydrobenzothiazinylcarbonyl]; carboxy;
ar(lower)alkylsulfinyl [more preferably phenyl(lower)-alkylsulfinyl; most preferably benzylsulfinyl];
ar(lower)alkylthio [more preferably phenyl(lower)-alkylthio; most preferably benzylthio]; cyano;
heterocyclic group which may have suitable substituent(s) [more preferably unsaturated 3 to 8-membered (more preferably 5 or 6-membered) heteromonocyclic group containing 1 to 4 nitrogen atom(s) which may have aryl,
unsaturated 3 to 8-membered (more preferably 5 or 6-membered) heteromonocyclic group containing 1 to 2-oxygen atom(s) and 1 to 3 nitrogen atom(s) which may have aryl, or
unsaturated condensed heterocyclic group containing 1 to 4 nitrogen atom(s) which may have lower alkyl; most preferably imidazolinyl, phenylimidazolinyl, tetrazolyl, phenyltetrazolyl, oxadiazolyl, phenyloxadiazolyl, benzimidazolyl, lower alkylbenzimidazolyl, quinolyl or isoquinolyl],

Z is O or S and

n is 0, 1 or 2.

The following Preparations and Examples are given for the purpose of illustrating the present invention in more detail.

Preparation 1

To a solution of 6-methylthio-2H-3,1-benzoxazine-2,4(1H)-dione (13 g) in N,N-dimethylacetamide (130 ml), sodium hydride (2.74 g, 60% in mineral oil) was slowly added and the mixture was stirred for 1 hour at room temperature. Methyl iodide (4.26 ml) was added and the reaction was allowed to stir for 3 hours at room temperature. The reaction mixture was poured into ice-water (650 ml). The precipitates were filtered, washed with water, and dried to give yellow crystals of 1-methyl-6-methylthio-2H-3,1-benzoxazine-2,4(1H)-dione (12.8 g).

mp : 183-191°C

IR (Nujol) : 1770, 1720, 1610, 1590 cm^{-1}

NMR (DMSO-d_6, δ) : 2.54 (3H, s), 3.45 (3H, s), 7.3-7.8 (3H, m)

Preparation 2

To a solution of N-methyl-N-phenylmethanesulfonamide (25 g) in tetrahydrofuran (250 ml) was added dropwise 1.6M n-butyllithium in hexane (89 ml), keeping the temperature of the reaction below 20°C. Then a solution of diethyl carbonate (8.2 ml) in tetrahydrofuran (40 ml) was added dropwise, keeping the temperature of the reaction below -30°C. The mixture was allowed to warm to room temperature and concentrated in vacuo. Water was added to the residue, and the resulting solution was acidified and extracted with chloroform. Removal of the solvent furnished an oil (30 g), which was purified by column chromatography on silica gel (200 g) eluting with toluene to give a yellow oil of ethyl (N-methyl-N-phenylamino)-sulfonylacetate (12.5 g).

IR (Film) : 1740, 1600, 1495, 1355 cm^{-1}

NMR ($CDCl_3$, δ) : 1.31 (3H, t, J=7.1Hz), 3.41 (3H, s), 3.94 (2H, s), 4.25 (2H, q, J=7.1Hz),

7.1-7.6 (5H, m)
Mass (m/z) : 257 (M^+)

Preparation 3

The following compounds were obtained according to a similar manner to that of Preparation 1.

(1) 6-Ethylthio-1-methyl-2H-3,1-benzoxazine-2,4(1H)-dione
mp : 143-150°C
IR (Nujol) : 1785, 1730, 1610, 1590 cm^{-1}
NMR (DMSO-d_6, δ) : 1.23 (3H, t, J=7.3Hz), 2.99 (2H, q, J=7.3Hz), 3.45 (3H, s), 7.41 (1H, d, J=9.0Hz), 7.7-7.9 (2H, m)
Mass (m/z) : 237 (M^+)

(2) 1-Methyl-6-(neopentylthio)-2H-3,1-benzoxazine-2,4(1H)-dione
mp : 128-131°C
IR (Nujol) : 1780, 1765, 1735, 1610, 1580 cm^{-1}
NMR (DMSO-d_6, δ) : 1.00 (9H, s), 2.98 (2H, s), 3.45 (3H, s), 7.3-7.9 (3H, m)
Mass (m/z) : 279 (M^+)

(3) 1-Ethyl-6-methylthio-2H-3,1-benzoxazine-2,4(1H)-dione
mp : 135-145°C
IR (Nujol) : 1780, 1720, 1605, 1580 cm^{-1}
NMR (DMSO-d_6, δ) : 1.22 (3H, t, J=7.1Hz), 2.54 (3H, s), 4.08 (2H, q, J=7.1Hz), 7.4-7.8 (3H, m)

(4) 1-Benzyl-6-methylthio-2H-3,1-benzoxazine-2,4(1H)-dione
mp : 169-171°C
IR (Nujol) : 1780, 1720, 1620, 1580 cm^{-1}
NMR (DMSO-d_6, δ) : 2.51 (3H, s), 5.28 (2H, s), 7.1-7.8 (8H, m)

Mass (m/z) : 299 (M^+)

(5) 1-Methoxymethyl-6-methylthio-2H-3,1-benzoxazine-2,4(1H)-dione
mp : 122-126°C
IR (Nujol) : 1780, 1760, 1725, 1605, 1585 cm^{-1}
NMR (DMSO-d_6, δ) : 2.54 (3H, s), 3.36 (3H, s), 5.43 (2H, s), 7.3-7.8 (3H, m)

(6) 6-Methylthio-1-propyl-2H-3,1-benzoxazine-2,4(1H)-dione
mp : 126-131°C
IR (Nujol) : 1775, 1730, 1605, 1580 cm^{-1}
NMR (DMSO-d_6, δ) : 0.95 (3H, t, J=7.3Hz), 1.64 (2H, sextet, J=7.3Hz), 2.54 (3H, s), 3.95 (2H, t, J=7.3Hz), 7.46 (1H, d, J=8.9Hz), 7.7-7.8 (2H, m)

(7) 1-Methyl-6-phenylthio-2H-3,1-benzoxazine-2,4(1H)-dione
mp : 118-121°C
IR (Nujol) : 1790, 1770, 1735, 1610 cm^{-1}
NMR (DMSO-d_6, δ) : 3.45 (3H, s), 7.3-7.5 (6H, m), 7.7-7.9 (2H, m)
Mass (m/z) : 285 (M^+)

(8) 6-(4-Fluorophenylthio)-1-methyl-2H-3,1-benzoxazine-2,4-(1H)-dione
mp : 131-133°C
IR (Nujol) : 1780, 1745, 1715, 1610, 1585 cm^{-1}
NMR (DMSO-d_6, δ) : 3.45 (3H, s), 7.2-7.9 (7H, m)
Mass (m/z) : 303 (M^+)

Preparation 4

A mixture of 5-mercapto-2-nitrobenzoic acid (4 g) and potassium carbonate (2.76 g) in 2-methoxyethanol (40 ml)

was stirred for 10 minutes. Neopentyl tosylate (6.3 g) was added and the mixture was refluxed for 1.5 hours. The solvent was evaporated, and the residue was dissolved in water, washed with isopropyl ether, acidified with hydrochloric acid, and extracted with dichloromethane. The extract was evaporated to give 5-(neopentylthio)-2-nitrobenzoic acid (yellow solid, 5.2 g).

mp : 145-198°C

IR (Nujol) : 1715, 1605, 1570, 1515 cm^{-1}

NMR (DMSO-d_6, δ) : 1.03 (9H, s), 3.10 (2H, s), 7.5-8.1 (3H, m)

Mass (m/z) : 269 (M^+)

Preparation 5

(1) To a mixture of 5-(neopentylthio)-2-nitrobenzoic acid (4.8 g), sodium hydroxide (0.86 g), ferric chloride (0.29 g), activated carbon (0.2 g), and isopropyl alcohol (2 ml) in water (34 ml) was added hydrazine hydrate (2.1 ml) at 75°C. The mixture was stirred at 75-80°C for 90 minutes and filtered through celite. The filtrate was cooled and acidified to pH=4.6. The precipitates were collected by filtration, washed with water, and dried to give a yellow solid of 5-(neopentylthio)anthranilic acid (2.7 g).

mp : 115-122°C

IR (Nujol) : 3550, 3430, 1680, 1620, 1580, 1560 cm^{-1}

NMR (DMSO-d_6, δ) : 0.95 (9H, s), 2.73 (2H, s), 6.72 (1H, d, J=8.6Hz), 7.30 (1H, dd, J=8.6, 2.1Hz), 7.75 (1H, d, J=2.1Hz), 8.71 (2H, broad s)

Mass (m/z) : 239 (M^+)

The following compound was obtained according to a similar manner to that of Preparation 5-(1).

(2) 5-(4-Fluorophenylthio)anthranilic acid

mp : 184-186°C

IR (Nujol) : 3520, 3400, 1680, 1610, 1580, 1550 cm^{-1}
NMR (DMSO-d_6, δ) : 6.8-7.4 (6H, m), 7.86 (1H, d, J=2.2Hz), 8.88 (1H, broad s)
Mass (m/z) : 263 (M^+)

Preparation 6

Into a solution of 5-(ethylthio)anthranilic acid (3.5 g), sodium hydroxide (1.42 g) and dry-ice (8.9 g) in water (89 ml) was bubbled phosgene prepared from trichloromethyl chloroformate (1.62 ml) and activated carbon (0.2 g) at room temperature for 10 minutes. The mixture was stirred for 2 hours, and the precipitates were collected by filtration, washed with water and dried in the air to give green-yellow crystals of 6-ethylthio-2H-3,1-benzoxazine-2,4(1H)-dione (2.9 g).

mp : >300°C
IR (Nujol) : 3150, 3080, 1780, 1740, 1715, 1620 cm^{-1}
NMR (DMSO-d_6, δ) : 1.22 (3H, t, J=7.3Hz), 2.99 (2H, q, J=7.3Hz), 7.12 (1H, d, J=8.4Hz), 7.6-7.8 (2H, m), 11.8 (1H, s)
Mass (m/z) : 223 (M^+)

Preparation 7

(1) A mixture of 5-(neopentylthio)anthranilic acid (5.8 g) and ethyl chloroformate (11.6 ml) in xylene (58 ml) was refluxed for 24 hours and cooled. The precipitates were collected by filtration and washed with ether to give a gray powder of 6-(neopentylthio)-2H-3,1-benzoxazine-2,4(1H)-dione (1.9 g).

mp : 221-225°C
IR (Nujol) : 3250, 1790, 1765, 1700, 1615 cm^{-1}
NMR (DMSO-d_6, δ) : 0.99 (9H, s), 2.95 (2H, s), 7.0-7.8 (3H, m), 11.7 (1H, s)
Mass (m/z) : 265 (M^+)

The following compounds were obtained according to a similar manner to that of Preparation 7-(1).

(2) 6-Phenylthio-2H-3,1-benzoxazine-2,4(1H)-dione
mp : 135-138°C
IR (Nujol) : 3250, 1790, 1765, 1700, 1615 cm^{-1}
NMR (DMSO-d_6, δ) : 7.1-7.5 (6H, m), 7.7-7.8 (2H, m), 11.88 (1H, s)
Mass (m/z) : 271 (M^+), 227

(3) 6-(4-Fluorophenylthio)-2H-3,1-benzoxazine-2,4-(1H)-dione
mp : 237-240°C
IR (Nujol) : 3250, 3180, 1790, 1760, 1695, 1615, 1585 cm^{-1}
NMR (DMSO-d_6, δ) : 7.1-7.8 (7H, m), 11.85 (1H, s)
Mass (m/z) : 289 (M^+), 245

Preparation 8

(1) A mixture of ethyl 2-(methylamino)-5-(methylthio)-benzoate (2.25 g), benzoylacetic acid (1.9 g), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (2.7 g) and 4-dimethylaminopyridine (10 mg) in dichloromethane (50 ml) was stirred at room temperature overnight. The mixture was washed with brine, dried and concentrated in vacuo. The residue (4.2 g) was purified by column chromatography on silica gel (70 g) eluting with a mixture of ethyl acetate and n-hexane (1:3) to give a yellow oil of ethyl 2-{N-methyl-N-(2-benzoylacetyl)amino}-5-(methylthio)benzoate (2.9 g).

NMR (DMSO-d_6, δ) : 1.17 (3H, t, J=7Hz), 2.58 (3H, s), 3.22 (3H, s), 4.24 (2H, q, J=7Hz), 5.18 (1H, s), 7.3-8.1 (8H, m), 15.1 (1H, s)

The following compounds were obtained according to a

similar manner to that of Preparation 8-(1).

(2) Ethyl 2-[{2-(N-phenyl-N-methylcarbamoyl)acetyl}-amino]-5-(methylthio)benzoate

mp : 115-117°C

IR (Nujol) : 1705, 1680, 1660, 1595, 1495 cm^{-1}

NMR (DMSO-d_6, δ) : 1.32 (3H, t, J=7.1Hz), 2.49 (3H, s), 3.21 (3H, s), 3.27 (2H, s), 4.31 (2H, q, J=7.1Hz), 7.3-8.2 (8H, m), 10.6 (1H, s)

(3) Ethyl 2-[N-methyl-N-{3-oxo-3-(1-phenyl-1-cyclopropyl)propionyl}amino]-5-(methylthio)benzoate

IR (Film) : 1725, 1705, 1660, 1615, 1490 cm^{-1}

NMR ($CDCl_3$, δ) : 1.1-1.2 (2H, m), 1.27 (3H, t, J=7.1Hz), 1.5-1.6 (2H, m), 2.55 (3H, s), 3.10 (3H, s), 4.26 (2H, q, J=7.1Hz), 6.73 (1H, d, J=8.3Hz), 7.1-7.4 (6H, m), 7.74 (1H, d, J=2.3Hz)

Mass (m/z) : 411 (M^+)

Preparation 9

A solution of potassium hydroxide (7.3 g) in methanol (40 ml) and water (3 ml) was added to a mixture of 4-fluorobenzenethiol (6.5 g) and 5-chloro-2-nitrobenzoic acid (10.1 g) in methanol (30 ml) under a nitrogen atmosphere. The mixture was refluxed for 6 hours, cooled, and poured into water (350 ml). The solution obtained was acidified, and the precipitates were collected by filtration and washed with water. The product was recrystallized twice from a mixture of ethanol and water to give a white powder of 5-(4-fluorophenylthio)-2-nitrobenzoic acid (10 g).

mp : 150-153°C

IR (Nujol) : 1710, 1590, 1570, 1535 cm^{-1}

NMR (DMSO-d_6, δ) : 7.3-7.8 (6H, m), 7.95 (1H, d, J=8.6Hz), 14.0 (1H, broad s)

Mass (m/z) : 293 (M^+)

Preparation 10

Sodium hydride (1.5 g) was added to a solution of 1-acetyl-1-phenylcyclopropane (5 g) and diethyl carbonate (18.8 ml) in tetrahydrofuran (62 ml). The mixture was refluxed for 1 hour, cooled, diluted with an saturated aqueous ammonium chloride solution, and extracted with ether. The extract was washed with brine, dried, and concentrated. The residue (7.7 g) was purified by column chromatography on silica gel (230 g) eluting with a mixture of ether and hexane (3:20) to give a light orange oil of ethyl 3-oxo-3-(1-phenyl-1-cyclopropyl)propionate (5 g).

IR (Film) : 1745, 1700, 1605, 1500 cm^{-1}

NMR ($CDCl_3$, δ) : 1.1-1.3 (5H, m), 1.6-1.8 (2H, m), 3.34 (2H, s), 4.10 (2H, q, J=7.1Hz), 7.3-7.5 (5H, m)

Mass (m/z) : 232 (M^+)

Preparation 11

A mixture of ethyl 3-oxo-3-(1-phenyl-1-cyclopropyl)-propionate (4.9 g) in 1N aqueous sodium hydroxide (21 ml) was stirred at room temperature overnight. The solution obtained was washed with ether, acidified with hydrochloric acid, and extracted with dichloromethane. The extract was dried and concentrated. The residue was kept in a freezer to give a white powder of 3-oxo-3-(1-phenyl-1-cyclopropyl)propionic acid (3.9 g).

mp : 50-55°C

IR (Film) : 1745, 1710, 1605, 1500 cm^{-1}

NMR ($CDCl_3$, δ) : 1.3-1.4 (2H, m), 1.7-1.8 (2H, m), 3.39 (2H, s), 7.37 (5H, s)

Mass (m/z) : 204

Example 1

(1) To a solution of ethyl 3-(N-methyl-N-phenylamino)-3-oxopropionate (16.8 g) in N,N-dimethylacetamide (48 ml), sodium hydride (3.03 g, 60%) was slowly added and the mixture was stirred for 30 minutes at room temperature. To the mixture was added dropwise a solution of 1-methyl-6-methylthio-2H-3,1-benzoxazine-2,4(1H)-dione (16 g) in N,N-dimethylacetamide (160 ml) at 80°C. Then the mixture was stirred at 120°C for 5 hours. The mixture was poured into ice-water (1 ℓ) and neutralized with concentrated hydrochloric acid (7 ml). The precipitates were collected, washed with water, and dissolved in chloroform (250 ml). The solution was filtered and the filtrate was concentrated. The residue was heated in ethanol and cooled to give pale brown crystals of 1-methyl-2-oxo-3-(N-methyl-N-phenylcarbamoyl)-4-hydroxy-6-methylthio-1,2-dihydroquinoline (13.4 g).

mp : 200-202°C (dec.)

IR (Nujol) : 1650, 1635, 1615, 1590, 1565, 1500 cm^{-1}

NMR (DMSO-d_6, δ) : 2.49 (3H, s), 3.29 (3H, s), 3.42 (3H, s), 7.0-7.8 (8H, m), 11.3 (1H, s)

Mass (m/z) : 354 (M^+)

Elemental Analysis Calcd. for $C_{19}H_{18}N_2O_3S$: C 64.39, H 5.12, N 7.91

Found : C 64.54, H 5.07, N 7.69

The following compounds were obtained according to a similar manner to that of Example 1-(1).

(2) 1-Methyl-2-oxo-3-(N-methyl-N-phenylaminosulfonyl)-4-hydroxy-6-methylthio-1,2-dihydroquinoline

mp : 154-156°C

IR (Nujol) : 1635, 1560 cm^{-1}

NMR (DMSO-d_6, δ) : 2.51 (3H, s), 3.51 (3H, s), 3.60 (3H, s), 7.2-7.8 (8H, m)

Mass (m/z) : 390 (M^+)

Elemental Analysis Calcd. for $C_{18}H_{18}N_2O_4S_2$:
C 55.37, H 4.65, N 7.18

Found : C 55.08, H 4.59, N 7.11

(3) 1-Methyl-2-oxo-3-ethoxycarbonyl-4-hydroxy-6-methylthio-1,2-dihydroquinoline

mp : 114-115°C

IR (Nujol) : 1660, 1630, 1565, 1490 cm^{-1}

NMR (DMSO-d_6, δ) : 1.30 (3H, t, J=7.1Hz), 2.54 (3H, s), 3.51 (3H, s), 4.32 (2H, q, J=7.1Hz), 7.4-7.9 (3H, m)

Mass (m/z) : 293 (M^+)

(4) 1-Methyl-2-oxo-3-benzylsulfonyl-4-hydroxy-6-methylthio-1,2-dihydroquinoline

mp : 157-159°C

IR (Nujol) : 1645, 1575 cm^{-1}

NMR (DSMO-d_6, δ) : 2.51 (3H, s), 3.63 (3H, s), 5.00 (2H, s), 7.32 (5H, s), 7.5-7.8 (3H, m)

Mass (m/z) : 375 (M^+)

Elemental Analysis Calcd. for $C_{18}H_{17}NO_4S_2$:
C 57.58, H 4.56, N 3.73, S 17.08

Found : C 57.40, H 4.50, N 3.69, S 17.09

Example 2

To an ice-cooled solution of 1-methyl-2-oxo-3-(N-methyl-N-phenylcarbamoyl)-4-hydroxy-6-methylthio-1,2-dihydroquinoline (1.45 g) in dichloromethane (40 ml) was added portionwise 80%-m-chloroperbenzoic acid (0.883 g). The mixture was stirred at 5°C for 1 hour, washed with water, dried over anhydrous magnesium sulfate, and concentrated in vacuo. The residue was crystallized from acetone to give colorless crystals of 1-methyl-2-oxo-3-(N-methyl-N-phenylcarbamoyl)-4-hydroxy-

6-methylsulfinyl-1,2-dihydroquinoline (1.5 g).

mp : 218-219°C (dec.)

IR (Nujol) : 1635, 1595, 1500 cm^{-1}

NMR (DMSO-d_6, δ) : 2.75 (3H, s), 3.30 (3H, s), 3.48 (3H, s), 7.0-8.2 (8H, m), 11.7 (1H, s)

Mass (m/z) : 370 (M^+)

Elemental Analysis Calcd. for $C_{19}H_{18}N_2O_4S \cdot 1/7H_2O$: C 61.18, H 4.94, N 7.51

Found : C 60.95, H 5.00, N 7.24

Example 3

A mixture of 1-methyl-2-oxo-3-ethoxycarbonyl-4-hydroxy-6-methylthio-1,2-dihydroquinoline (2 g) and indoline (0.94 ml) in pyridine (10 ml) was stirred at 100°C for 4 hours. The solvent was evaporated and the residue was dissolved in chloroform. The solution was filtered and the filtrate was concentrated in vacuo. The residue was crystallized from ethanol to give pale brown crystals of 1-methyl-2-oxo-3-(1-indolinylcarbonyl)-4-hydroxy-6-methylthio-1,2-dihydroquinoline (2.1 g).

mp : 220-222°C (dec.)

IR (Nujol) : 1655, 1625, 1605, 1580, 1560 cm^{-1}

NMR (DMSO-d_6, δ) : 2.55 (3H, s), 3.08 (2H, t, J=8.3Hz), 3.59 (3H, s), 3.88 (2H, t, J=8.3Hz), 7.0-8.3 (7H, m), 11.5 (1H, s)

Mass (m/z) : 366 (M^+)

Elemental Analysis Calcd. for $C_{20}H_{18}N_2O_3S \cdot 0.28H_2O$: C 64.66, H 5.04, N 7.54

Found : C 64.47, H 4.92, N 7.42

Example 4

A mixture of 1-methyl-2-oxo-3-ethoxycarbonyl-4-hydroxy-6-methylthio-1,2-dihydroquinoline (2.2 g) and hydrobromic acid (1.7 ml) in acetic acid (6 ml) was stirred at 70°C for 4 hours. The mixture was cooled to

5°C, and the precipitates were collected, washed with water and dried in vacuo at 60°C to give pale yellow crystals of 1-methyl-2-oxo-3-carboxy-4-hydroxy-6-methylthio-1,2-dihydroquinoline (1.8 g).

mp : 162-163°C

IR (Nujol) : 1690, 1630, 1600, 1490 cm^{-1}

NMR (DMSO-d_6, δ) : 2.57 (3H, s), 3.67 (3H, s), 7.6-7.9 (3H, m)

Mass (m/z) : 265 (M^+)

Example 5

Phosphorus trichloride (0.347 ml) was added dropwise to a solution of N-methyl-4-fluoroaniline (2.99 g) in toluene (18 ml) under stirring. After stirring was continued at room temperature for 30 minutes, to the resultant solution 1-methyl-2-oxo-3-carboxy-4-hydroxy-6-methylthio-1,2-dihydroquinoline (2.11 g) was added. The mixture was heated at 100°C for 2 hours and then cooled down. The reaction mixture was extracted with 2N sodium hydroxide solution. The extract was acidified with hydrochloric acid and extracted with chloroform. The extract obtained above was dried over magnesium sulfate, filtered and evaporated to dryness. The residue was washed with acetone and dried in vacuo to give pale brown crystals of 1-methyl-2-oxo-3-{N-(4-fluorophenyl)-N-methylcarbamoyl}-4-hydroxy-6-methylthio-1,2-dihydroquinoline (2.1 g).

mp : 201-203°c

IR (Nujol) : 1650, 1635, 1615, 1595, 1570, 1510 cm^{-1}

NMR (DMSO-d_6, δ) : 2.50 (3H, s), 3.28 (3H, s), 3.43 (3H, s), 7.0-7.8 (7H, m), 11.4 (1H, s)

Mass (m/z) : 372 (M^+)

Elemental Analysis Calcd. for $C_{19}H_{17}FN_2O_3S$:
C 61.27, H 4.60, N 7.52

Found : C 61.29, H 4.50, N 7.45

Example 6

The following compounds were obtained according to a similar manner to that of Example 1-(1).

(1) 1-Methyl-2-oxo-3-cyano-4-hydroxy-6-methylthio-1,2-dihydroquinoline
mp : 258-260°C
IR (Nujol) : 2240, 1620, 1585, 1550 cm^{-1}
NMR (DMSO-d_6, δ) : 2.53 (3H, s), 3.53 (3H, s), 7.4-8.0 (3H, m)
Mass (m/z) : 246 (M^+)

(2) 1-Methyl-2-oxo-3-[N-methyl-N-phenylamino-(thiocarbonyl)]-4-hydroxy-6-methylthio-1,2-dihydroquinoline
mp : 174-176°C
IR (Nujol) : 1620, 1570 cm^{-1}
NMR (DMSO-d_6, δ) : 2.48 (3H, s), 3.41 (3H, s), 3.74 (3H, s), 7.1-7.7 (8H, m), 10.9 (1H, s)
Mass (m/z) : 370 (M^+), 263
Elemental Analysis Calcd. for $C_{19}H_{18}N_2O_2S_2$: C 61.60, H 4.90, N 7.56, S 17.31
Found : C 61.29, H 4.87, N 7.42, S 17.09

(3) 1-Methyl-2-oxo-3-(1-phenyl-5-tetrazolyl)-4-hydroxy-6-methylthio-1,2-dihydroquinoline
mp : 263-265°C (dec.)
IR (Nujol) : 1630, 1605, 1590, 1560, 1515 cm^{-1}
NMR (DMSO-d_6, δ) : 2.53 (3H, s), 3.51 (3H, s), 7.52 (5H, s), 7.4-7.9 (3H, m)
Mass (m/z) : 365 (M^+), 337

(4) 1-Methyl-2-oxo-3-(5-phenyl-1,3,4-oxadiazol-2-yl)-4-hydroxy-6-methylthio-1,2-dihydroquinoline
mp : 240-242°C

IR (Nujol) : 1660, 1640, 1580, 1535 cm^{-1}
NMR (DMSO-d_6, δ) : 2.57 (3H, s), 3.79 (3H, s), 7.2-8.3 (8H, m)
Mass (m/z) : 365 (M^+)

(5) 1-Methyl-2-oxo-3-(1-methyl-1H-benzimidazol-2-yl)-4-hydroxy-6-methylthio-1,2-dihydroquinoline
mp : 198-204°C
IR (Nujol) : 1605, 1575, 1530 cm^{-1}
NMR (DMSO-d_6, δ) : 2.51 (3H, s), 3.53 (3H, s), 3.79 (3H, s), 7.3-8.0 (7H, m)
Mass (m/z) : 351 (M^+)

(6) 1-Methyl-2-oxo-3-(1-phenylimidazolin-2-yl)-4-hydroxy-6-methylthio-1,2-dihydroquinoline
mp : 120-130°C
IR (Nujol) : 1590, 1560, 1525 cm^{-1}
NMR (DMSO-d_6, δ) : 2.45 (3H, s), 3.27 (3H, s), 3.88 (2H, t, J=8.9Hz), 4.25 (2H, t, J=8.9Hz), 7.0-7.8 (8H, m), 10.4 (1H, s)
Mass (m/z) : 365 (M^+)

(7) 1-Methyl-2-oxo-3-(1-isoquinolyl)-4-hydroxy-6-methylthio-1,2-dihydroquinoline
mp : 136-140°C
IR (Nujol) : 1645, 1620, 1610, 1585, 1565, 1515 cm^{-1}
NMR (DMSO-d_6, δ) : 2.53 (3H, s), 3.56 (3H, s), 7.4-8.5 (9H, m)
Mass (m/z) : 347

(8) 1-Methyl-2-oxo-3-(2-quinolyl)-4-hydroxy-6-methylthio-1,2-dihydroquinoline
mp : 225-227°C
IR (Nujol) : 1640, 1610, 1570, 1505 cm^{-1}
NMR (DMSO-d_6, δ) : 2.55 (3H, s), 3.60 (3H, s),

7.4-8.1 (7H, m), 8.63 (1H, d, J=9.4Hz), 9.49 (1H, d, J=9.4Hz)

Mass (m/z) : 348 (M^+)

(9) 1-Methyl-2-oxo-3-{N-(2-methoxyphenyl)-N-methylcarbamoyl}-4-hydroxy-6-methylthio-1,2-dihydroquinoline

mp : 178-180°C

IR (Nujol) : 1610, 1570, 1490 cm^{-1}

NMR (DMSO-d_6, δ) : 2.49 (3H, s), 3.21 (3H, s), 3.36 (3H, s), 3.71 (3H, s), 6.6-7.8 (7H, m), 11.0 (1H, s)

Mass (m/z) : 384 (M^+), 247

Elemental Analysis Calcd. for $C_{20}H_{20}N_2O_4S$: C 62.48, H 5.24, N 7.29

Found : C 62.17, H 5.29, N 7.15

(10) 1-Methyl-2-oxo-3-{N-(2-chlorophenyl)-N-methylcarbamoyl}-4-hydroxy-6-methylthio-1,2-dihydroquinoline

mp : 175-183°C

IR (Nujol) : 1630, 1620, 1585, 1570 cm^{-1}

NMR (DMSO-d_6, δ) : 2.50 (3H, s), 3.27 (3H, s), 3.38 (3H, s), 7.1-8.0 (7H, m), 11.3 (1H, broad s)

Mass (m/z) : 388 (M^+), 247

(11) 1-Methyl-2-oxo-3-{N-methyl-N-(2-methylphenyl)-carbamoyl}-4-hydroxy-6-methylthio-1,2-dihydroquinoline

mp : 188-194°C

IR (Nujol) : 1635, 1620, 1595, 1575, 1495 cm^{-1}

NMR (DMSO-d_6, δ) : 2.34 (3H, s), 2.49 (3H, s), 3.20 (3H, s), 3.38 (3H, s), 6.9-8.0 (7H, m)

Mass (m/z) : 368 (M^+), 247

Elemental Analysis Calcd. for $C_{20}H_{20}N_2O_3S$: C 65.20, H 5.47, N 7.60

Found : C 65.75, H 5.79, N 7.30

(12) 1-Methyl-2-oxo-3-(N-methyl-N-phenylcarbamoyl)-4-hydroxy-6-ethylthio-1,2-dihydroquinoline
mp : 140-148°C
IR (Nujol) : 1650, 1610, 1585, 1560 cm^{-1}
NMR (DMSO-d_6, δ) : 1.19 (3H, t, J=7.3Hz), 2.93 (2H, q, J=7.3Hz), 3.30 (3H, s), 3.43 (3H, s), 7.1-7.8 (8H, m), 11.3 (1H, s)
Mass (m/z) : 368 (M^+), 261

(13) 1-Methyl-2-oxo-3-(N-methyl-N-phenylcarbamoyl)-4-hydroxy-6-(neopentylthio)-1,2-dihydroquinoline
mp : 121-123°C
IR (Nujol) : 1655, 1630, 1610, 1585 cm^{-1}
NMR (DMSO-d_6, δ) : 0.98 (9H, s), 2.92 (2H, s), 3.29 (3H, s), 3.42 (3H, s), 7.1-7.9 (8H, m), 11.3 (1H, broad s)
Mass (m/z) : 410 (M^+)

(14) 1-Ethyl-2-oxo-3-(N-methyl-N-phenylcarbamoyl)-4-hydroxy-6-methylthio-1,2-dihydroquinoline
mp : 174-180°C
IR (Nujol) : 1640, 1620, 1580 cm^{-1}
NMR (DMSO-d_6, δ) : 1.23 (3H, t, J=7Hz), 2.49 (3H, s), 3.29 (3H, s), 4.10 (2H, q, J=7Hz), 7.0-7.8 (8H, m), 11.3 (1H, s)
Mass (m/z) : 368 (M^+)
Elemental Analysis Calcd. for $C_{20}H_{20}N_2O_3S$:
C 65.20, H 5.47, N 7.60, S 8.70
Found : C 65.52, H 5.59, N 7.34, S 8.74

(15) 1-Benzyl-2-oxo-3-(N-methyl-N-phenylcarbamoyl)-4-hydroxy-6-methylthio-1,2-dihydroquinoline
mp : 185-195°C
IR (Nujol) : 1640, 1620, 1590, 1500 cm^{-1}
NMR (DMSO-d_6, δ) : 2.45 (3H, s), 3.33 (3H, s),

6.7-7.8 (13H, m), 11.5 (1H, s)
Mass (m/z) : 430 (M^+)
Elemental Analysis Calcd. for $C_{25}H_{22}N_2O_3S$:
C 65.20, H 5.47, N 7.60, S 8.70
Found : C 65.52, H 5.59, N 7.34, S 8.74

(16) 1-Methoxymethyl-2-oxo-3-(N-methyl-N-phenylcarbamoyl)-4-hydroxy-6-methylthio-1,2-dihydroquinoline
mp : 152-156°C
IR (Nujol) : 1645, 1605, 1580, 1560 cm^{-1}
NMR (DMSO-d_6, δ) : 2.49 (3H, s), 2.95 (3H, s), 3.30 (3H, s), 5.49 (2H, s), 7.0-7.8 (8H, m), 11.6 (1H, broad s)
Mass (m/z) : 384 (M^+)

(17) 1-Propyl-2-oxo-3-(N-methyl-N-phenylcarbamoyl)-4-hydroxy-6-methylthio-1,2-dihydroquinoline
mp : 142-152°C
IR (Nujol) : 1640, 1630, 1605, 1580 cm^{-1}
NMR (DMSO-d_6, δ) : 0.76 (3H, t, J=7.1Hz), 1.3-1.6 (2H, m), 2.48 (3H, s), 3.29 (3H, s), 3.9-4.1 (2H, m), 7.0-7.8 (8H, m), 11.3 (1H, s)
Mass (m/z) : 382 (M^+)
Elemental Analysis Calcd. for $C_{21}H_{22}N_2O_3S$:
C 65.95, H 5.80, N 7.32, S 8.38
Found : C 66.07, H 6.22, N 7.08, S 8.38

(18) 1-Methyl-2-oxo-3-(N-methyl-N-phenylcarbamoyl)-4-hydroxy-6-phenylthio-1,2-dihydroquinoline
mp : 110-115°C
NMR (DMSO-d_6, δ) : 3.28 (3H, s), 3.44 (3H, s), 7.0-8.0 (13H, m)

(19) 1-Methyl-2-thioxo-3-ethoxycarbonyl-4-hydroxy-6-methylthio-1,2-dihydroquinoline

mp : 135-137°C
IR (Nujol) : 1690, 1610, 1530 cm^{-1}
NMR (DMSO-d_6, δ) : 1.28 (3H, t, J=7.1Hz), 2.57 (3H, s), 4.17 (3H, s), 4.26 (2H, q, J=7.1Hz), 7.6-8.0 (3H, m)

(20) 1-Methyl-2-oxo-3-(N-methyl-N-phenylcarbamoyl)-4-hydroxy-6-(4-fluorophenylthio)-1,2-dihydroquinoline
IR (Nujol) : 1640, 1615, 1585, 1550, 1510 cm^{-1}
NMR (DMSO-d_6, δ) : 3.26 (3H, s), 3.37 (3H, s), 7.0-7.6 (11H, m), 8.02 (1H, broad s)
Mass (m/z) : 327

Example 7

The following compounds were obtained according to a similar manner to that of Example 2.

(1) 1-Methyl-2-oxo-3-(N-methyl-N-phenylcarbamoyl)-4-methoxy-6-methylsulfinyl-1,2-dihydroquinoline
mp : 322-325°C (dec.)
IR (Nujol) : 1640, 1630, 1595, 1495 cm^{-1}
NMR (DMSO-d_6, δ) : 2.74 (3H, s), 3.36 (3H, s), 3.53 (3H, s), 4.15 (3H, s), 7.1-8.4 (8H, m)
Mass (m/z) : 384 (M^+)

(2) 1-Methyl-2-oxo-3-(N-methyl-N-phenylcarbamoyl)-4-hydroxy-6-phenylsulfinyl-1,2-dihydroquinoline
mp : 216-223°C
IR (Nujol) : 1640, 1600, 1590, 1495 cm^{-1}
NMR (DMSO-d_6, δ) : 3.29 (3H, s), 3.42 (3H, s), 7.0-8.3 (13H, m), 11.7 (1H, s)
Mass (m/z) : 432 (M^+)
Elemental Analysis Calcd. for $C_{24}H_{20}N_2O_4S$: C 66.65, H 4.66, N 6.48
Found : C 66.55, H 4.67, N 6.37

Example 8

The following compounds were obtained according to a similar manner to that of Example 3.

(1) 1-Methyl-2-oxo-3-(N-benzyl-N-methylcarbamoyl)-4-hydroxy-6-methylthio-1,2-dihydroquinoline
mp : 186-188°C
IR (Nujol) : 1645, 1635, 1605, 1575, 1500 cm^{-1}
NMR (DMSO-d_6, δ) : 2.54 (3H, s), 2.79 (3H, s), 3.58 (3H, s), 4.3-4.8 (2H, m), 7.2-8.0 (8H, m)
Mass (m/z) : 368 (M^+), 247
Elemental Analysis Calcd. for $C_{20}H_{20}N_2O_3S$:
C 65.19, H 5.47, N 7.60
Found : C 65.52, H 5.46, N 7.52

(2) 1-Methyl-2-oxo-3-{N-(2-thiazolyl)carbamoyl}-4-hydroxy-6-methylthio-1,2-dihydroquinoline
mp : 264-267°C
IR (Nujol) : 1630, 1600, 1540 cm^{-1}
NMR (DMSO-d_6, δ) : 2.58 (3H, s), 3.69 (3H, s), 7.4-8.0 (5H, m)
Mass (m/z) : 347 (M^+), 247
Elemental Analysis Calcd. for $C_{15}H_{13}N_3O_3S_2$:
C 51.86, H 3.77, N 12.10
Found : C 51.39, H 3.56, N 11.85

(3) 1-Methyl-2-oxo-3-(N-cyclohexyl-N-methylcarbamoyl)-4-hydroxy-6-methylthio-1,2-dihydroquinoline
mp : 144-147°C
IR (Nujol) : 1645, 1635, 1590, 1570, 1500 cm^{-1}
NMR (DMSO-d_6, δ) : 1.0-1.8 (10H, m), 2.52 (3H, s), 2.78 (3H, s), 3.3-3.6 (1H, m), 3.54 (3H, s), 7.4-7.9 (3H, m)
Mass (m/z) : 360 (M^+), 247

Elemental Analysis Calcd. for $C_{19}H_{24}N_2O_3S$:
C 63.30, H 6.71, N 7.77
Found : C 63.01, H 6.85, N 7.48

(4) 1-Methyl-2-oxo-3-{N-(2-pyridyl)carbamoyl}-4-hydroxy-6-methylthio-1,2-dihydroquinoline
mp : 212-213°C
IR (Nujol) : 1640, 1630, 1600, 1570, 1550, 1530 cm^{-1}
NMR (DMSO-d_6, δ) : 2.57 (3H, s), 3.67 (3H, s), 7.1-8.5 (7H, m), 13.0 (1H, broad s)
Mass (m/z) : 341 (M^+), 247
Elemental Analysis Calcd. for $C_{17}H_{15}N_3O_3S$:
C 59.81, H 4.43, N 12.31
Found : C 59.90, H 4.34, N 12.23

(5) 1-Methyl-2-oxo-3-(N-phenylcarbamoyl)-4-hydroxy-6-methylthio-1,2-dihydroquinoline
mp : 176-178°C
IR (Nujol) : 1650, 1600, 1590, 1565 cm^{-1}
NMR (DMSO-d_6, δ) : 2.57 (3H, s), 3.67 (3H, s), 7.1-8.0 (8H, m), 12.7 (1H, s)
Mass (m/z) : 340 (M^+), 247
Elemental Analysis Calcd. for $C_{18}H_{16}N_2O_3S$:
C 63.51, H 4.74, N 8.23
Found : C 63.52, H 4.57, N 8.14

(6) 1-Methyl-2-oxo-3-{N-(2-methylphenyl)carbamoyl}-4-hydroxy-6-methylthio-1,2-dihydroquinoline
mp : 159-160°C
IR (Nujol) : 1640, 1625, 1590, 1565 cm^{-1}
NMR (DMSO-d_6, δ) : 2.37 (3H, s), 2.57 (3H, s), 3.67 (3H, s), 7.1-8.2 (7H, m), 12.6 (1H, s)
Mass (m/z) : 354 (M^+), 247
Elemental Analysis Calcd. for $C_{19}H_{18}N_2O_3S$:
C 64.39, H 5.12, N 7.91
Found : C 64.06, H 4.97, N 7.83

(7) 1-Methyl-2-oxo-3-{N-(2-chlorophenyl)carbamoyl}-4-hydroxy-6-methylthio-1,2-dihydroquinoline
mp : 189-190°C
IR (Nujol) : 1660, 1640, 1590, 1580, 1555 cm^{-1}
NMR (DMSO-d_6, δ) : 2.57 (3H, s), 3.67 (3H, s), 7.1-8.4 (7H, m), 13.1 (1H, s)
Mass (m/z) : 374 (M^+), 247
Elemental Analysis Calcd. for $C_{18}H_{15}N_2ClO_3S$: C 57.67, H 4.03, N 7.48
Found : C 57.68, H 3.76, N 7.38

(8) 1-Methyl-2-oxo-3-{N-(2,6-dichlorophenyl)carbamoyl}-4-hydroxy-6-methylthio-1,2-dihydroquinoline
mp : 198-200°C
IR (Nujol) : 1645, 1635, 1600, 1565, 1520 cm^{-1}
NMR (DMSO-d_6, δ) : 2.57 (3H, s), 3.69 (3H, s), 7.4-8.0 (6H, m), 12.2 (1H, s)
Mass (m/z) : 408 (M^+), 247

(9) 1-Methyl-2-oxo-3-{N-(2,6-dimethylphenyl)carbamoyl}-4-hydroxy-6-methylthio-1,2-dihydroquinoline
mp : 215-216°C
IR (Nujol) : 1640, 1600, 1580, 1555 cm^{-1}
NMR (DMSO-d_6, δ) : 2.21 (6H, s), 2.57 (3H, s), 3.68 (3H, s), 7.16 (3H, s), 7.6-7.9 (3H, m), 11.9 (1H, s)
Mass (m/z) : 368 (M^+), 247

(10) 4-Oxo-5-(1-indolinylcarbonyl)-6-hydroxy-8-methylthio-1,2-dihydro-4H-pyrrolo[3,2,1-ij]quinoline
mp : 246-249°C (dec.)
IR (Nujol) : 1655, 1610, 1550, 1495 cm^{-1}
NMR (DMSO-d_6, δ) : 2.52 (3H, s), 3.08 (2H, t, J=8Hz), 3.37 (2H, t, J=8Hz), 3.89 (2H, t, J=8Hz), 4.27 (2H, t, J=8Hz), 6.9-8.2 (6H, m),

11.3 (1H, broad s)
Mass (m/z) : 378 (M^+)

Example 9

The following compounds were obtained according to a similar manner to that of Example 4.

(1) 4-Oxo-5-carboxy-6-hydroxy-8-methylthio-1,2-dihydro-4H-pyrrolo[3,2,1-ij]quinoline
mp : 270-278°C (dec.)
IR (Nujol) : 1680, 1630, 1600 cm^{-1}
Mass (m/z) : 277 (M^+), 259

(2) 1-Methyl-2-thioxo-3-carboxy-4-hydroxy-6-methylthio-1,2-dihydroquinoline
mp : 139-148°C (dec.)
IR (Nujol) : 1680, 1610, 1550 cm^{-1}
NMR (DMSO-d_6, δ) : 2.60 (3H, s), 4.19 (3S, s), 7.6-8.0 (3H, m)
Mass (m/z) : 281 (M^+)

Example 10

The following compounds were obtained according to a similar manner to that of Example 5.

(1) 1-Methyl-2-oxo-3-{N-(4-methoxyphenyl)-N-methylcarbamoyl}-4-hydroxy-6-methylthio-1,2-dihydroquinoline
mp : 171-173°C (dec.)
IR (Nujol) : 1640, 1620, 1590, 1560, 1510 cm^{-1}
NMR (DMSO-d_6, δ) : 2.49 (3H, s), 3.25 (3H, s), 3.43 (3H, s), 3.62 (3H, s), 6.75 (2H, d, J=8.8Hz), 7.21 (2H, d, J=8.8Hz), 7.3-7.8 (3H, m), 11.2 (1H, s)
Mass (m/z) : 247

Elemental Analysis Calcd. for $C_{20}H_{20}N_2O_4S$:
C 62.48, H 5.24, N 7.29
Found : C 62.54, H 5.31, N 7.20

(2) 1-Methyl-2-oxo-3-(N-ethyl-N-phenylcarbamoyl)-4-hydroxy-6-methylthio-1,2-dihydroquinoline
mp : 204-205°C (dec.)
IR (Nujol) : 1645, 1605, 1580, 1560 cm^{-1}
NMR (DMSO-d_6, δ) : 1.07 (3H, t, J=7.0Hz), 2.49 (3H, s), 3.41 (3H, s), 3.80 (2H, q, J=7.0Hz), 7.1-7.8 (8H, m), 11.2 (1H, s)
Mass (m/z) : 247
Elemental Analysis Calcd. for $C_{20}H_{20}N_2O_3S$:
C 65.19, H 5.47, N 7.60
Found : C 65.26, H 5.59, N 7.62

(3) 1-Methyl-2-oxo-3-{N-(5-indanyl)-N-methylcarbamoyl}-4-hydroxy-6-methylthio-1,2-dihydroquinoline
mp : 136-140°C (dec.)
IR (Nujol) : 1650, 1630, 1595, 1565 cm^{-1}
NMR ($CDCl_3$, δ) : 2.04 (2H, quin, J=7.3Hz), 2.55 (3H, s), 2.84 (4H, t, J=7.3Hz), 3.36 (3H, s), 3.46 (3H, s), 6.9-8.0 (6H, m)
Mass (m/z) : 247
Elemental Analysis Calcd. for $C_{22}H_{22}N_2O_3S$:
C 66.98, H 5.62, N 7.10
Found : C 66.56, H 5.70, N 6.81

(4) 1-Methyl-2-oxo-3-{(3,4-dihydro-2H-1,4-benzothiazin-4-yl)carbonyl}-4-hydroxy-6-methylthio-1,2-dihydroquinoline
mp : 191-194°C
IR (Nujol) : 3300, 1640, 1620, 1585 cm^{-1}
NMR (DMSO-d_6, δ) : 2.52 (3H, s), 3.29 (2H, broad s), 3.49 (3H, s), 3.92 (2H, broad s), 6.7-8.0 (7H,

m), 11.5 (1H, broad s)
Mass (m/z) : 398 (M^+), 247
Elemental Analysis Calcd. for $C_{20}H_{18}N_2O_3S_2$:
C 60.28, H 4.55, N 7.03
Found : C 60.02, H 4.53, N 6.88

(5) 1-Methyl-2-oxo-3-{(3,4-dihydro-2H-1,4-benzoxazin-4-yl)carbonyl}-4-hydroxy-6-methylthio-1,2-dihydroquinoline
mp : 202-204°C
IR (Nujol) : 1640, 1600, 1585, 1560, 1495 cm^{-1}
NMR (DMSO-d_6, δ) : 2.54 (3H, s), 3.54 (3H, s), 3.72 (2H, s), 4.30 (2H, s), 6.5-8.4 (7H, m), 11.6 (1H, s)
Mass (m/z) : 382 (M^+), 247
Elemental Analysis Calcd. for $C_{20}H_{18}N_2O_4S$:
C 62.81, H 4.74, N 7.33
Found : C 62.47, H 4.58, N 7.20

(6) 1-Methyl-2-oxo-3-{N-methyl-N-(4-methylthiophenyl)-carbamoyl}-4-hydroxy-6-methylthio-1,2-dihydroquinoline
mp : 168-169°C (dec.)
IR (Nujol) : 1645, 1625, 1565, 1495 cm^{-1}
NMR (DMSO-d_6, δ) : 2.36 (3H, s), 2.49 (3H, s), 3.27 (3H, s), 3.44 (3H, s), 7.0-7.8 (7H, m), 11.3 (1H, s)
Mass (m/z) : 400 (M^+), 247
Elemental Analysis Calcd. for $C_{20}H_{20}N_2O_3S_2$:
C 59.98, H 5.03, N 7.00
Found : C 60.08, H 5.25, N 6.75

(7) 1-Methyl-2-oxo-3-{N-(1,3-benzodioxol-5-yl)-N-methyl-carbamoyl}-4-hydroxy-6-methylthio-1,2-dihydroquinoline
mp : 141-144°C (dec.)
IR (Nujol) : 1640, 1620, 1600, 1565, 1500 cm^{-1}

NMR (DMSO-d_6, δ) : 2.50 (3H, s), 3.24 (3H, s), 3.45 (3H, s), 5.93 (2H, s), 6.6-7.8 (6H, m), 11.2 (1H, s)

Mass (m/z) : 398 (M^+), 247

Elemental Analysis Calcd. for $C_{20}H_{18}N_2O_5S$:
C 60.29, H 4.55, N 7.03

Found : C 60.08, H 4.93, N 6.72

(8) 1-Methyl-2-oxo-3-{N-methyl-N-(4-methylphenyl)-carbamoyl}-4-hydroxy-6-methylthio-1,2-dihydroquinoline

mp : 192-193°C (dec.)

IR (Nujol) : 1650, 1630, 1590, 1565, 1515 cm^{-1}

NMR (DMSO-d_6, δ) : 2.14 (3H, s), 2.49 (3H, s), 3.26 (3H, s), 3.43 (3H, s), 6.9-7.8 (7H, m), 11.3 (1H, s)

Mass (m/z) : 368 (M^+), 247

Elemental Analysis Calcd. for $C_{20}H_{20}N_2O_3S$:
C 65.19, H 5.47, N 7.60

Found : C 65.14, H 5.55, N 7.49

(9) 1-Methyl-2-oxo-3-{N-(2,4-difluorophenyl)-N-methylcarbamoyl}-4-hydroxy-6-methylthio-1,2-dihydroquinoline

mp : 129-131°C

IR (Nujol) : 1650, 1600, 1565, 1515 cm^{-1}

NMR (DMSO-d_6, δ) : 2.51 (3H, s), 3.27 (3H, s), 3.40 (3H, s), 6.8-8.0 (6H, m), 11.5 (1H, broad s)

Mass (m/z) : 390 (M^+), 274

Elemental Analysis Calcd. for $C_{19}H_{16}N_2F_2O_3S$:
C 58.45, H 4.13, N 7.18

Found : C 58.56, H 3.88, N 7.08

(10) 4-Oxo-5-(N-methyl-N-phenylcarbamoyl)-6-hydroxy-8-methylthio-1,2-dihydro-4H-pyrrolo[3,2,1-ij]quinoline

mp : 120-121°C (dec.)

IR (Nujol) : 3400, 1640, 1630, 1590, 1495 cm^{-1}
NMR (DMSO-d_6, δ) : 2.46 (3H, s), 3.29 (3H, s), 3.2-3.4 (2H, m), 4.0-4.2 (2H, m), 7.0-7.5 (7H, m), 11.1 (1H, broad s)
Mass (m/z) : 259

(11) 1-Methyl-2-thioxo-3-(N-methyl-N-phenylcarbamoyl)-4-hydroxy-6-methylthio-1,2-dihydroquinoline
mp : 130-150°C
IR (Nujol) : 1620, 1595, 1565, 1500 cm^{-1}
NMR (DMSO-d_6, δ) : 2.53 (3H, s), 3.30 (3H, s), 4.06 (3H, s), 7.0-8.0 (8H, m)
Mass (m/z) : 370 (M^+), 263

(12) 1-Methyl-2-oxo-3-[N-methyl-N-{4-(trifluoromethoxy)-phenyl}carbamoyl]-4-hydroxy-6-methylthio-1,2-dihydroquinoline
IR (Nujol) : 1640, 1620, 1565, 1510 cm^{-1}
NMR ($CDCl_3$, δ) : 2.55 (3H, s), 3.28 (3H, s), 3.49 (3H, s), 7.0-8.0 (7H, m)
Mass (m/z) : 438 (M^+), 247

(13) 1-Methyl-2-oxo-3-[N-methyl-N-{3-(trifluoromethyl)-phenyl}carbamoyl]-4-hydroxy-6-methylthio-1,2-dihydroquinoline
IR (Nujol) : 1640, 1625, 1610, 1570, 1495 cm^{-1}
NMR ($CDCl_3$, δ) : 2.56 (3H, s), 3.28 (3H, s), 3.52 (3H, s), 7.1-7.6 (6H, m), 7.97 (1H, d, J=2.2Hz), 12.5 (1H, broad s)
Mass (m/z) : 422 (M^+), 247

Example 11

(1) A mixture of 1-methyl-2-oxo-3-carboxy-4-hydroxy-6-methylthio-1,2-dihydroquinoline (1 g), 2-methylamino-1,3,4-thiadiazole (451 mg) and

1,3-dicyclohexylcarbodiimide (986 mg) in toluene (10 ml) was stirred at 90°C for 1 hour. The mixture was cooled, and the insoluble material was collected by filtration washed with toluene, and suspended in 2N-sodium hydroxide aqueous solution (12 ml). The suspension was filtered. The filtrate was acidified with hydrochloric acid and extracted with chloroform. The extract was dried and concentrated. The residue was recrystallized from acetone to give pale yellow crystals of 1-methyl-2-oxo-3-{N-methyl-N-(1,3,4-thiadiazol-2-yl)carbamoyl}-4-hydroxy-6-methylthio-1,2-dihydroquinoline (0.47 g).

mp : 187-189°C (dec.)

IR (Nujol) : 1660, 1610, 1580 cm^{-1}

NMR (DMSO-d_6, δ) : 2.55 (3H, s), 3.60 (6H, s), 7.5-8.0 (3H, m), 9.30 (1H, s), 11.9 (1H, broad s)

Mass (m/z) : 247

Elemental Analysis Calcd. for $C_{15}H_{14}N_4O_3S_2$: C 49.71, H 3.89, N 15.46

Found : C 49.55, H 3.84, N 15.15

The following compounds were obtained according to a similar manner to that of Example 11-(1).

(2) 1-Methyl-2-oxo-3-{N-methyl-N-(2-pyridyl)carbamoyl}-4-hydroxy-6-methylthio-1,2-dihydroquinoline

mp : 151-154°C

IR (Nujol) : 1655, 1620, 1605, 1575 cm^{-1}

NMR (DMSO-d_6, δ) : 2.52 (3H, s), 3.37 (3H, s), 3.50 (3H, s), 7.1-8.4 (7H, m)

Mass (m/z) : 247

(3) 1-Methyl-2-oxo-3-{N-methyl-N-(1-methyl-5-pyrazolyl)-carbamoyl}-4-hydroxy-6-methylthio-1,2-dihydroquinoline

mp : 114-118°C (dec.)

IR (Nujol) : 3380, 1665, 1600, 1570, 1550 cm^{-1}

NMR (DMSO-d_6, δ) : 2.51 (3H, s), 3.22 (3H, s), 3.45 (3H, s), 3.72 (3H, s), 6.0-8.0 (5H, m), 11.5 (1H, broad s)

Mass (m/z) : 247

Elemental Analysis Calcd. for $C_{17}H_{18}N_4O_3S$:
C 54.24, H 5.35, N 14.89
Found : C 54.04, H 5.45, N 14.69

(4) 1-Methyl-2-oxo-3-{N-(4-acetylphenyl)-N-methylcarbamoyl}-4-hydroxy-6-methylthio-1,2-dihydroquinoline

mp : 110-112°C

IR (Nujol) : 1690, 1645, 1600, 1565, 1500 cm^{-1}

NMR (DMSO-d_6, δ) : 2.50 (6H, s), 3.34 (3H, s), 3.47 (3H, s), 7.3-7.9 (7H, m), 11.5 (1H, broad s)

Mass (m/z) : 396 (M^+), 247

Elemental Analysis Calcd. for $C_{21}H_{20}N_2O_4S \cdot 1/6H_2O$:
C 63.14, H 5.13, N 7.01
Found : C 63.10, H 5.35, N 6.79

(5) 1-Methyl-2-oxo-3-[N-{4-(dimethylamino)phenyl}-N-methylcarbamoyl]-4-hydroxy-6-methylthio-1,2-dihydroquinoline

mp : 165-168°C

IR (Nujol) : 1640, 1615, 1565, 1525 cm^{-1}

NMR (DMSO-d_6, δ) : 2.49 (3H, s), 2.77 (6H, s), 3.21 (3H, s), 3.43 (3H, s), 6.49 (2H, d, J=8.7Hz), 7.10 (2H, d, J=8.7Hz), 7.3-7.7 (3H, m)

Mass (m/z) : 397 (M^+), 247

(6) 1-Methyl-2-oxo-3-[N-{4-(methoxycarbonyl)phenyl}-N-methylcarbamoyl]-4-hydroxy-6-methylthio-1,2-dihydroquinoline

mp : 149-151°C

IR (Nujol) : 1725, 1645, 1630, 1605, 1565, 1500 cm^{-1}

NMR (DMSO-d_6, δ) : 2.50 (3H, s), 3.34 (3H, s), 3.46 (3H, s), 3.77 (3H, s), 7.3-7.9 (7H, m), 11.5 (1H, broad s)

Mass (m/z) : 412 (m^+), 247

Elemental Analysis Calcd. for $C_{21}H_{20}N_2O_5S$:
C 61.15, H 4.89, N 6.79
Found : C 60.91, H 5.00, N 6.53

(7) 1-Methyl-2-oxo-3-[N-methyl-N-(1-pyrrolyl)carbamoyl]-4-hydroxy-6-methylthio-1,2-dihydroquinoline

mp : 116-118°C (dec.)

IR (Nujol) : 3030, 1680, 1620, 1600, 1575, 1500 cm^{-1}

NMR (DMSO-d_6, δ) : 2.50 (3H, s), 3.39 (3H, s), 3.45 (3H, s), 5.83 (2H, broad s), 6.77 (2H, broad s), 7.3-7.8 (3H,m), 11.5 (1H, s)

Mass (m/z) : 343 (M^+)

Elemental Analysis Calcd. for $C_{17}H_{17}N_3O_3S \cdot EtOH$:
C 58.59, H 5.95, N 10.79
Found : C 58.77, H 6.22, N 10.77

(8) 1-Methyl-2-oxo-3-[N-(4-cyanophenyl)-N-methylcarbamoyl]-4-hydroxy-6-methylthio-1,2-dihydroquinoline

mp : 171-181°C

IR (Nujol) : 2230, 1645, 1630, 1590, 1565, 1510 cm^{-1}

NMR (DMSO-d_6, δ) : 2.51 (3H, s), 3.34 (3H, s), 3.47 (3H, s), 7.3-7.9 (7H, m), 11.6 (1H, broad s)

Mass (m/z) : 379 (M^+), 247

(9) 1-Methyl-2-oxo-3-[N-methyl-N-(4-nitorophenyl)-carbamoyl]-4-hydroxy-6-methylthio-1,2-dihydroquinoline

mp : 112-116°C

IR (Nujol) : 1640, 1630, 1610, 1580, 1525, 1495 cm^{-1}

NMR (DMSO-d_6, δ) : 2.51 (3H, s), 3.37 (3H, s), 3.48 (3H, s), 7.3-8.2 (7H, m), 11.6 (1H, broad s)
Mass (m/z) : 399 (M^+), 247

Example 12

A mixture of 1-methyl-2-oxo-3-[N-{4-(methoxycarbonyl)phenyl}-N-methylcarbamoyl]-4-hydroxy-6-methylthio-1,2-dihydroquinoline (0.55 g) and sodium hydroxide (0.21 g) in water (6 ml) was stirred at room temperature for 2 hours. The mixture was filtered and the filtrate was acidified with hydrochloric acid. The precipitates were collected and washed with water to give pale yellow crystals of 1-methyl-2-oxo-3-{N-(4-carboxyphenyl)-N-methylcarbamoyl}-4-hydroxy-6-methylthio-1,2-dihydroquinoline (0.5 g).

mp : 123-137°C
IR (Nujol) : 1710, 1630, 1600, 1570, 1500 cm^{-1}
NMR (DMSO-d_6, δ) : 2.50 (3H, s), 3.33 (3H, s), 3.47 (3H, s), 7.3-7.9 (7H, m), 11.5 (1H, broad s), 12.9 (1H, broad s)
Mass (m/z) : 399 (M^+), 354

Example 13

A mixture of 1-methyl-2-oxo-3-(N-methyl-N-phenylcarbamoyl)-4-hydroxy-6-methylthio-1,2-dihydroquinoline (2.5 g) and m-chloroperbenzoic acid (3.8 g) in dichloromethane (70 ml) was stirred at room temperature for 7 hours. The mixture was extracted with an aqueous solution of sodium bicarbonate and the extract was acidified with hydrochloric acid. The precipitates were collected by filtration and purified by column chromatography on silica gel (150 g) eluting with a mixture of chloroform and ethanol (20:1) and a mixture of chloroform, ethanol and acetic acid (100:10:1), successively. The purified product was washed with

ethanol to give pale brown crystals of 1-methyl-2-oxo-3-(N-methyl-N-phenylcarbamoyl)-4-hydroxy-6-methylsulfonyl-1,2-dihydroquinoline (1.2 g).

mp : 221-223°C (dec.)

IR (Nujol) : 1640, 1620, 1590, 1550, 1495 cm^{-1}

NMR (DMSO-d_6, δ) : 3.23 (3H, s), 3.31 (3H, s), 3.49 (3H, s), 7.0-8.4 (8H, m), 11.9 (1H, broad s)

Mass (m/z) : 386 (M^+)

Example 14

A mixture of 5-(methylthio)indoline (2 g) and tri(ethoxycarbonyl)methane (3.1 ml) was stirred at 150°C for 1 hour, at 200°C for 1 hour, and at 220°C for 1.5 hours. The product was purified by column chromatography on silica gel (60 g) eluting with a mixture of ethyl acetate and ethanol (10:1) to give a brown solid of 4-oxo-5-ethoxycarbonyl-6-hydroxy-8-methylthio-1,2-dihydro-4H-pyrrolo[3,2,1-ij]quinoline (1.3 g).

IR ($CHCl_3$) : 1655, 1620, 1560, 1490 cm^{-1}

NMR (DMSO-d_6, δ) : 1.29 (3H, t, J=7.1Hz), 2.51 (3H, s), 3.32 (2H, t, J=7.8Hz), 4.1-4.4 (4H, m), 7.47 (1H, s), 7.51 (1H, s)

Mass (m/z) : 305 (M^+), 259

Example 15

To a stirred mixture of ethyl benzylsulfinylacetate (0.5 g) and 1-methyl-6-methylthio-2H-3,1-benzoxazine-2,4(1H)-dione (0.49 g) in tetrahydrofuran (11 ml) was added sodium hydride (0.18 g) at 3°C. After 30 minutes, the reaction mixture was quenched with water, acidified with 1N hydrochloric acid (5 ml) and extracted with dichloromethane. The extract was dried and concentrated. The residue was dissolved in toluene (15 ml) and the solution was allowed to stand at room temperature overnight. The precipitates were collected and washed

with toluene to give colorless crystals of 1-methyl-2-oxo-3-benzylsulfinyl-4-hydroxy-6-methylthio-1,2-dihydroquinoline (0.39 g).

mp : 158-160°C (dec.)

IR (Nujol) : 1615, 1565 cm^{-1}

NMR (DMSO-d_6, δ) : 2.49 (3H, s), 3.59 (3H, s), 4.33 (1H, d, J=13Hz), 4.60 (1H, d, J=13Hz), 7.1-7.8 (8H, m)

Mass (m/z) : 359 (M^+)

Example 16

A mixture of diisopropylamine (2.8 ml) and 1.6 M n-butyl lithium in hexane (12.5 ml) in tetrahydrofuran (75 ml) was stirred at 5°C for 10 minutes. Ethyl (benzylthio)acetate (2.1 g) was added at -78°C and the mixture was stirred for 1 hour. To the mixture was added 1-methyl-6-methylthio-2H-3,1-benzoxazine-2,4(1H)-dione (2.2 g). The resulting mixture was slowly warmed to room temperature, stirred for 2 hours, quenched with an aqueous solution of ammonium chloride, and extracted with dichloromethane. The extract was dried and concentrated, and the residue was dissolved in toluene (25 ml) and refluxed for 90 minutes. The residue obtained by evaporation of the solvent was purified by column chromatography on silica gel (150 g) eluting with dichloromethane-isopropanol (20:1), followed by recrystallization from acetone to give colorless crystals of 1-methyl-2-oxo-3-benzylthio-4-hydroxy-6-methylthio-1,2-dihydroquinoline (0.86 g).

mp : 110-112°C

IR (Nujol) : 1635, 1610, 1585, 1560 cm^{-1}

NMR (DMSO-d_6, δ) : 2.51 (3H, s), 3.61 (3H, s), 4.06 (2H, s), 7.0-7.7 (8H, m), 10.45 (1H, s)

Mass (m/z) : 343 (M^+)

Elemental Analysis Calcd. for $C_{18}H_{17}NO_2S_2$:
C 62.95, H 4.99, N 4.08, S 18.67
Found : C 62.91, H 4.92, N 4.00, S 18.54

Example 17

(1) A mixture of ethyl 2-{N-methyl-N-(2-benzoylacetyl)-amino}-5-(methylthio)benzoate (2.9 g) and sodium ethoxide (1.1 g) in ethanol (39 ml) was stirred at room temperature for 2 hours. 3N Hydrochloric acid (6 ml) was added thereto, and the precipitates were collected by filtration and washed with ethanol to give a yellow solid of 1-methyl-2-oxo-3-benzoyl-4-hydroxy-6-methylthio-1,2-dihydroquinoline (2 g).

mp : 170-171°C
IR (Nujol) : 1650, 1625, 1595, 1565 cm^{-1}
NMR (DMSO-d_6, δ) : 2.55 (3H, s), 3.54 (3H, s), 7.4-8.0 (8H, m), 11.8 (1H, s)
Mass (m/z) : 324
Elemental Analysis Calcd. for $C_{18}H_{15}NO_3S$:
C 66.44, H 4.65, N 4.30, S 9.85
Found : C 66.31, H 4.60, N 4.31, S 9.84

The following compounds were obtained according to a similar manner to that of Example 17-(1).

(2) 2-Oxo-3-(N-methyl-N-phenylcarbamoyl)-4-hydroxy-6-methylthio-1,2-dihydroquinoline
mp : 259°C (dec.)
IR (Nujol) : 1650, 1625, 1595, 1500 cm^{-1}
NMR (DMSO-d_6, δ) : 2.46 (3H, s), 3.29 (3H, s), 7.0-7.7 (8H, m), 11.25 (1H, s)
Mass (m/z) : 340 (M^+), 233

(3) 1-Methyl-2-oxo-3-(1-phenyl-1-cyclopropylcarbonyl)-4-hydroxy-6-methylthio-1,2-dihydroquinoline

mp : 170-173°C

IR (Nujol) : 1665, 1590, 1565 cm^{-1}

NMR (DMSO-d_6, δ) : 1.3-1.4 (2H, m), 1.5-1.6 (2H, m), 2.51 (3H, s), 3.43 (3H, s), 7.1-7.6 (7H, m), 7.82 (1H, d, J=2.1Hz), 11.86 (1H, s)

Mass (m/z) : 365 (M^+), 337

Elemental Analysis Calcd. for $C_{21}H_{19}NO_3S \cdot 1/4H_2O$: C 68.18, H 5.31, N 3.79

Found : C 68.27, H 5.12, N 3.79

Example 18

A mixture of 1-methyl-2-oxo-3-(N-methyl-N-phenylcarbamoyl)-4-hydroxy-6-methylthio-1,2-dihydroquinoline (2.35 g) and phosphorus oxychloride (7.05 ml) was stirred at 80°C for 1 hour. Ice-water was added thereto and the preceipitates were collected to give pale yellow crystals of 1-methyl-2-oxo-3-(N-methyl-N-phenylcarbamoyl)-4-chloro-6-methylthio-1,2-dihydroquinoline (2 g).

mp : 209-210°C

IR (Nujol) : 1645, 1630, 1590, 1560 cm^{-1}

NMR (DMSO-d_6, δ) : 2.51 (3H, s), 3.36 (3H, s), 3.56 (3H, s), 7.1-7.9 (8H, m)

Mass (m/z) : 372 (M^+), 337, 266

Example 19

(1) A mixture of 1-methyl-2-oxo-3-(N-methyl-N-phenylcarbamoyl)-4-chloro-6-methylthio-1,2-dihydroquinoline (2.4 g) and ammonia solution (28%; 10 ml) in methanol (20 ml) was heated at 100°C for 48 hours in a sealed tube. The solvent was evaporated and the residue was purified by column chromatography on silica gel eluting with a mixture of chloroform and methanol (20:1) to give colorless crystals of 1-methyl-2-oxo-3-(N-methyl-N-phenylcarbamoyl)-4-amino-6-methylthio-1,2-dihydroquinoline (1.1 g).

mp : 138-140°C
IR (Nujol) : 3370, 3200, 1620, 1590, 1560, 1495 cm^{-1}
NMR (DMSO-d_6, δ) : 2.51 (3H, s), 3.29 (3H, s), 3.37 (3H, s), 6.55 (2H, s), 7.0-7.5 (7H, m), 7.84 (1H, s)
Mass (m/z) : 353 (M^+)

The following compound was obtained according to a similar manner to that of Example 19-(1).

(2) 1-Methyl-2-oxo-3-(N-methyl-N-phenylcarbamoyl)-4-methylamino-6-methylthio-1,2-dihydroquinoline
mp : 244-246°C
IR (Nujol) : 3350, 1620, 1585, 1550 cm^{-1}
Mass (m/z) : 367 (M^+), 261

Example 20

A mixture of 1-methyl-2-oxo-3-(N-methyl-N-phenylcarbamoyl)-4-chloro-6-methylthio-1,2-dihydroquinoline (1.5 g), S-potassium thioacetate (1.8 g) and sodium iodide (10 mg) in acetone (30 ml) was refluxed for 48 hours. The solvent was evaporated, and the residue was dissolved in chloroform and washed with water. The organic layer was extracted with an aqueous sodium bicarbonate solution. The extract was acidified with hydrochloric acid and extracted with chloroform. The residue obtained from the extract was crystallized from acetone to give yellow crystals of 1-methyl-2-oxo-3-(N-methyl-N-phenylcarbamoyl)-4-mercapto-6-methylthio-1,2-dihydroquinoline (0.5 g).

mp : 210-212°C
IR (Nujol) : 1610, 1580, 1540, 1480 cm^{-1}
NMR (DMSO-d_6, δ) : 2.49 (3H, s), 3.37 (3H, s), 3.53 (3H, s), 7.1-7.7 (8H, m)
Mass (m/z) : 370 (M^+)

Elemental Analysis Calcd. for $C_{19}H_{18}N_2O_2S_2$:
C 61.60, H 4.90, N 7.56
Found : C 61.60, H 4.78, N 7.45

Example 21

A mixture of 1-methyl-2-oxo-3-(N-methyl-N-phenylcarbamoyl)-4-chloro-6-methylthio-1,2-dihydroquinoline (0.3 g) and sodium methoxide (0.11 g) in methanol (5 ml) was stirred at 40°C for 3.5 hours. The mixture was filtered, and the filtrate was evaporated. The residue was washed with water to give colorless crystals of 1-methyl-2-oxo-3-(N-methyl-N-phenylcarbamoyl)-4-methoxy-6-methylthio-1,2-dihydroquinoline (0.28 g).

mp : 148-151°C
IR (Nujol) : 1640, 1620, 1590, 1575, 1495 cm^{-1}
NMR (DMSO-d_6, δ) : 2.48 (3H, s), 3.35 (3H, s), 3.47 (3H, s), 4.10 (3H, s), 7.1-7.9 (8H, m)
Mass (m/z) : 368 (M^+), 262

Example 22

A mixture of 1-methyl-2-oxo-3-[N-methyl-N-(4-nitrophenyl)carbamoyl]-4-hydroxy-6-methylthio-1,2-dihydroquinoline (0.28 g), iron powder (0.28 g), and ammonium chloride (30 mg) in ethanol (8 ml) and water (3 ml) was refluxed and stirred for 2 hours. The solvent was evaporated, and the residue was suspended in a mixture of chloroform and water, followed by filtration. The organic layer was separated, dried, and evaporated. The residue (0.26 g) was washed with ethanol to give a brown powder of 1-methyl-2-oxo-3-[N-(4-aminophenyl)-N-methylcarbamoyl]-4-hydroxy-6-methylthio-1,2-dihydroquinoline (0.1 g).

IR (Nujol) : 3450, 3350, 3250, 1630, 1610, 1570, 1540, 1515 cm^{-1}
Mass (m/z) : 369 (M^+)

Example 23

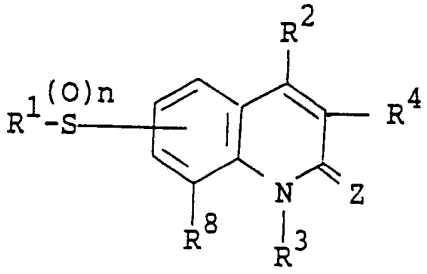
A mixture of formic acid (51 µl) and acetic anhydride (128 µl) was stirred at 50°C for 30 minutes, and then cooled. 1-Methyl-2-oxo-3-[N-(4-aminophenyl)-N-methylcarbamoyl]-4-hydroxy-6-methylthio-1,2-dihydroquinoline (0.1 g) was added and the mixture was stirred for 40 minutes at room temperature. Then, acetic anhydride (0.5 ml) was added and the resulting mixture was stirred for 3 hours. The reaction mixture was poured into ice-water, and the precipitates were collected and washed with water. The product was dissolved in 0.4N sodium hydroxide (1 ml) and the solution was filtered. The filtrate was acidified with hydrochloric acid and the precipitates were collected to give a brown powder of 1-methyl-2-oxo-3-[N-[4-(formylamino)phenyl]-N-methylcarbamoyl]-4-hydroxy-6-methylthio-1,2-dihydroquinoline (58 mg).

IR (Nujol) : 3450 , 3250, 1630, 1565, 1510 cm^{-1}

Mass (m/z) : 397 (M^+), 247

C L A I M S

1. A compound of the formula :



wherein R^1 is lower alkyl or aryl which may have suitable substituent(s),
R^2 is hydroxy, protected hydroxy, lower alkoxy, halogen, amino, substituted amino, mercapto or protected mercapto,
R^3 is hydrogen, lower alkyl, lower alkoxy(lower)alkyl or ar(lower)alkyl and
R^8 is hydrogen, or
R^3 and R^8 are linked together to form lower alkylene,
R^4 is an organic group,
Z is O or S, and
n is 0, 1 or 2,
and pharmaceutically acceptable salts thereof.

2. A compound of claim 1, wherein
R^1 is lower alkyl, or phenyl which may have halogen,
R^2 is hydroxy, acyloxy, lower alkoxy, halogen, amino, lower alkylamino, protected amino, mercapto or acylthio,
R^3 is hydrogen, lower alkyl, lower alkoxy(lower)alkyl, or phenyl(lower)alkyl and
R^8 is hydrogen, or

R^3 and R^8 are linked together to form lower alkylene, and

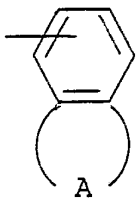
R^4 is acyl, carboxy, ar(lower)alkylsulfinyl, ar(lower)alkylthio, cyano, or heterocyclic group which may have suitable substituent(s).

3. A compound of claim 2, wherein

R^1 is lower alkyl, phenyl or halophenyl,

R^2 is hydroxy, acyloxy, lower alkoxy, halogen, amino, lower alkylamino, acylamino, mercapto or lower alkanoylthio, and

R^4 is carbamoyl which may be substituted with one or two suitable substituent(s) selected from the group consisting of lower alkyl; phenyl which may have 1 to 3 suitable substituent(s) selected from the group consisting of lower alkyl, halogen, lower alkoxy, lower alkylthio, acyl, di(lower)alkylamino, cyano, mono(or di or tri)halo(lower)alkyl, mono(or di or tri)halo(lower)alkoxy, carboxy, protected carboxy, nitro, amino and acylamino; heterocyclic group which may have lower alkyl; phenyl(lower)alkyl; lower cycloalkyl and a group of the formula :



(in which A is lower alkylene);
thiocarbamoyl which may be substituted with one or two suitable substituent(s) selected from the group consisting of lower alkyl and aryl;
lower alkoxycarbonyl;

aminosulfonyl which may be substituted with one or two suitable substituent(s) selected from the group consisting of lower alkyl and aryl; aroyl; ar(lower)cycloalkylcarbonyl; ar(lower)alkylsulfonyl; heterocycliccarbonyl; carboxy; ar(lower)alkylsulfinyl; ar(lower)alkylthio; cyano; or heterocyclic group which may have lower alkyl or aryl.

4. A compound of claim 3, wherein

R^4 is carbamoyl which may be substituted with one or two suitable substituent(s) selected from the group consisting of lower alkyl, phenyl, mono(or di)(lower)alkylphenyl, mono(or di)halophenyl, (lower)alkoxyphenyl, lower alkylthiophenyl, lower alkanoylphenyl, N,N-di(lower)alkylaminophenyl, cyanophenyl, trihalo(lower)alkylphenyl, trihalo(lower)alkoxyphenyl, carboxyphenyl, lower alkoxycarbonylphenyl, nitrophenyl, aminophenyl, lower alkanoylaminophenyl, pyridyl, lower alkylpyrazolyl, pyrrolyl, thiazolyl, thiadiazolyl, benzodioxolyl, phenyl(lower)alkyl, lower cycloalkyl and indanyl;
thiocarbamoyl which may be substituted with one or two suitable substituent(s) selected from the group consisting of lower alkyl and phenyl; lower alkoxycarbonyl;
aminosulfonyl which may be substituted with one or two suitable substituent(s) selected from the group consisting of lower alkyl and phenyl; benzoyl; phenyl(lower)cycloalkylcarbonyl; phenyl(lower)alkylsulfonyl; indolinylcarbonyl;

dihydrobenzoxazinylcarbonyl;
dihydrobenzothiazinylcarbonyl; carboxy;
phenyl(lower)alkylsulfinyl;
phenyl(lower)alkylthio; cyano;
imidazolinyl or tetrazolyl, each of which may have aryl;
oxadiazolyl which may have aryl; or
benzimidazolyl, quinolyl or isoquinolyl, each of which may have lower alkyl.

5. A compound of claim 4, wherein
R^4 is carbamoyl which may be substituted with one or two suitable substituent(s) selected from the group consisting of lower alkyl, phenyl, mono(or di)(lower)alkylphenyl, mono(or di)halophenyl, (lower)alkoxyphenyl, lower alkylthiophenyl, lower alkanoylphenyl, N,N-di(lower)alkylaminophenyl, cyanophenyl, trihalo(lower)alkylphenyl, trihalo(lower)alkoxyphenyl, carboxyphenyl, lower alkoxycarbonylphenyl, nitrophenyl, aminophenyl, lower alkanoylaminophenyl, pyridyl, lower alkylpyrazolyl, pyrrolyl, thiazolyl, thiadiazolyl, 1,3-benzodioxolyl, phenyl(lower)alkyl, lower cycloalkyl and indan-2-yl;
thiocarbamoyl which may be substituted with one or two suitable substituent(s) selected from the group consisting of lower alkyl and phenyl;
lower alkoxycarbonyl;
aminosulfonyl which may be substituted with one or two suitable substituent(s) selected from the group consisting of lower alkyl and phenyl;
benzoyl; phenyl(lower)cycloalkylcarbonyl;
phenyl(lower)alkylsulfonyl; indolinylcarbonyl;

dihydrobenzoxazinylcarbonyl; dihydrobenzothiazinylcarbonyl; carboxy; phenyl(lower)alkylsulfinyl; phenyl(lower)alkylthio; cyano; imidazolinyl; phenylimidazolinyl; tetrazolyl; phenyltetrazolyl; oxadiazolyl; phenyloxadiazolyl; benzimidazolyl; lower alkylbenzimidazolyl; quinolyl; or isoquinolyl.

6. A compound of claim 5, wherein
R^1 is lower alkyl, phenyl or halophenyl
R^2 is hydroxy,
R^3 is lower alkyl and
R^8 is hydrogen, or
R^3 and R^8 are linked together to form lower alkylene,
R^4 is carbamoyl which may have one or two suitable substituent(s) selected from the group consisting of lower alkyl, phenyl, mono(or di)halophenyl, lower alkoxyphenyl, lower alkylphenyl, cyanophenyl, pyrrolyl, trihalo(lower)alkoxyphenyl, trihalo(lower)alkylphenyl, nitrophenyl, aminophenyl, 1,3-benzodioxolyl and lower alkanoylaminophenyl, or phenyl(lower)cycloalkylcarbonyl,
Z is O or S, and
n is 0 or 1.

7. A compound of claim 6, which is selected from the group consisting of

(1) 1-Methyl-2-oxo-3-{N-(4-fluorophenyl)-N-methylcarbamoyl}-4-hydroxy-6-methylthio-1,2-dihydroquinoline,

(2) 1-Methyl-2-oxo-3-{N-(4-methoxyphenyl)-N-

methylcarbamoyl}-4-hydroxy-6-methylthio-1,2-dihydroquinoline,

(3) 1-Methyl-2-oxo-3-(N-methyl-N-phenylcarbamoyl)-4-hydroxy-6-methylsulfinyl-1,2-dihydroquinoline,

(4) 1-Methyl-2-oxo-3-[N-methyl-N-phenylamino(thiocarbonyl)]-4-hydroxy-6-methylthio-1,2-dihydroquinoline,

(5) 1-Methyl-2-oxo-3-(N-methyl-N-phenylcarbamoyl)-4-hydroxy-6-ethylthio-1,2-dihydroquinoline,

(6) 1-Methyl-2-oxo-3-[N-methyl-N-phenylcarbamoyl]-4-hydroxy-6-phenylthio-1,2-dihydroquinoline,

(7) 1-Methyl-2-oxo-3-{N-(2-methylphenyl)carbamoyl}-4-hydroxy-6-methylthio-1,2-dihydroquinoline,

(8) 1-Methyl-2-oxo-3-(N-ethyl-N-phenylcarbamoyl)-4-hydroxy-6-methylthio-1,2-dihydroquinoline,

(9) 4-Oxo-5-(N-methyl-N-phenylcarbamoyl)-6-hydroxy-8-methylthio-1,2-dihydro-4H-pyrrolo[3,2,1-ij]-quinoline,

(10) 1-Methyl-2-thioxo-3-(N-methyl-N-phenylcarbamoyl)-4-hydroxy-6-methylthio-1,2-dihydroquinoline,

(11) 1-Methyl-2-oxo-3-(N-methyl-N-phenylcarbamoyl)-4-hydroxy-6-phenylsulfinyl-1,2-dihydroquinoline,

(12) 1-Methyl-2-oxo-3-(N-methyl-N-phenylcarbamoyl)-4-hydroxy-6-(4-fluorophenylthio)-1,2-

dihydroquinoline,

(13) 1-Methyl-2-oxo-3-(1-phenyl-1-cyclopropyl-carbonyl)-4-hydroxy-6-methylthio-1,2-dihydro-quinoline,

(14) 1-Methyl-2-oxo-3-[N-methyl-N-(1-pyrrolyl)-carbamoyl]-4-hydroxy-6-methylthio-1,2-dihydro-quinoline,

(15) 1-Methyl-2-oxo-3-[N-(4-cyanophenyl)-N-methyl-carbamoyl]-4-hydroxy-6-methylthio-1,2-dihydro-quinoline,

(16) 1-Methyl-2-oxo-3-[N-methyl-N-{4-(trifluoro-methoxy)phenyl}carbamoyl]-4-hydroxy-6-methylthio-1,2-dihydroquinoline,

(17) 1-Methyl-2-oxo-3-[N-methyl-N-{3-(trifluoro-methyl)phenyl}carbamoyl]-4-hydroxy-6-methylthio-1,2-dihydroquinoline,

(18) 1-Methyl-2-oxo-3-[N-methyl-N-(4-nitrophenyl)-carbamoyl]-4-hydroxy-6-methylthio-1,2-dihydroquinoline,

(19) 1-Methyl-2-oxo-3-[N-(4-aminophenyl)-4-methyl-carbamoyl]-4-hydroxy-6-methylthio-1,2-dihydro-quinoline,

(20) 1-Methyl-2-oxo-3-[N-[4-(formylamino)phenyl]-N-methylcarbamoyl]-4-hydroxy-6-methylthio-1,2-dihydroquinoline,

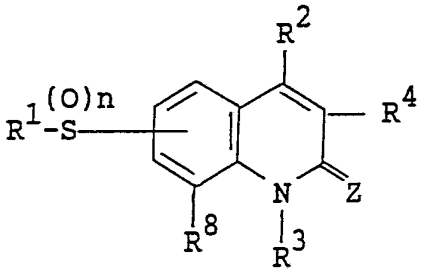
(21) 1-Methyl-2-oxo-3-{N-(1,3-benzodioxol-5-yl)-N-

methylcarbamoyl}-4-hydroxy-6-methylthio-1,2-dihydroquinoline,

(22) 1-Methyl-2-oxo-3-{N-(2,4-difluorophenyl)-N-methylcarbamoyl}-4-hydroxy-6-methylthio-1,2-dihydroquinoline and

(23) 1-Methyl-2-oxo-3-{N-methyl-N-(4-methylphenyl)-carbamoyl}-4-hydroxy-6-methylthio-1,2-dihydroquinoline.

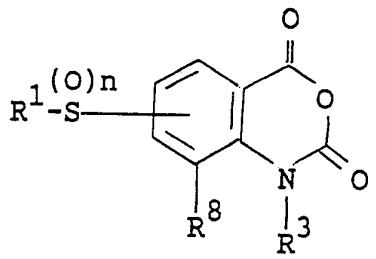
8. A process for preparing a compound of the formula :



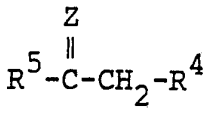
wherein R^1 is lower alkyl or aryl which may have suitable substituent(s),
R^2 is hydroxy, protected hydroxy, lower alkoxy, halogen, amino, substituted amino, mercapto or protected mercapto,
R^3 is hydrogen, lower alkyl, lower alkoxy(lower)alkyl or ar(lower)alkyl and
R^8 is hydrogen, or
R^3 and R^8 are linked together to form lower alkylene,
R^4 is an organic group,
Z is O or S, and
n is 0, 1 or 2,
or a salt thereof,

which comprises

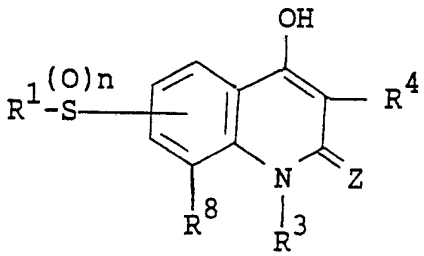
(1) reacting a compound of the formula :



wherein R^1, R^3, R^8 and n are each as defined above, or a salt thereof with a compound of the formula :

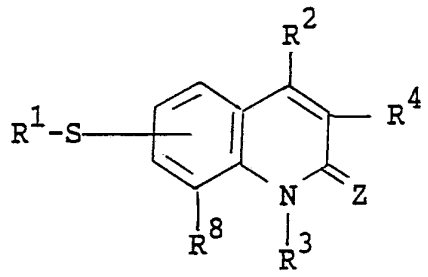


wherein R^4 and Z are each as defined above, and R^5 is a leaving group, or a salt thereof to give a compound of the formula :



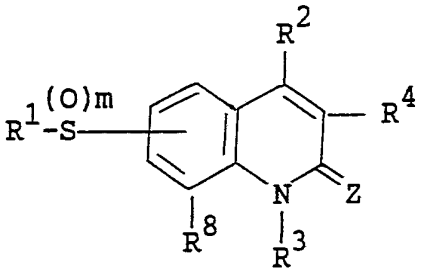
wherein R^1, R^3, R^4, R^8, Z and n are each as defined above, or a salt thereof, or

(2) subjecting a compound of the formula :



wherein R^1, R^2, R^3, R^4, R^8 and Z are each as defined above,

or a salt thereof to oxidation reaction to give a compound of the formula :

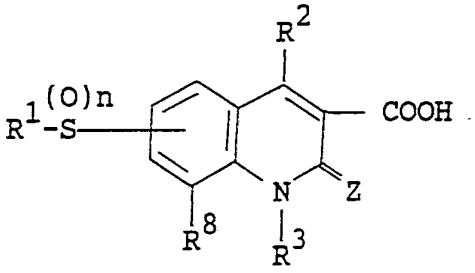


wherein R^1, R^2, R^3, R^4, R^8 and Z are each as defined above, and

m is 1 or 2,

or a salt thereof, or

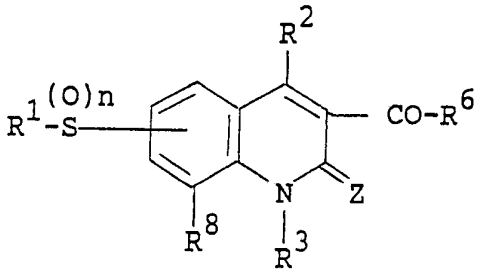
(3) subjecting a compound of the formula :



wherein R^1, R^2, R^3, R^8, Z and n are each as defined above,

or its reactive derivative at the carboxy group

or a salt thereof to amidation reaction to give a compound of the formula :

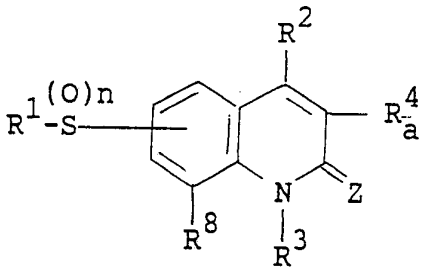


wherein R^1, R^2, R^3, R^8, Z and n are each as defined above, and

a group of the formula : $-CO-R^6$ is amidated carboxy,

or a salt thereof, or

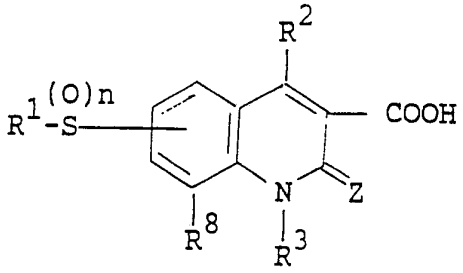
(4) subjecting a compound of the formula :



wherein R^1, R^2, R^3, R^8, Z and n are each as defined above, and

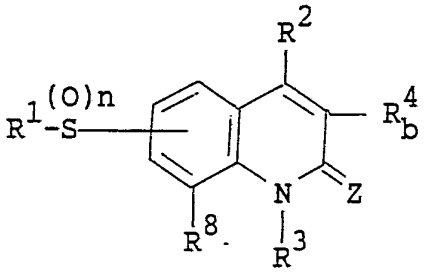
R_a^4 is protected carboxy,

or a salt thereof to elimination reaction of the carboxy protective group in R_a^4 to give a compound of the formula :

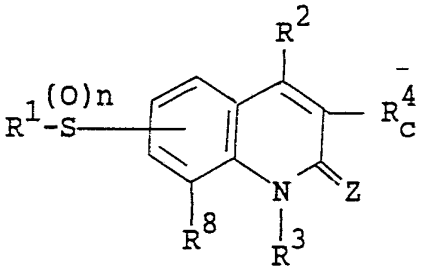


wherein R^1, R^2, R^3, R^8, Z and n are each as defined above,
or a salt thereof, or

(5) subjecting a compound of the formula :

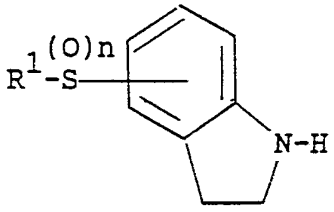


wherein R^1, R^2, R^3, R^8, Z and n are each as defined above, and
R_b^4 is acyl having protected carboxy,
or a salt thereof to elimination reaction of the carboxy protective group to give a compound of the formula :



wherein R^1, R^2, R^3, R^8, Z and n are each as defined above, and
R_c^4 is acyl having carboxy,
or a salt thereof, or

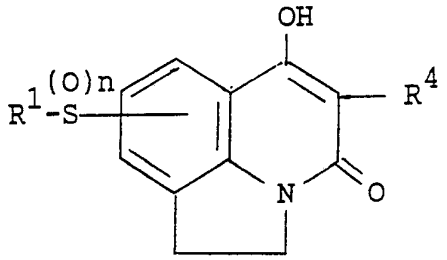
(6) reacting a compound of the formula :



wherein R^1, and n are each as defined above,
or a salt thereof with a compound of the formula :

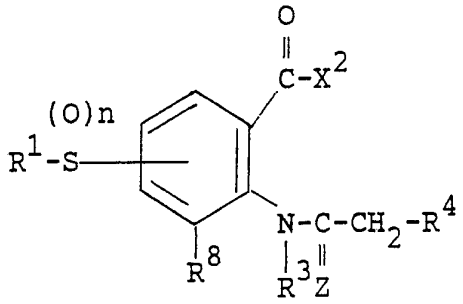
$$R^4\text{-}CH(COX^1)_2$$

wherein R^4 is as defined above, and
X^1 is a leaving group,
or a salt thereof to give a compound of the formula :

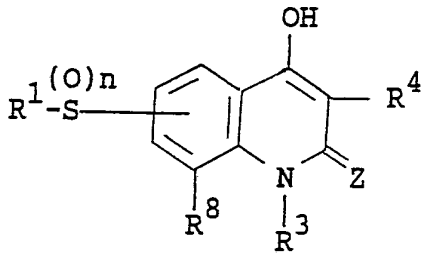


wherein R^1, R^4 and n are each as defined above,
or a salt thereof, or

(7) subjecting a compound of the formula :

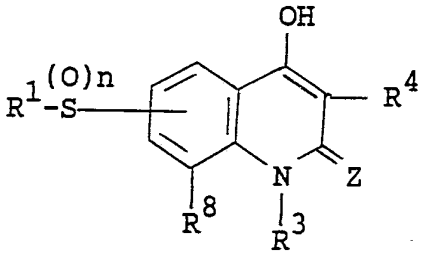


wherein R^1, R^3, R^4, R^8, Z and n are each as defined above, and
X^2 is a leaving group,
or a salt thereof to cyclization reaction to give a compound of the formula :

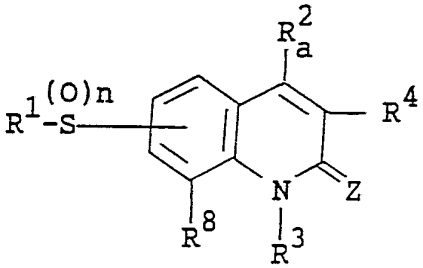


wherein R^1, R^3, R^4, R^8, Z and n are each as defined above,
or a salt thereof, or

(8) subjecting a compound of the formula :

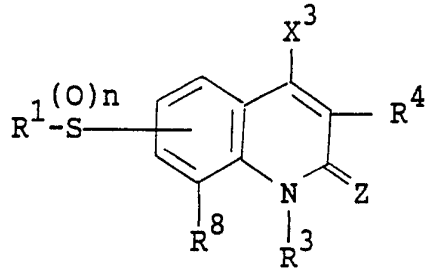


wherein R^1, R^3, R^4, R^8, Z and n are each as defined above,
or a salt thereof to halogenation reaction to give a compound of the formula :



wherein R^1, R^3, R^4, R^8, Z and n are each as defined above, and
R_a^2 is halogen,
or a salt thereof, or

(9) reacting a compound of the formula :



wherein R^1, R^3, R^4, R^8, Z and n are each as defined above, and

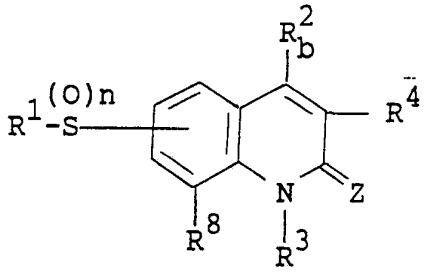
X^3 is a leaving group,

or a salt thereof with a compound of the formula :

$$H - R_b^2$$

wherein R_b^2 is amino or substituted amino,

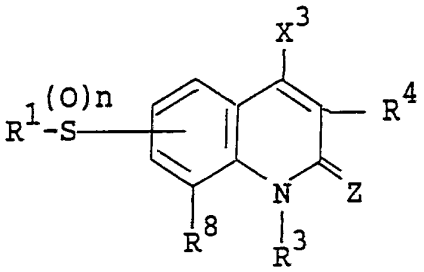
or a salt thereof to give a compound of the formula :



wherein R^1, R_b^2, R^3, R^4, R^8, Z and n are each as defined above,

or a salt thereof, or

(10) reacting a compound of the formula :



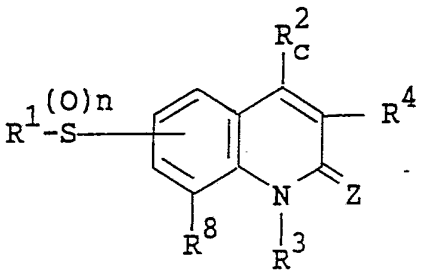
wherein R^1, R^3, R^4, R^8, Z, n and X^3 are each as defined above,

or a salt thereof with a compound of the formula :

$$R^2_C - M^1$$

wherein $R^2_{C_1}$ is protected mercapto, and M^1 is an alkali metal,

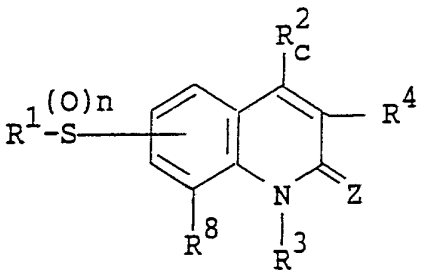
or a salt thereof to give a compound of the formula :



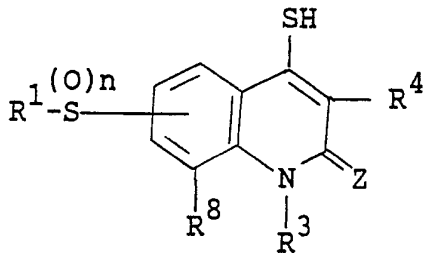
wherein R^1, R^2_C, R^3, R^4, R^8, Z and n are each as defined above,

or a salt thereof, or

(11) subjecting a compound of the formula :

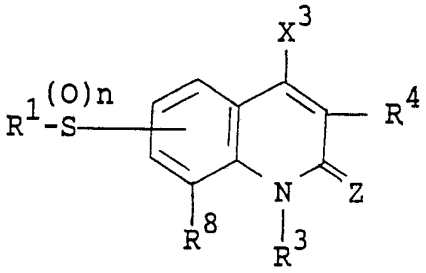


wherein R^1, R^2_c, R^3, R^4, R^8, Z and n are each as defined above,
or a salt thereof to elimination reaction of the mercapto protective group to give a compound of the formula :



wherein R^1, R^3, R^4, R^8, Z and n are each as defined above,
or a salt thereof, or

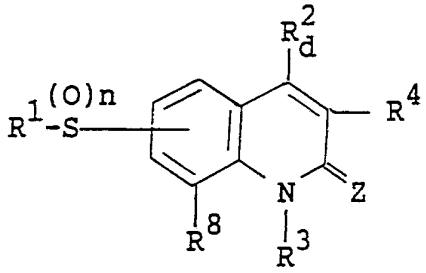
(12) reacting a compound of the formula :



wherein R^1, R^3, R^4, R^8, Z, n and X^3 are each as defined above,
or a salt thereof with a compound of the formula :

$$R^2_d - M^2$$

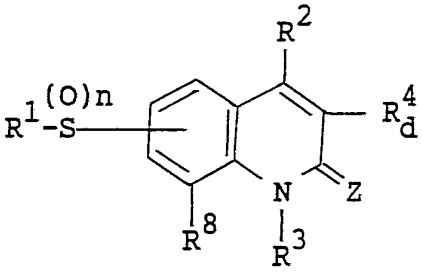
wherein R^2_d is lower alkoxy and
M^2 is an alkali metal,
or a salt thereof to give a compound of the formula :



wherein R^1, R^2_d, R^3, R^4, R^8, Z and n are each as defined above,

or a salt thereof, or

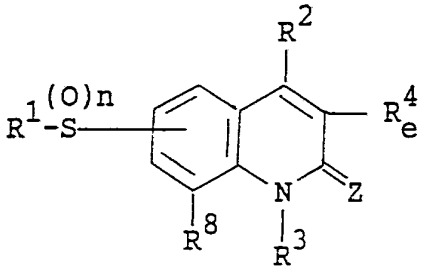
(13) subjecting a compound of the formula :



wherein R^1, R^2, R^3, R^8, Z and n are each as defined above, and

R^4_d is acyl having nitro,

or a salt thereof to reduction reaction to give a compound of the formula :

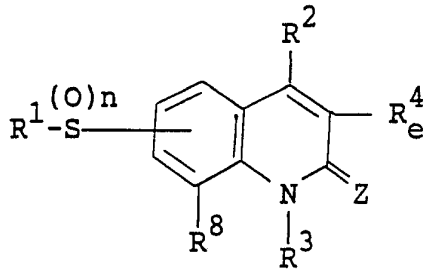


wherein R^1, R^2, R^3, R^8, Z and n are each as defined above, and

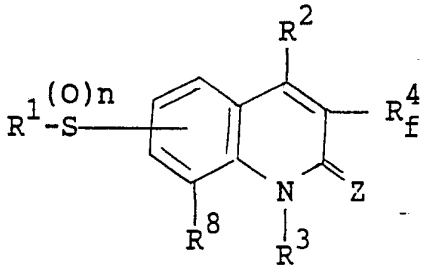
R^4_e is acyl having amino,

or a salt thereof, or

(14) subjecting a compound of the formula :



wherein R^1, R^2, R^3, R^4_e, R^8, Z and n are each as defined above,
or a salt thereof to acylation reaction to give a compound of the formula :



wherein R^1, R^2, R^3, R^4, R^8, Z and n are each as defined above, and
R^4_f is acyl having acylamino,
or a salt thereof.

9. A pharmaceutical composition which comprises, as an active ingredient, a compound of claim 1 or a pharmaceutically acceptable salt thereof in admixture with pharmaceutically acceptable carriers.

10. A use of a compound of claim 1 or a pharmaceutically acceptable salt thereof as immunomodulating agent, anti-inflammatory agent or anti-cancer agent.

11. A method for the prophylactic or therapeutic treatment of inflammatory conditions, various pains, collagen diseases, autoimmune diseases, various immunity diseases or cancer which comprises administering a compound of claim 1 or a pharmaceutically acceptable salt thereof to human or animals.

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

INTERNATIONAL SEARCH REPORT

International Application No PCT/JP 92/00510

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

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

Int.Cl.5 C 07 D 215/56 A 61 K 31/47 C 07 D 215/36
C 07 D 401/06 C 07 D 401/04 C 07 D 413/04 C 07 D 417/12
C 07 D 471/06

II. FIELDS SEARCHED

Minimum Documentation Searched[7]

Classification System	Classification Symbols
Int.Cl.5	C 07 D 215/00 C 07 D 401/00 C 07 D 413/00 C 07 D 417/00 C 07 D 471/00 C 07 D 405/00

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

III. DOCUMENTS CONSIDERED TO BE RELEVANT[9]

Category °	Citation of Document,[11] with indication, where appropriate, of the relevant passages[12]	Relevant to Claim No.[13]
A	WO,A,9015052 (PHARMACIA AB) 13 December 1990, see pages 1-2	1,9,10
A	EP,A,0059698 (AB LEO) 8 September 1982, see page 4, lines 25-27; claim 1	1,9,10
A	EP,A,0012639 (ROUSSEL-UCLAF) 25 June 1980, see page 17, line 35 - page 18; claim 1	1,9,10
A	EP,A,0214004 (ROUSSEL-UCLAF) 11 March 1987, see page 5, lines 55-57; claim 1	1,9,10
A	US,A,3625969 (CIBA CORP.) 7 December 1971, see column 1	1,9,10

° Special categories of cited documents :[10]

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

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

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

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

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

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

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

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

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
17-06-1992	16. 09. 92
International Searching Authority	Signature of Authorized Officer
EUROPEAN PATENT OFFICE	Natalie Welnberg

INTERNATIONAL SEARCH REPORT

I national application No.

PCT/JP 92/00510

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

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

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
REMARK: ALTHOUGH CLAIM 11 IS DIRECTED TO A METHOD OF TREATMENT OF (DIAGNOSTIC METHOD PRACTISED ON) THE HUMAN/ANIMAL BODY THE SEARCH HAS BEEN CARRIED OUT AND BASED ON THE ALLEGED EFFECTS OF THE COMPOUND/COMPOSITION.

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

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

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

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

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

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

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

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

Remark on Protest

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

☐ No protest accompanied the payment of additional search fees.

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO. JP 9200510 SA 58439

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on 06/08/92
The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO-A- 9015052	13-12-90	AU-A- 5923490	07-01-91
		CA-A- 2033211	10-12-90
		EP-A- 0429627	05-06-91
		JP-T- 4500373	23-01-92
EP-A- 0059698	08-09-82	AU-B- 547849	07-11-85
		AU-A- 8107682	09-09-82
		CA-A- 1182455	12-02-85
		JP-A- 57171975	22-10-82
		US-A- 4547511	15-10-85
		US-A- 4738971	19-04-88
EP-A- 0012639	25-06-80	FR-A- 2443467	04-07-80
		AU-B- 531501	25-08-83
		AU-A- 5358579	12-06-80
		CA-A- 1137985	21-12-82
		EP-A,B 0049555	14-04-82
		JP-C- 1481124	10-02-89
		JP-A- 55081878	20-06-80
		JP-B- 63030914	21-06-88
		US-A- 4299831	10-11-81
EP-A- 0214004	11-03-87	FR-A- 2585356	30-01-87
		AU-B- 609377	02-05-91
		AU-A- 6050986	29-01-87
		CA-A- 1262903	14-11-89
		JP-A- 62029585	07-02-87
		SU-A- 1584749	07-08-90
		US-A- 4845105	04-07-89
		US-A- 4988708	29-01-91
US-A- 3625969	07-12-71	BE-A- 705381	19-04-68
		CH-A- 473807	15-06-69
		DE-A- 1670477	11-02-71
		FR-M- 7267	15-09-69
		FR-M- 7375	27-10-69
		FR-A- 1567070	16-05-69
		GB-A- 1161448	13-08-69
		NL-A- 6714214	22-04-68